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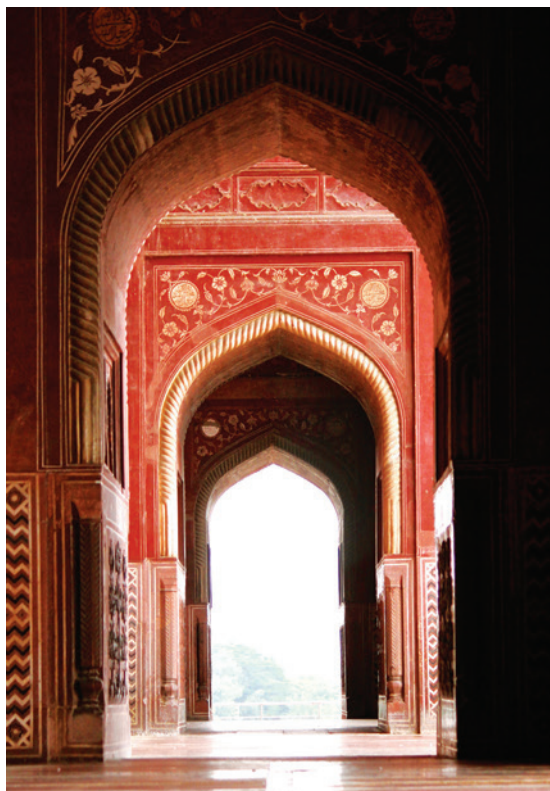
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SCAN GUIDELINES

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*"No pessimist ever discovered the secret of the stars,
or sailed to an uncharted land, or opened
a new doorway for the human spirit."*

Hellen Keller (1880 – 1968)
American author

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The Singapore Cancer Network (SCAN) Guidelines: A New Beginning

Min-Han Tan,^{1,2,3} MBBS, FRCP, PhD

The Singapore Cancer Network (SCAN) guidelines on systemic therapy published in this special issue represent the first effort by Singapore oncologists to develop a national consensus on cancer care. Nine specialist workgroups, involving over 70 subspecialists from both the public and private sectors, have written 15 guidelines, defining a framework for systemic treatments of nearly all common solid tumours in Singapore. The guidelines have been internationally peer-reviewed and endorsed by the Chapter of Medical Oncologists of the Academy of Medicine, Singapore (AMS) as well as the Singapore Society of Oncology (SSO).

The audience envisioned for these guidelines would include professionals, patients and policymakers. For clinicians, including medical oncologists, radiation oncologists, surgeons, oncology pharmacists and other disciplines, the SCAN guidelines serve as a framework of quality care for systemic therapy in Singapore as defined by subspecialists. For patients, a national consensus on cancer care developed within Singapore will provide both education and reassurance. Finally, for policymakers, the guidelines serve as an independent professional national reference useful for understanding a complex and challenging field of medicine.

In terms of membership, each SCAN guideline workgroup was composed of a panel of clinicians with relevant advanced subspecialist training and experience derived from both public and private sectors. Each autonomous workgroup was chaired by an internally elected member.

A major goal during guideline development was to limit complexity in the creation and subsequent updating of the SCAN guidelines. Since 2000, the Ministry of Health has regularly released Singapore clinical practice guidelines (CPGs) in many fields of medicine based on best available evidence. While useful in establishing local clinical practice recommendations in many areas, utilisation of these CPGs has been more limited in oncology, because of the rapidity of developments in the field. To address the concern of administrative complexity, the ADAPTE methodology¹ was

used to allow rapid calibration of international guidelines to the Singapore setting, as opposed to *de novo* creation. The ADAPTE method essentially reviews available international oncology guidelines, with consensus selection of appropriate recommendations, with additional calibration as needed. It was anticipated that this approach would allow for annual updating of the SCAN guidelines, which would reflect the frequency of practice-changing research developments. Such an approach would also be well aligned with the archetypal Singapore style of identifying best practices all around the world for local deployment. During guideline development, workgroup members holding minority opinions were also explicitly invited to submit comments alongside the majority view in order to reflect diversity of opinion and minimise groupthink.

Best practices in Singapore do not always mirror recommendations in USA or Europe due to differences in local cancer epidemiology and adverse drug reaction profiles. For example, standard first-line treatment options for epidermal growth factor receptor (*EGFR*)-mutant metastatic lung cancer in Singapore have differed from those in the USA for many years, and some chemotherapy drugs are commonly prescribed at lower doses in Singapore.² Singapore has the highest national rate of adverse drug reaction reporting in the world, and it may be possible that drug dosing in Singapore represents more calibrated real-world use.

One key feature of the SCAN guidelines was that no funding from pharmaceutical companies was received in the course of guideline development. Instead, the publication of the SCAN guidelines was funded by grants from AMS and SSO. Industry is a valued partner in cancer care, and conducts the commercial development of innovations to bring compounds to market to improve patient outcomes. However, involvement of industry would almost certainly have complicated the process of guideline writing. One major guideline organisation in the USA, the National Comprehensive Cancer Network (NCCN), accepts industry funding, but only for guideline distribution and

¹Lead Editor, Singapore Cancer Network, Singapore

²Division of Medical Oncology, National Cancer Centre Singapore, Singapore

³Division of Biodevices and Diagnostics, Institute of Bioengineering and Nanotechnology, Singapore

Address for Correspondence: Dr Min-Han Tan, Division of Medical Oncology, National Cancer Centre Singapore, 11 Hospital Drive, Singapore 169610.

Email: tan.min.han@nccs.com.sg

not for guideline development. For individual workgroup members involved, a self-declaration process aligned with the International Committee of Medical Journal Editors (ICMJE) has been used. It is helpful to recognise that some professional interactions with industry are crucial to advancing patient interests and safety, for example, when physicians conduct trials or advise on clinical trial design. At the same time, full and transparent disclosure of interactions between physician and industry would certainly be in the common interest.

It is often said that guidelines are not tramlines. Clinical judgment remains paramount in patient management. There are certainly times when it would be medically inappropriate to follow guidelines, such as in the setting of multiple patient comorbidities or when interactions with existing medications are anticipated. Additionally, oncology drug costs are a real dimension to patient care. While these guidelines were developed with an explicit remit to focus on clinical benefit, it would be remiss to divorce treatment costs, also known as “financial toxicity”,³ from real-world practice and individualised patient counseling. To maximise clarity, each workgroup was tasked to report absolute benefits as far as possible⁴ (for example, a drug improving survival at 3 years from 80% to 85% would be most appropriately reported as a 5% absolute benefit at 3 years, and not as 25% relative benefit). Corresponding results of international state-driven cost-effectiveness studies were requested as adjunct information, but not used to guide recommendations. Such background, while secondary to the key recommendations, provide helpful context.

In the Singapore context, healthcare (and by proxy cancer care) have been traditionally supported by the 3Ms—Medisave, Medishield and Medifund. Medishield Life, replacing Medishield, is the most important transformation of Singapore healthcare since the introduction of Medisave in 1984. It should be noted that the coincidence in the introduction dates for Medishield Life and the SCAN guidelines (both in November 2015) is just that—a coincidence. Nonetheless, with the increase in chemotherapy claim limit from S\$1240 (per 21/28-day cycle) to S\$3000/month, Medishield Life is expected to have a major impact on shaping cancer care over the next few years.

There are certainly limitations to the first edition of SCAN. With the exception of sarcoma management, treatment recommendations are restricted primarily to systemic therapies, with limited consideration of surgery or radiotherapy, both crucial elements of multimodality care. In its effort to define quality care in Singapore, it does not consider treatment cost-effectiveness. Like all consensus guidelines, it suffers from common limitations: recommendations are limited by available literature, in which there is a paucity of randomised controlled trials. For

example, in an independent analysis of 10 NCCN guidelines conducted in 2010, only 8% of therapeutic recommendations were supported by >1 randomised controlled trial.⁵ When available data is weak or conflicting, recommendations may represent more expert opinion than science, but it may be argued that consensus expert opinion provides better guidance than having no views at all.

In conclusion, the SCAN guidelines published here represent the first systematically developed national practice framework in Singapore. These were developed through evaluation and selection of best practices worldwide, followed by calibration for the Singapore setting. It is anticipated that future editions of the SCAN guidelines will expand to other disciplines involved in cancer care, to best provide a holistic framework for our practice and patients.

Conflicts of Interest

Dr Tan is a named inventor of methods for cancer diagnostics, with patents filed and owned by his employers. He is receiving current research funding from Pfizer for translational research. No other conflict of interest is reported.

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Singapore Cancer Network (SCAN) Guidelines for Adjuvant Trastuzumab Use in Early Stage HER2 Positive Breast Cancer

The Singapore Cancer Network (SCAN) Breast Cancer Workgroup

Abstract

Introduction: The SCAN breast cancer workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for adjuvant trastuzumab use in early stage HER2 positive breast cancer. **Materials and Methods:** The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. **Results:** Five international guidelines were evaluated—those developed by the National Comprehensive Cancer Network (2015), the National Institute of Health and Clinical Excellence (2006, 2009), the European Society of Medical Oncology (2013), the Breast Cancer Disease Site Group in conjunction with the Program in Evidence-Based Care and Cancer Care Ontario (2011) and the Scottish Intercollegiate Guidelines Network (2013). Recommendations on suitable candidacy for adjuvant trastuzumab, whether adjuvant trastuzumab should be given concurrently with a taxane or sequentially after completion of adjuvant chemotherapy, the optimal frequency of cardiac monitoring during adjuvant trastuzumab and the optimal duration of adjuvant trastuzumab were developed. **Conclusion:** These adapted guidelines form the SCAN Guidelines 2015 for adjuvant trastuzumab use in early stage HER2 positive breast cancer.

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Key words: Guideline adaptation, Anti-HER2 targeted therapy

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Introduction

Breast cancer is the most common malignancy among Singaporean females, with approximately 1700 new cases and 400 deaths per year in the period between 2008 and 2012.¹

Approximately 20% to 25% of invasive breast cancers in Singapore are HER2 positive as defined by either immunohistochemistry (IHC) or fluorescence in-situ hybridisation (FISH).^{2,3} HER2 positivity is an independent prognostic marker of increased risk of disease recurrence and mortality.^{2,4} Older studies have reported that even for small node negative HER2 positive breast cancers measuring 1 to 10 mm in size, distant recurrence risk can be as high as 15% to 30%,⁵⁻⁸ although these studies did not distinguish outcomes between T1a (1 to 5 mm) and T1b (>5 to 10 mm) tumours. More recently, a cohort study reported similar

distant recurrence risks for node negative estrogen receptor negative HER2 positive T1a tumours (n = 49, 5-year distant relapse-free survival 93%, 95% CI, 0.80 to 0.98) and T1b tumours (n = 17, 5-year distant recurrence-free survival 94%, 95% CI, 0.63 to 0.99) treated by surgery alone, although confidence intervals were wide due to the small patient numbers.⁹ In contrast, a separate cohort study using the National Comprehensive Cancer Network Database found a very low risk of distant recurrence for untreated T1a and T1b tumours but not in T1b tumours measuring exactly 1 cm where the 5-year distant recurrence risk-free survival was 93% (95% CI, 76% to 98%).¹⁰

The advent of anti-HER2 directed therapy has dramatically improved outcomes for HER2 positive breast cancer in the adjuvant¹¹ and advanced disease settings.^{11,12} One such drug is trastuzumab, a fully humanised monoclonal antibody

Address for Correspondence: Dr Wong Nan Soon, Oncocare Cancer Centre, 6 Napier Road, #02-17/18/19, Gleneagles Medical Centre, Singapore 258499.
Email: ns_wong@oncocare.sg

which targets the extracellular domain of HER2.

Individual trials¹³⁻¹⁷ and meta-analyses^{18,19} have demonstrated that the addition of adjuvant trastuzumab to a variety of chemotherapy regimens reduces the risk of disease recurrence by 40% and the risk of mortality by one-third. A single outlier is a relatively small study involving sequential rather than concurrent trastuzumab which demonstrated a 14% reduction in the risk of disease recurrence that did not reach statistical significance.²⁰

Although trastuzumab has such strong efficacy data, trastuzumab is associated with an increased risk of asymptomatic decline in cardiac ejection fraction as well as overt congestive cardiac failure.^{13,21,22} In particular, concurrent trastuzumab with a taxane immediately following adjuvant anthracycline-based regimens is associated with a 3% to 4% risk of congestive cardiac failure.^{14, 21,22} Hence, risks may outweigh benefits in a subset of patients with low risk node negative HER2 positive breast cancers. This has led to significant practice variation in the threshold for inclusion of patients for adjuvant trastuzumab.

Data from a single randomised trial comparing 4 cycles of doxorubicin cyclophosphamide followed by 3 months of paclitaxel with concurrent trastuzumab against a sequential approach in which trastuzumab is administered after completion of the same adjuvant chemotherapy suggests superiority for the concurrent approach.²³ However, a number of international guidelines have advocated the use of sequential trastuzumab after completion of all adjuvant chemotherapy rather than concurrent trastuzumab with a taxane as described above.

A third area in need of consensus is the frequency of cardiac monitoring during trastuzumab therapy, for which local institutional guidelines are lacking.

The SCAN Guidelines for Adjuvant Trastuzumab Use in Early Stage HER2 Positive Breast Cancer

The SCAN Guidelines are clinical practice guidelines for adjuvant trastuzumab use in early stage HER2 positive breast cancer.

These first edition guidelines are intended to serve as treatment recommendations by members of this working group reflecting their views on current existing international guidelines for the management of early stage HER2 positive breast cancer. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

Target Users of the Guidelines

The guidelines will be of interest to oncologists, oncology

nurse specialists, pharmacists, allied health workers and general practitioners involved in the management of women with breast cancer.

Guideline Recommendations/Development

The SCAN breast cancer workgroup comprises a panel of 11 medical oncologists and 1 oncology pharmacist, all of whom have subspecialty interest in breast cancer management. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICJME) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the authors. Guideline searching was conducted by a Pubmed search using the following keywords: breast cancer, adjuvant therapy, trastuzumab, pertuzumab, management guidelines. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework²⁴ was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, high quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to answer the following questions pertaining to adjuvant trastuzumab use in early stage HER2 positive breast cancer (Table 1):

1. Which HER2 positive early breast cancer patients are candidates for adjuvant trastuzumab?
2. Should adjuvant trastuzumab be given concurrently

with a taxane or sequentially after completion of adjuvant chemotherapy?

3. What is the frequency of cardiac monitoring during adjuvant trastuzumab?
4. What is the optimal duration of adjuvant trastuzumab?

Five international guidelines were selected for review (Supplementary Table 1):

- “NCCN Clinical Practice Guidelines in Oncology Breast Cancer” (version 2.2015) by the National Comprehensive Cancer Network (NCCN, USA)²⁵
- “Early and Locally Advanced Breast Cancer: Diagnosis and Treatment (CG80)”, 2009 and “Trastuzumab as Adjuvant Treatment for Early Stage HER2 Positive Breast Cancer” (NICE Technology Appraisal Guidance 107), 2006 by the National Institute of Health and Clinical Excellence (NICE)^{26,27}
- “Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up” by the European Society for Medical Oncology (ESMO), 2013²⁸
- “The Role of Trastuzumab in Adjuvant and Neoadjuvant Therapy in Women with HER2 Overexpressing Breast Cancer Evidence Based Series 1-24 Version 2” by the Breast Cancer Disease Site Group (DSG), Program in Evidence-Based Care (PEBC) and Cancer Care Ontario (CCO), 2011. In Review²⁹
- “Treatment of Primary Breast Cancer (SIGN134)” by the Scottish Intercollegiate Guidelines Network (SIGN), 2013³⁰

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of early stage HER2 positive breast cancer, it will be reviewed earlier.

1. Which HER2 Positive Early Breast Cancer Patients are Candidates for Adjuvant Trastuzumab?

Systematic Recommendations

The SCAN workgroup voted 9 to 3 in support of the adoption of the ESMO guidelines (Supplementary Table 1) for the inclusion of patients for adjuvant trastuzumab.

Under these guidelines, adjuvant trastuzumab can be considered for node negative HER2 positive breast cancers under 1 cm, especially if the patient is unresponsive to hormonal therapy as defined by lack of expression of oestrogen and progesterone receptors. For HER2 positive tumours larger than 1 cm or with lymph node involvement, adjuvant trastuzumab is recommended.

While distant recurrence risk is significant for patients with small node negative HER2 positive early breast cancers, there is little or conflicting data^{9,10} to suggest a clear demarcation of risk between tumours which are T1a (1 to 5 mm) versus T1b (>5 and up to 10 mm). As such, the workgroup members who are in favour of the ESMO guidelines indicate that ESMO guidelines offer higher flexibility in daily practice compared to the NCCN guidelines in this regard.

Support for the ESMO guidelines was not unanimous. One workgroup member expressed that although several retrospective studies have suggested a higher risk of relapse when HER2 is overexpressed, there is no Level I evidence supporting the administration of trastuzumab-based postoperative chemotherapy in small under 1 cm HER2 positive tumours, and preferred the more conservative NICE guidelines^{26,27} with regards to recommending trastuzumab and chemotherapy to this group of patients. A separate workgroup member supported the NCCN guidelines as it is more specific in its recommendation for T1a versus T1b node negative tumours.

Table 1. Singapore Cancer Network (SCAN) Guidelines for Adjuvant Trastuzumab Use in Early Stage HER2 Positive Breast Cancer

Guideline Recommendations	
Which HER2 positive early breast cancer patients are candidates for adjuvant trastuzumab?	ESMO Guidelines: Can be considered for node negative tumours less than 1 cm especially if ER and PR negative; recommended for tumours larger than 1 cm or node positive tumours.
Should adjuvant trastuzumab be given concurrently with a taxane or sequentially after completion of adjuvant chemotherapy?	Adjuvant trastuzumab should be given concurrently.
What is the frequency of cardiac monitoring during adjuvant trastuzumab?	ESMO Guidelines: Frequency of cardiac monitoring should be 3-monthly.
What is the optimal duration of adjuvant trastuzumab?	Until data from other studies comparing a shorter duration versus 1 year of adjuvant trastuzumab become available, the standard duration for adjuvant trastuzumab is 1 year.

ESMO: European Society for Medical Oncology

The workgroup notes that under the latest NCCN Clinical Practice Guidelines in Oncology Breast Cancer version 2.2015, adjuvant chemotherapy and trastuzumab can be considered for patients with T1a tumours, and as such, there is now less distinction between the ESMO and NCCN recommendations with regard to T1a and T1b HER2 positive breast cancers.

The SCAN breast cancer workgroup acknowledges that there is no local efficacy data on adjuvant trastuzumab in early breast cancer.

In reviewing the risk benefits, the workgroup considered the pooled analysis of adjuvant trastuzumab which shows a relative reduction in the risk of distant disease recurrence by 40% and a relative reduction in the risk of death by 30%.¹³⁻¹⁹

The main toxicity of concern associated with adjuvant trastuzumab is New York Heart Association (NYHA) class III or IV congestive cardiac failure, the incidence of which varies according to the choice of chemotherapy backbone used. With a non-anthracycline containing adjuvant regimen, this risk is approximately 0.5%^{15,31} but increases to 3% to 4% with a regimen comprising an anthracycline followed by concurrent trastuzumab and taxane.^{21,22}

Local data for trastuzumab-induced cardiotoxicity has been presented in which the overall rate of symptomatic decline in left ventricular ejection fraction is 9%. However, the rate of NYHA class III or IV congestive cardiac failure attributable to trastuzumab, independent of cardiac events caused by anthracyclines prior to the use of trastuzumab is not described and the paper has only been presented in abstract form.³²

2. Should Adjuvant Trastuzumab be Given Concurrently with a Taxane or Sequentially after Completion of Adjuvant Chemotherapy?

Systematic Recommendations

The workgroup was also unanimous in its recommendation to use trastuzumab in a concurrent fashion during taxane-based chemotherapy rather than sequentially only after completion of all adjuvant chemotherapy, based on direct randomised evidence from one trial²³ and indirect evidence from 2 studies.^{13,20}

3. What is the Frequency of Cardiac Monitoring during Adjuvant Trastuzumab?

Systematic Recommendations

There is no data comparing various intervals for cardiac monitoring and the workgroup members unanimously

adopted the 3 monthly interval recommended by ESMO for simplicity.

4. What is the Optimal Duration of Adjuvant Trastuzumab?

Two years versus 1 year of adjuvant trastuzumab does not confer any advantage,³³ while 6 months of adjuvant trastuzumab failed to show non-inferiority compared to 1 year.³⁴ Until data from other studies comparing a shorter duration versus 1 year of adjuvant trastuzumab become available, the standard duration for adjuvant trastuzumab is 1 year.

Cost-Effectiveness Analyses

The cost-effectiveness of adjuvant trastuzumab is approximately USD \$27,790 per additional quality adjusted life years (QALY) gained for the 3-weekly regimen based on estimates from the NICE evidence review group.²⁷ Other scenarios modelled on this estimate by the same group gave incremental costs per QALY gained ranging from USD \$24,700 to USD \$50,950.

A study based on local societal costs and benefits found that average cost per QALY was USD \$19,175 (median: USD \$18,994) in 2005.³⁵

Unsystematic Recommendations

There are no unsystematic recommendations.

Pertuzumab is a monoclonal antibody which binds to the dimerisation domain of HER2. When combined with trastuzumab and a taxane-based chemotherapy, the addition of pertuzumab has been shown to increase pathological complete response rate in the neoadjuvant setting³⁶ and improve overall survival in the metastatic setting³⁷ for HER2 positive breast cancer.

Given the above data, the latest NCCN Clinical Practice Guidelines in Oncology Breast Cancer version 2.2015 considers it reasonable to incorporate pertuzumab concurrently with trastuzumab and a taxane into the adjuvant therapy for patients with $\geq T2$ or $\geq N1$ HER2 positive breast cancer who did not receive prior neoadjuvant pertuzumab.²⁵ Given the absence of direct evidence of benefit from adjuvant pertuzumab, the overwhelming majority of the SCAN breast cancer workgroup members do not endorse this recommendation.

The workgroup notes the ongoing APHINITY trial which is assessing the addition of a pertuzumab to chemotherapy and trastuzumab in the adjuvant setting.³⁸ If the results are positive and the use of pertuzumab is incorporated in other international guidelines, the SCAN guidelines will be amended accordingly in the future.

Lastly, subcutaneous trastuzumab has been found to be non-inferior to intravenous trastuzumab in terms of efficacy, pharmacokinetic profile and safety.³⁹ The workgroup will await incorporation of this product in international guidelines before further assessment of its applicability in the local context.

Conflicts of Interest

Dr Ang reports receiving advisory board fees from Roche; Dr Dent, receiving advisory board fees from Roche; Dr Khoo, receiving conference support and advisory board fees from Roche; Dr Lee, receiving conference support and lecture fees from Roche and receiving advisory board fees from Roche, Pfizer, Astra Zeneca and Novartis; Dr Shang, receiving advisory board fees from Roche; Dr Wong, receiving conference support from Roche; Dr Wong, receiving travel grants and advisory board fees from Roche; Dr Yap, receiving conference support and advisory board fees from Roche; Dr Lim, Dr Ng, Dr Shih and Dr Tan have nothing to disclose.

Workgroup Members

The Members of the SCAN Breast Cancer Workgroup are Section Lead and Workgroup Chairperson: Nan Soon Wong, MBBS (S'pore), MRCP (UK), FAMS (Med Onc), Oncocare Cancer Centre, Singapore; Workgroup Members (Voting): Peter Ang, MBBS (S'pore), MRCP (UK), FAMS (Med Onc), Oncocare Cancer Centre, Singapore; Rebecca Dent, MSc (Canada), MD (Canada), FRCP (Canada), Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Soo Chin Lee, MBBS, MRCP (UK), FAMS, Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore; Siew Eng Lim, MBChB BAO, ABIM (Int Med), ABIM (Med Oncology), Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore; Kei Siong Khoo, MBBS (S'pore), FRCP (Edin), FAMS (Med Onc), Parkway Cancer Centre, Singapore; Raymond Ng, MB ChB (Otago), FRACP (NZ), MPH (NUS), Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Vivianne Shih, Pharm D, BCOP, Department of Pharmacy, National Cancer Centre Singapore, Singapore; Sing Huang Tan, MBBS (S'pore), MRCP, FAMS, Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore; Karmen Wong, MBBS (Adelaide), MRCP (UK), FAMS (Singapore), Karmen Wong Medical Oncology, Singapore; Yoon Sim Yap, MBBS (Adelaide), FRACP (Med Onc), Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Yeap Shang, MBBS, FRACP, Novena Cancer Centre, Singapore.

Reviewers

Invited reviewers were Ian F Tannock, MD, PhD, DSc, Princess Margaret Cancer Centre, University of Toronto, Canada; Gilberto Lopes, MD, MBA, Oncoclinicas Group, Brazil; Fatima Cardoso, MD, Breast Unit, Champalimaud Clinical Center, Portugal.

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Supplementary Table 1. International Guidelines for Adjuvant Trastuzumab Use in Early Stage HER2 Positive Breast Cancer

Guideline Title	NCCN Clinical Practice Guidelines in Oncology Breast Cancer Version 2.2015	NICE Early and Locally Advanced Breast Cancer: Diagnosis and Treatment (CG80) and NICE Trastuzumab as Adjuvant Treatment for Early Stage HER2 Positive Breast Cancer (NICE Technology Appraisal Guidance 107)	Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	The Role of Trastuzumab in Adjuvant and Neoadjuvant Therapy in Women with HER2 Overexpressing Breast Cancer Evidence-Based Series 1 – 24 Version 2 In Review		Treatment of Primary Breast Cancer SIGN134	SCAN Systematic Recommendations	SCAN Unsystematic Recommendations
	Date Released	6 March 2014	February 2009, June 2007	22 August 2013	15 September 2011	1 September 2013	March 2014	March 2014
Guideline Developer	National Cancer Comprehensive Network (NCCN), United States	National Institute of Health and Clinical Excellence (NICE), United Kingdom	European Society for Medical Oncology (ESMO)	Breast Cancer Disease Site Group (DSG), Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)	Scottish Intercollegiate Guidelines Network (SIGN)	SCAN Breast Cancer Workgroup	SCAN Breast Cancer Workgroup	SCAN Breast Cancer Workgroup
Description of Method of Guideline Validation	Statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Validation method not specified.	Guideline development group made up of health professionals, representatives of patient and carer groups and technical experts assesses the available evidence and makes recommendations. After the guideline development group finalises the recommendations, the collaborating centre produces the final guideline. NICE formally approves the final guideline and issues its guidance to the NHS.	Recommendations developed from discussion at consensus conferences (CCs). Group decision-making that seeks the consensus of experts and the fulfilment of objectives.Guidelines are endorsed by the Japanese Society of Medical Oncology (JSMO)	Based on comprehensive systematic review of the clinical evidence, an interpretation of and consensus agreement on that evidence by the Breast Cancer DSG and Guideline Development Group, PEBC, CCO, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant.	Guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systemic review of the evidence. The guideline is reviewed in draft form by independent expert referees and the guideline group addresses every comment made by the external reviewers and must justify any disagreement with the reviewers' comments.	Systematic recommendations are derived from existing guidelines with support of at least 50% of voting workgroup members (excluding abstaining individuals). Recommended changes in dosing of established standard drugs may be included under systematic recommendations. Abstaining is not recommended unless the member belongs to a different specialty or has a significant conflict of interest.	Unsystematic recommendations are not derived from existing guidelines, but represent best practice recommendations in Singapore supported by at least two-thirds of voting workgroup members, excluding abstaining individuals. Abstaining is not recommended unless the member belongs to a different specialty or has a significant conflict of interest.	
	Target Population	HER2 positive early breast cancer	HER2 positive early breast cancer	HER2 positive early breast cancer	HER2 positive early breast cancer	HER2 positive early breast cancer	HER2 positive early breast cancer	HER2 positive early breast cancer
Candidates for Adjuvant Trastuzumab	≤0.5 cm: consider; ≤0.5 cm and N1mic or 0.6 – 1 cm N0: consider; >1 cm: recommended	Early HER2 positive breast cancer; EF >55%	<1 cm: consider especially if ER and PR negative; >1 cm or node positive: recommended	>1 cm or node positive; patients who have received adjuvant chemotherapy	All patients who have received adjuvant chemotherapy	ESMO Guidelines	NA	

NA: Not applicable; NHS: National Health Service

Supplementary Table 1. International Guidelines for Adjuvant Trastuzumab Use in Early Stage HER2 Positive Breast Cancer (Con't)

Guideline Title	NCCN Clinical Practice Guidelines in Oncology Breast Cancer Version 2.2015		NICE Early and Locally Advanced Breast Cancer: Diagnosis and Treatment (CG80) and NICE Trastuzumab as Adjuvant Treatment for Early Stage HER2 Positive Breast Cancer (NICE Technology Appraisal Guidance 107)		Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up		The Role of Trastuzumab in Neoadjuvant Therapy in Women with HER2 Overexpressing Breast Cancer Evidence-Based Series 1-24 Version 2 In Review		Treatment of Primary Breast Cancer SIGN134	SCAN Systematic Recommendations	SCAN Unsystematic Recommendations		
Member Votes			9 out of 3 votes									NA	NA
Frequency of Cardiac Monitoring	Baseline, 3, 6 and 9 months	Every 3 months	Periodic monitoring	Not discussed	Regular monitoring required				ESMO Guidelines	NA	NA		
Member Votes			12 of 12 votes									NA	NA
Duration of Adjuvant Trastuzumab	1 year	1 year	1 year	1 year	1 year				1 year	1 year	NA	NA	
Member Votes			12 of 12 votes									12 of 12 votes	NA
Sequential or Concurrent Trastuzumab (With Taxane But Not Anthracycline)	Concurrent preferred	Sequential after chemotherapy	Concurrent preferred	Sequential	Concurrent or sequential				Concurrent	NA	NA		
Member Votes			12 of 12 votes									12 of 12 votes	NA

NA: Not applicable; NHS: National Health Service

Singapore Cancer Network (SCAN) Guidelines for Bisphosphonate Use in the Adjuvant Breast Cancer Setting

The Singapore Cancer Network (SCAN) Breast Cancer Workgroup

Abstract

Introduction: The SCAN breast cancer workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines regarding the optimal time-point for initiation of bisphosphonates when using adjuvant aromatase inhibitors (AIs) and provide a consensus for their role in modifying clinical breast cancer outcomes. **Materials and Methods:** The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. **Results:** Six international guidelines were evaluated—those developed by the National Cancer Comprehensive Network (2015), the European Society of Medical Oncology (2014), the National Institute for Clinical Evidence (2012), the Scottish Intercollegiate Guidelines Network (2013), the British Columbia Cancer Agency (2013) and the treatment algorithm based on the National Osteoporosis Foundation guidelines (2006). Recommendations on the use of bisphosphonates in postmenopausal women initiating adjuvant AIs in breast cancer to preserve bone health and the use of adjuvant bisphosphonates to improve breast cancer outcomes were developed. **Conclusion:** These adapted guidelines form the SCAN Guidelines on the use of adjuvant bisphosphonates to influence breast cancer outcomes and maintenance of bone health when on AIs.

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Key words: Aromatase inhibitors, Bone health, Breast cancer outcomes

Introduction

Breast cancer is the leading female cancer in our multiethnic Singaporean population and the most frequent cause of cancer mortality in females. The age-standardised incidence rate of newly diagnosed breast cancers in females has increased almost 3-fold in the last 4 decades from 23.8 per 100,000 in 1975 to 1979 to 64.7 per 100,000 in 2010 to 2014.¹ With our rapidly aging population demographics, the percentage of total breast cancers in women aged 55 years and above has correspondingly increased from 43.4% in 2004 to 2008 to 51.3% in 2009 to 2013.¹ Fortunately, due to improved education, increased public awareness and the implementation of our national screening programme, the majority of breast cancers are now being diagnosed earlier. Hormone receptor-positive breast cancers comprise the most common breast cancer subtypes, accounting for 75% of the cases.

The selective estrogen receptor modulator, tamoxifen, has been the standard of care in the adjuvant hormone-receptor positive setting for close to 3 decades, but

over the past 10 years, the advent of third-generation aromatase inhibitors (AIs) such as anastrozole, letrozole and exemestane has improved clinical outcomes in terms of breast cancer recurrence for postmenopausal women. The utility of AIs with respect to disease-free survival (DFS) has been demonstrated when administered as upfront therapy as shown in the Arimidex or Tamoxifen Alone or in Combination (ATAC) and Breast International Group (BIG) 1-98 studies,^{2,3} sequentially after 2 to 3 years of tamoxifen as in the International Exemestane Study (IES), the Italian Tamoxifen Anastrozole (ITA) and Arimidex-Nolvadex (ARNO) 95/Austrian Breast and Colorectal Study Group (ABCSG) 8 trials⁴⁻⁶ or after 5 years of tamoxifen as in the MA.17 data.⁷

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2015 meta-analyses comparing a 5-year course of an AI versus tamoxifen, a 5-year course of an AI versus 2 to 3 years of tamoxifen, then an AI to year 5, and 2 to 3 years of tamoxifen followed by an AI to year 5 versus 5 years of tamoxifen demonstrated that AIs gave a 30%

Address for Correspondence: Dr Tan Sing Huang, Department of Haematology-Oncology, National University Cancer Institute, Singapore, 1E Kent Ridge Road, NUHS, Tower Block, Level 7, Singapore 119228.
Email: sing_huang_tan@nuhs.edu.sg

proportionate reduction in recurrence rates compared with tamoxifen while treatments differed but not thereafter. Additionally, 5 years of an AI reduced the 10-year breast cancer mortality rates by about 15% compared with 5 years of tamoxifen.⁸

However, a common side effect of AIs is bone loss resulting in increased risk of osteoporotic fractures, due to their action of inhibiting the conversion of peripheral androgens to estrogen and causing a decline in estrogen levels. This is an especially pertinent issue in Singapore as since the 1960s, osteoporotic hip fractures have increased 5-fold in women over the age of 50, the age group in which AIs will potentially be used.

Bisphosphonates, although introduced as bone protective agents in osteoporosis management, now form an integral part of the treatment armamentarium to reduce cancer therapy-induced bone loss in breast cancer patients. Bisphosphonates are specific inhibitors of osteoclast-mediated bone resorption consisting of 2 major groups: non-nitrogen containing (clodronate and etidronate) and nitrogen containing or aminobisphosphonates (alendronate, risedronate, pamidronate and zoledronate).⁹ While oral bisphosphonates are generally well tolerated by most women, some have upper gastrointestinal tract adverse effects such as nausea (~4% to 11%), vomiting ($\leq 1\%$ to 3%), abdominal pain (~1% to 12%) and dyspepsia (~1% to 11%).¹⁰⁻¹³ There are some less common but potentially serious side effects of intravenous bisphosphonates including hypocalcaemia ($\leq 3\%$ to 17%), renal toxicity (~8% to 20%) and osteonecrosis of the jaw [ONJ] (~1% to 2%).^{10,14,15} Because of the risk of ONJ especially with intravenous bisphosphonates, and the attendant debilitating consequences, early screening and initiation of appropriate dental care are recommended before commencing bisphosphonate therapy.¹⁶ Patients should inform the dentist of their use of bisphosphonates before undergoing dental procedures.

In addition to bone protective effects, preclinical models have revealed an antitumour effect of bisphosphonates,^{17,18} leading to several clinical trials investigating their adjuvant use to improve cancer outcome in early breast cancer. Some data including a meta-analysis showed promising clinical outcomes¹⁹⁻²¹ while benefit was not demonstrated in some other studies.²² The exact mechanism for a possible antitumour effect of bisphosphonates remains unclear. In light of the complexity of this issue, guidelines are needed to aid the decision-making process with regard to using bisphosphonates to influence breast cancer outcomes.

The SCAN Guidelines for Bisphosphonate Use in the Adjuvant Breast Cancer Setting

The SCAN Guidelines are clinical practice guidelines for bisphosphonate use in early breast cancer patients.

This includes 1) women who may need bisphosphonates to preserve bone health when initiating AI therapy, or 2) women with primary breast cancer who may be considered for bisphosphonates as adjuvant therapy to improve breast cancer outcomes irrespective of their bone health.

These first edition guidelines are intended to serve as treatment recommendations by members of this working group reflecting their views on current existing international guidelines for these management issues. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

Target Users of the Guidelines

The guidelines will be of interest to oncologists, oncology nurse specialists, pharmacists, allied health workers and general practitioners involved in the management of women with breast cancer.

Guideline Recommendations/Development

The SCAN breast cancer workgroup comprises a panel of 11 medical oncologists and 1 oncology pharmacist from Singapore with special subspecialty interest in the management of breast cancer. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead with input from the workgroup members. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework²³ was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, specific breast cancer-related issues of relevance were identified and the scope and distribution of tasks was finalised. High quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. The guidelines were chosen based on their high quality, currency and applicability to

our patient population. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to address the 2 main management issues which were selected for this topic:

1. Use of bisphosphonates to preserve bone health in postmenopausal women initiating adjuvant AIs in breast cancer.
2. Use of adjuvant bisphosphonates to improve breast cancer outcomes.

For the first management issue, 5 international guidelines were selected for review (Supplementary Table 1):

- “NCCN Guidelines for Breast Cancer Version 3.2015” (v3.2015) by the National Cancer Comprehensive Network (NCCN, USA)²⁴
- “Bone Health in Cancer Patients: ESMO Clinical Practice Guidelines”, April 2014²⁵
- “Early and Locally Advanced Breast Cancer: Diagnosis and Treatment” by the National Institute for Clinical Evidence (NICE), February 2009²⁶ Last reviewed on April 2012 and decision made not to update pre-existing guidelines at that time.
- “SIGN 134. Treatment of Primary Breast Cancer” by the Scottish Intercollegiate Guidelines Network (SIGN); September 2013²⁷
- “Aromatase Inhibitors and Bone Health in Women with Breast Cancer”—Treatment Algorithm Based on the National Osteoporosis Foundation Guidelines²⁸

For the second management issue, guideline availability was limited. The following 2 guidelines were considered (Supplementary Table 2):

- “Bone Health in Cancer Patients: ESMO Clinical Practice Guidelines”, April 2014²⁵
- “Breast Cancer Management. Bone Modifying Agents” by the British Columbia (BC) Cancer Agency, January 2013²⁹

Although the following 3 guidelines were screened, 1) and 2) were considered of limited utility as they were released more than 10 years ago (2003, 2004), and 3) did not have a formal recommendation:

1. “Update on the Role of Bisphosphonates and Bone Health Issues in Women with Breast Cancer” by the American Society of Clinical Oncology, 2003³⁰
2. “Use of Bisphosphonates in Women with Breast Cancer” by the Breast Cancer Disease Site Group (DSG), Program in Evidence-Based Care (PEBC) and Cancer Care Ontario (CCO), April 2004.³¹ Reviewed in February 2012 and update in progress.
3. “Early and Locally Advanced Breast Cancer: Diagnosis and Treatment” by NICE, February 2009²⁶

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of breast cancer with regard to bisphosphonate use, it will be reviewed earlier.

1. Use of Bisphosphonates to Preserve Bone Health in Postmenopausal Women Initiating Adjuvant AIs in Breast Cancer

Oral Bisphosphonates

The use of bisphosphonates to reduce therapy-induced bone loss has been investigated in several clinical studies. Earlier studies have evaluated oral bisphosphonates such as clodronate³² and risedronate^{33,34} with 2-year mean differences in lumbar spine (LS) bone mineral density (BMD) ranging from +2.2% to 2.9%, and hip BMD of up to +3.7% in favour of bisphosphonate-containing over no bisphosphonate or placebo arms. The ARIBON trial of oral ibandronate (150 mg/month) versus placebo for 2 years in postmenopausal women with hormone receptor-positive early breast cancer having osteopenia while on anastrozole showed a significant increase in LS and hip BMD of 2.98% and 0.6% respectively in the ibandronate group compared to placebo ($P < 0.01$), with no fragility fractures in either group.³⁵

Intravenous Zoledronate

More recent trials have focused on the efficacy of intravenous zoledronate. In particular, the Austrian Breast and Colorectal Cancer Study Group (ABCSG)-12 bone substudy which randomised premenopausal women with hormone receptor (HR)-positive early breast cancer to receive endocrine therapy (goserelin/anastrozole or goserelin/tamoxifen) alone or with adjuvant zoledronate (4 mg, 6-monthly) for 3 years reported increased LS (+4%, $P = 0.02$) and trochanter (+3.9%, $P = 0.07$) BMD from baseline at 5 years.³⁶ For those not receiving zoledronate, the LS and trochanter BMD remained below baseline even at 5 years. The study was not powered to assess proportion of fractures between groups.

The Z-FAST and ZO-FAST trials studied the efficacy

of zoledronate (4 mg, 6-monthly) given up to a maximum of 5 years, either upfront or in a delayed fashion based on BMD T-scores <-2.0 or non-traumatic fractures, in postmenopausal women receiving adjuvant letrozole. In the Z-FAST study, the mean differences in LS and total hip BMD between upfront versus delayed therapy at 5 years were +8.9% and +6.7% respectively ($P < 0.0001$ for both) in favour of upfront zoledronate, with no significant difference in fracture rates.³⁷ Mean differences at 5 years in LS and total hip BMD between the upfront and delayed groups were +4.3% and -5.4% ($P < 0.0001$) in the ZO-FAST trial, with statistically similar fracture rates in both groups.³⁸

Treatment Algorithm Based on the National Osteoporosis Foundation Guidelines

A useful algorithm based on the National Osteoporosis Foundation (NOF) guidelines was developed by Chien and Goss.²⁸ Under this algorithm, all patients on adjuvant AIs are required to have a thorough history and physical examination focusing on prior fractures, family history of fractures and height decrease and undergo a baseline BMD and annual height measurements, in addition to lifestyle modifications. Lifestyle modifications recommended include the following: total calcium intake of 1200 to 1500 mg/day, vitamin D3 supplementation of 800 U/day, weight-bearing exercises, moderate alcohol consumption (1 to 2 drinks/day) and smoking cessation. Subsequent management is based upon the T-score as follows:

- T-score $>-1 \rightarrow$ rescreen in 1 year. If 1-year T-score >-1.0 , screen every 1 to 2 years.
- T-score between -1.0 and $-1.5 \rightarrow$ annual screening.
- T-score between -1.5 and $-2.0 \rightarrow$ check vitamin D level [25(OH)D]. Consider bisphosphonate therapy depending on risk factors (advanced age, female sex, personal history of fracture as an adult, history of fracture in a first-degree relative, chronic corticosteroid use, immobility and inadequate physical activity, cigarette smoking, excessive alcohol consumption [>2 drinks/day], low body weight, estrogen deficiency [early menopause, menopause, bilateral ovariectomy, prolonged amenorrhea of >1 year], lifelong low calcium intake, vitamin D deficiency, chronic illness [i.e. hyperthyroidism, hyperparathyroidism, inflammatory bowel disease]).
- T-score $<-2.0 \rightarrow$ check vitamin D level [25(OH)D]. Treat with bisphosphonate therapy.

However, it remains unclear whether a particular bisphosphonate is superior.

Cost-effectiveness Analyses

Using a Markov state transition model in a hypothetical cohort of women aged 60 years with hormone receptor-positive early breast cancer starting a 5-year course of adjuvant AI, a policy of baseline and annual BMD screening followed by selective treatment with oral bisphosphonates for those diagnosed with osteoporosis was found to be the most cost-effective use of societal resources. Incremental cost-effectiveness ratio (ICER) for annual BMD screening followed by oral bisphosphonates for those with osteoporosis, annual BMD screening followed by oral bisphosphonates for those with osteopenia, and universal treatment with oral bisphosphonates were US\$87,300, US\$129,300, and US\$283,600 per quality-adjusted life year (QALY) gained, respectively.³⁹ Results were sensitive to age at AI initiation, post-treatment residual effects of oral bisphosphonates, types of bisphosphonates, and a potential adjuvant benefit of intravenous bisphosphonates. Analysis of intravenous bisphosphonates use increased the ICERs for all strategies to more than USD \$100,000 per QALY gained, but if potential of breast cancer recurrence reduction was considered, its use became more cost-effective, regardless of its impact on bone health.

Local data for cost-effectiveness analysis is not available at present.

Recommendations Regarding the Use of Bisphosphonates to Preserve Bone Health in Postmenopausal Women Initiating Adjuvant AIs in Breast Cancer

Systematic Recommendations (Table 1)

The SCAN workgroup voted 10 to 2 in favour of the adoption of the treatment algorithm based on the NOF guidelines as this approach gives a comprehensive recommendation based upon lifestyle modifications, inclusion of osteoporosis risk factors in decision-making, and stratification of management based on T-score.

Two members supported the NCCN recommendations which state that the use of a bisphosphonate is generally a preferred intervention to improve BMD. One agreed that the use of bisphosphonates is generally a preferred intervention to improve BMD in women with early stage breast cancer. However, limited data on their effect on fracture rates in these patients exists, hence the choice of NCCN guidelines to reflect some uncertainties regarding optimal use of bisphosphonates. The other member preferred the flexibility the NCCN guidelines offered, in particular with regard to vitamin D testing, BMD evaluations and treatment. The optimal duration of bisphosphonate has not been established. Factors to consider include BMD, response to therapy, and risk factors for continued bone loss or fracture.

The workgroup acknowledges that there are no guidelines

Table 1. Singapore Cancer Network (SCAN) Guidelines for Bisphosphonate Use in the Adjuvant Breast Cancer Setting

Guideline Recommendations	
Use of Bisphosphonates to Preserve Bone Health in Postmenopausal Women Initiating Adjuvant Aromatase Inhibitors in Breast Cancer	National Osteoporosis Foundation Guidelines: History and physical examination, baseline bone mineral density (BMD) and annual height measurements, lifestyle modifications. T-score >-1: Rescreen in 1 year. If 1-year BMD >-1.0, screen every 1 – 2 years. T-score between -1.0 and -1.5: annual screening. T-score between -1.5 and -2.0: check vitamin D level [25(OH)D]. Consider bisphosphonate therapy depending on risk factors. T-score <-2.0: check vitamin D level [25(OH)D]. Treat with bisphosphonate therapy.
Use of Adjuvant Bisphosphonates to Improve Breast Cancer Outcomes	European Society for Medical Oncology (ESMO) Guidelines: Bisphosphonates reduce the frequency of bone metastases and improve survival in postmenopausal women (natural or induced) with breast cancer (I, A). Bisphosphonates do not improve disease outcomes in premenopausal women (I, A).

on the specific choice of bisphosphonate agent. Of note, the role of denosumab has only been addressed in the ESMO 2014 guidelines as it is a relatively newer agent on the market and hence is not covered in this edition of recommendations.

There are no unsystematic recommendations.

The workgroup acknowledges that local data regarding the use of bisphosphonates to preserve bone health in postmenopausal women initiating adjuvant AIs in breast cancer is lacking.

2. Use of Adjuvant Bisphosphonates to Improve Breast Cancer Outcomes

Evidence on the antitumour effects of adjuvant bisphosphonates has been conflicting. Early trials using adjuvant clodronate for 2 or 3 years in breast cancer patients failed to show a beneficial antitumour effect.^{40,41} The study by Saarto et al showed adjuvant clodronate to result in inferior 10-year DFS compared to control (45% vs 58%, $P = 0.01$);⁴⁰ while the NSABP B-34 trial showed no DFS benefit from adjuvant oral clodronate at a median follow-up of 90 months although interestingly, clodronate appeared to benefit women ≥ 50 years in secondary endpoints such as recurrence-free interval (0.75, $P = 0.045$), bone metastasis-free interval (0.62, $P = 0.027$), and non-bone metastasis-free interval (0.63, $P = 0.014$).⁴¹ Similarly, in the German Adjuvant Intergroup Node-positive (GAIN) trial, there was no reported difference in DFS between early breast cancer patients randomised to oral ibandronate at 50 mg daily versus standard of care for 2 years.⁴²

The ZO-FAST and Z-FAST studies, although not powered to study zoledronate as an adjuvant treatment, found conflicting results for their secondary endpoint of DFS, with the ZO-FAST study reporting a decrease in incidence of 5-year DFS events by 34% in the upfront compared to

the delayed group (HR = 0.66; 95% CI, 0.44 to 0.97; $P = 0.0375$)³⁸ and the Z-FAST study showing similar disease recurrence and deaths between the 2 groups at 5 years of follow-up.³⁷

The AZURE study investigating the role of adjuvant zoledronate over 5 years versus standard care in stage II and III breast cancer patients found no significant difference in the primary endpoint of DFS at a median follow-up of 5 years.^{22,43} Notably, both pre- and postmenopausal women were included. Of interest, a prespecified subgroup analysis showed a possible invasive-DFS benefit (HR = 0.77; 95% CI, 0.63 to 0.96) in those who had undergone menopause >5 years earlier.⁴³ The hazard ratios for overall survival were 0.81 (95% CI, 0.63 to 1.04) for this group compared to 1.04 (95% CI, 0.86 to 1.25) for those who were less than 5 years since menopause.

However, an earlier ABCSG-12 study by Gnant et al using adjuvant zoledronate every 6 months for 3 years in premenopausal women with HR-positive early breast cancer randomised to tamoxifen/goserelin or anastrozole/goserelin with or without zoledronate showed an absolute reduction of 3.2% and a relative reduction of 36% in the risk of disease progression (HR 0.64; $P = 0.01$) but no significant reduction in the risk of death.⁴⁴ This benefit was maintained in a subsequent updated analysis at 62 months follow-up.¹⁹ Only 5% of women in the ABCSG-12 study had prior chemotherapy, compared to about 95% in the AZURE study.

The recent EBCTCG meta-analyses examining the role of adjuvant bisphosphonates in early breast cancer, consisting of 18,766 women, mostly those in trials of 2 to 5 year of bisphosphonates, demonstrated that it produced highly significant reductions in recurrence (RR = 0.86; 95% CI, 0.78 to 0.94; $2P = 0.002$), distant recurrence (0.82; 0.74 to 0.92; $2P = 0.0003$), bone recurrence (0.72; 0.60 to 0.86, $2P = 0.0002$) and breast cancer mortality (0.82; 0.73 to 0.93;

2P = 0.002) among postmenopausal (natural or induced) women when treatment began; the effect of which was not similarly seen in premenopausal women.²¹ Only the preliminary results of the EBCTCG meta-analyses had been incorporated into the ESMO guidelines we reviewed.

The literature is still unclear with regards to the exact choice of bisphosphonates, the optimal dosing and duration of therapy.

Cost-effectiveness Analyses

In a recent cost-effectiveness analysis study of adjuvant bisphosphonates in a simulated cohort of 100,000 postmenopausal women with non-metastatic breast cancer followed over 10 years using available clinical trials and meta-analysis data, alendronate at 70 mg/week and ibandronate at 150 mg/month were cost saving compared to no therapy, while zoledronic acid at 4 mg/6 months had an ICER of USD \$10,317/QALY gained.⁴⁵ High-dose ibandronate at 50 mg/day and high-dose zoledronate (6 doses in the first 6 months, 8 doses in the next 24 months and 5 doses in the final 30 months) were not cost-effective at a willingness-to-pay threshold of \$50,000/QALY gained.

Local data for cost-effectiveness analysis is not available at present.

Recommendations Regarding the Use of Adjuvant Bisphosphonates to Improve Breast Cancer Outcomes

Systematic Recommendations (Table 1)

The SCAN Workgroup voted unanimously in support of the ESMO 2014 guidelines which state that adjuvant bisphosphonates reduce the frequency of bone metastases and improve survival in postmenopausal women (natural or induced) with breast cancer (I, A), but they do not improve disease outcomes in premenopausal women (I, A). The collective opinion from the members was in line with these recommendations that offering adjuvant bisphosphonates is justified in the postmenopausal but not premenopausal setting.

There are no unsystematic recommendations.

The workgroup acknowledges that local data regarding the use of adjuvant bisphosphonates to improve breast cancer outcomes is lacking.

Conflicts of Interest

Dr Dent reports receiving advisory board fees from Roche; Dr Shang, honoraria from Novartis; Dr Ang, Dr Khoo, Dr Lee, Dr Lim, Dr Ng, Dr Shih, Dr Tan, Dr Wong, Dr Wong and Dr Yap have nothing to disclose.

Workgroup Members

The Members of the SCAN Breast Cancer Workgroup are Section Lead: Sing Huang Tan, MBBS (S'pore), MRCP(UK), FAMS (Med Onc), Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore; Workgroup Chairperson: Nan Soon Wong, MBBS (S'pore), MRCP (UK), FAMS (Med Onc), Oncocare Cancer Centre, Singapore; Workgroup Members (Voting): Peter Ang, MBBS (S'pore), MRCP(UK), FAMS (Med Onc), Oncocare Cancer Centre, Singapore; Rebecca Dent, MSc (Canada), MD (Canada), FRCP (Canada), Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Kei Siong Khoo, MBBS (S'pore), FRCP (Edin), FAMS (Med Onc), Medical Oncology, Parkway Cancer Centre, Singapore; Soo Chin Lee, MBBS, MRCP (UK), FAMS (Med Onc), Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore; Siew Eng Lim, MB BCh BAO, ABIM (Int Med), ABIM (Med Oncology), Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore; Raymond Ng, MB ChB (Otago), FRACP (NZ), MPH (NUS), Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Vivianne Shih, Pharm.D, BCOP, Department of Pharmacy, National Cancer Centre Singapore, Singapore; Karmen Wong, MBBS (Adelaide), MRCP (UK), FAMS (Med Onc), Karmen Wong Medical Oncology, Singapore; Yoon Sim Yap, MBBS (Adelaide), FRACP (Med Onc), Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Shang Yeap, MBBS, FRACP, Novena Cancer Centre, Singapore.

Reviewers

Invited reviewers were Ian F Tannock, MD, PhD, DSc, Princess Margaret Cancer Centre, University of Toronto, Canada; Gilberto Lopes, MD, MBA, Oncoclinicas Group, Brazil; Fatima Cardoso, MD, Breast Unit, Champalimaud Clinical Center, Portugal.

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Supplementary Table 1. International Guidelines for the Use of Bisphosphonates for Bone Health When Using Adjuvant Aromatase Inhibitors

Guideline Title	Algorithm Based on Guidelines from National Osteoporosis Foundation	NCCN Clinical Practice Guidelines in Oncology Breast Cancer Version 3.2015	Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	NICE Early and Locally Advanced Breast Cancer: Diagnosis and Treatment Full Guideline	Treatment of Primary Breast Cancer SIGN134	SCAN Systematic Recommendations (Derived from Existing Guidelines, At Least 50% of Group Concur)	SCAN Unsystematic Recommendations (Not Derived from Existing Guidelines, If At Least 2/3rds of Workgroup Concur)
Date Released	November 2006	July 2015	April 2014	February 2009	September 2013	April 2014	April 2014
Guideline Developer	Chien and Goss. JCO 2006; 24:5305	National Cancer Comprehensive Network (NCCN), United States	European Society for Medical Oncology (ESMO)	National Institute of Health and Clinical Excellence (NICE), United Kingdom	Scottish Intercollegiate Guidelines Network (SIGN)	SCAN Breast Cancer Workgroup	SCAN Breast Cancer Workgroup
Description of Method of Guideline Validation	NA	Statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Validation method not specified.	Group decision-making that seeks the consensus of experts and the fulfillment of objectives. Guidelines approved by the ESMO Guidelines Working Group: March 2014.	Guideline development group made up of health professionals, representatives of patient and carer groups, and technical experts assess the available evidence and make recommendations. After the guideline development group finalises the recommendations, the collaborating centre produces the final guideline. NICE formally approves the final guideline and issues its guidance to the NHS.	SIGN guidelines are developed using an explicit methodology. - Development is carried out by multidisciplinary, nationally representative groups. - A systematic review is conducted to identify and critically appraise the evidence. - Recommendations are explicitly linked to the supporting evidence.	Systematic recommendations are derived from existing guidelines with support of at least 50% of voting workgroup members (excluding abstaining individuals). Recommended changes in dosing of established standard drugs may be included under systematic recommendations. Abstaining is not recommended unless the member belongs to a different specialty or has a significant conflict of interest.	Unsystematic recommendations are not derived from existing guidelines, but represent best practice recommendations in Singapore supported by at least two-thirds of voting workgroup members, excluding abstaining individuals. Abstaining is not recommended unless the member belongs to a different specialty or has a significant conflict of interest.
Target Population	Early breast cancer	Early breast cancer	Early breast cancer	Early breast cancer	Early breast cancer	Early breast cancer	Early breast cancer
Bisphosphonates for Osteoporosis Prevention	History and physical examination, baseline BMD and annual height measurements, lifestyle modifications. T-score > -1: rescreen in 1 year. If 1-year BMD > -1: screen every 1 – 2 years. T-score between -1.0 and -1.5: annual screening.	The use of a bisphosphonate is generally a preferred intervention to improve BMD. Optimal duration of bisphosphonate has not been established. Factors to consider include BMD, response to therapy, and risk factors for continued bone loss or fracture.	Bisphosphonates and denosumab prevent bone loss associated with use of ovarian suppression or aromatase inhibitors in early breast cancer (1B).	Qualifying statement: This recommendation is based on evidence from RCTs and guidance produced by Reid et al (2008). Guidance for the management of breast cancer treatment-induced bone loss: A consensus position statement from a UK Expert Group. Cancer Treatment Reviews. Volume 34 (Suppl 1), S3-S18.	Women who are postmenopausal and on AIs – High risk: T-score < -2 or known vertebral fracture > Bisphosphonates and calcium and vitamin D. Repeat axial DXA after 24 months and/or monitor if desired with biochemical markers after 6 months.	Algorithm based on guidelines from National Osteoporosis Foundation (Chien and Goss. JCO 2006; 24:5305)	NA

AI: Aromatase inhibitors; BMD: Bone mineral density; BMI: Body mass index; DXA: Dual energy X-ray absorptiometry; NA: Non-applicable; RCT: Randomised controlled trials; TH: Total hip

Supplementary Table 1. International Guidelines for the Use of Bisphosphonates for Bone Health When Using Adjuvant Aromatase Inhibitors (Con't)

Guideline Title	Algorithm Based on Guidelines from National Osteoporosis Foundation	NCCN Clinical Practice Guidelines in Oncology Breast Cancer Version 3.2015	Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	NICE Early and Locally Advanced Breast Cancer: Diagnosis and Treatment Full Guideline	Treatment of Primary Breast Cancer SIGN134	SCAN Systematic Recommendations (Derived from Existing Guidelines, At Least 50% of Group Concur)	SCAN Unsystematic Recommendations (Not Derived from Existing Guidelines, If At Least 2/3rds of Workgroup Concur)
				Women who are postmenopausal and on AIs – High risk: T-score <-2 or known vertebral fracture > Bisphosphonates and calcium and vitamin D. Repeat axial DXA after 24 months and/or monitor if desired with biochemical markers after 6 months. Medium risk: T-score between -1 and -2 > Lifestyle advice plus calcium and vitamin D. Repeat axial BMD after 24 months. If annual rate of bone loss >4% at LS or TH and /or T-score <-2.0 > bisphosphonates and treat under high risk category. Low risk: Both T-scores >-1. Lifestyle advice. Women >=75 years old with at least 1 major risk factor (previous low trauma fracture >50 years old, parental history of hip fracture, alcohol intake >=4 units/day, diseases associated with secondary osteoporosis, prior corticosteroids for >6 months, BMI <22): Bisphosphonates and calcium and vitamin D.			
	T-score between -1.5 and -2.0: check vitamin D level [25(OH)D]. Consider bisphosphonate therapy depending on risk factors.						
	T-score <-2.0: check vitamin D level [25(OH)D]. Treat with bisphosphonate therapy.						
Member Votes	10 out of 12 votes	2 out of 12 votes	Nil	Nil	Nil	10 out of 12 votes	NA

AI: Aromatase inhibitors; BMD: Bone mineral density; BMI: Body mass index; DXA: Dual energy X-ray absorptiometry; NA: Non-applicable; RCT: Randomised controlled trials; TH: Total hip

Supplementary Table 2. International Guidelines for the Use of Adjuvant Bisphosphonates to Influence Breast Cancer Outcomes

Guideline Title	Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	BC Cancer Agency: Breast Cancer Management. Miscellaneous Considerations	SCAN Systematic Recommendations (Derived from Existing Guidelines, At Least 50% of Group Concur)	SCAN Unsystematic Recommendations (Not Derived from Existing Guidelines, If At Least Two-thirds of Workgroup Concur)
Date Released	April 2014	January 2013	April 2014	April 2014
Guideline Developer	European Society for Medical Oncology (ESMO)	BC Cancer Agency	SCAN Breast Cancer Workgroup	SCAN Breast Cancer Workgroup
Description of Method of Guideline Validation	Group decision-making that seeks the consensus of experts and the fulfillment of objectives. Guidelines approved by the ESMO Guidelines Working Group: March 2014.	The BC Cancer Agency has prepared these cancer management guidelines, based on the accumulated experiences of this agency together with "best" practice evidence derived from major cancer centres throughout the world. The recommendations have been developed by provincial tumour groups composed of oncologists, radiologists, pathologists, oncology nurses, pharmacists and practitioners from health disciplines contributing to specialised oncology care at the BC Cancer Agency and University of British Columbia.	Systematic recommendations are derived from existing guidelines with support of at least 50% of voting workgroup members (excluding abstaining individuals). Recommended changes in dosing of established standard drugs may be included under systematic recommendations. Abstaining is not recommended unless the member belongs to a different specialty or has a significant conflict of interest.	Unsystematic recommendations are not derived from existing guidelines, but represent best practice recommendations in Singapore supported by at least two-thirds of voting workgroup members, excluding abstaining individuals. Abstaining is not recommended unless the member belongs to a different specialty or has a significant conflict of interest.
Target Population	Early breast cancer	Early breast cancer		
Bisphosphonates as Adjuvant Therapy	Bisphosphonates reduce the frequency of bone metastases and improve survival in postmenopausal women (natural or induced) with breast cancer (I, A). Bisphosphonates do not improve disease outcomes in premenopausal women (I, A).	There is insufficient evidence to routinely recommend bisphosphonate therapy to adjuvant breast cancer patients. Oncologists may recommend intermittent zoledronic acid for three years in selected early breast cancer patients based on existing evidence.	ESMO Clinical Practice Guidelines	NA
Member Votes	12 of 12 votes	Nil	12 of 12 votes	NA

Singapore Cancer Network (SCAN) Guidelines for Bisphosphonate Use in the Adjuvant Breast Cancer Setting

The Singapore Cancer Network (SCAN) Breast Cancer Workgroup

Abstract

Introduction: The SCAN breast cancer workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines regarding the optimal time-point for initiation of bisphosphonates when using adjuvant aromatase inhibitors (AIs) and provide a consensus for their role in modifying clinical breast cancer outcomes. **Materials and Methods:** The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. **Results:** Six international guidelines were evaluated—those developed by the National Cancer Comprehensive Network (2015), the European Society of Medical Oncology (2014), the National Institute for Clinical Evidence (2012), the Scottish Intercollegiate Guidelines Network (2013), the British Columbia Cancer Agency (2013) and the treatment algorithm based on the National Osteoporosis Foundation guidelines (2006). Recommendations on the use of bisphosphonates in postmenopausal women initiating adjuvant AIs in breast cancer to preserve bone health and the use of adjuvant bisphosphonates to improve breast cancer outcomes were developed. **Conclusion:** These adapted guidelines form the SCAN Guidelines on the use of adjuvant bisphosphonates to influence breast cancer outcomes and maintenance of bone health when on AIs.

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Key words: Aromatase inhibitors, Bone health, Breast cancer outcomes

Address for Correspondence: Dr Tan Sing Huang, Department of Haematology-Oncology, National University Cancer Institute, Singapore, 1E Kent Ridge Road, NUHS, Tower Block, Level 7, Singapore 119228.
Email: sing_huang_tan@nuhs.edu.sg

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Introduction

Breast cancer is the leading female cancer in our multiethnic Singaporean population and the most frequent cause of cancer mortality in females. The age-standardised incidence rate of newly diagnosed breast cancers in females has increased almost 3-fold in the last 4 decades from 23.8 per 100,000 in 1975 to 1979 to 64.7 per 100,000 in 2010 to 2014.¹ With our rapidly aging population demographics, the percentage of total breast cancers in women aged 55 years and above has correspondingly increased from 43.4% in 2004 to 2008 to 51.3% in 2009 to 2013.¹ Fortunately, due to improved education, increased public awareness and the implementation of our national screening programme, the majority of breast cancers are now being diagnosed earlier. Hormone receptor-positive breast cancers comprise the most common breast cancer subtypes, accounting for 75% of the cases.

The selective estrogen receptor modulator, tamoxifen, has been the standard of care in the adjuvant hormone-receptor positive setting for close to 3 decades, but

over the past 10 years, the advent of third-generation aromatase inhibitors (AIs) such as anastrozole, letrozole and exemestane has improved clinical outcomes in terms of breast cancer recurrence for postmenopausal women. The utility of AIs with respect to disease-free survival (DFS) has been demonstrated when administered as upfront therapy as shown in the Arimidex or Tamoxifen Alone or in Combination (ATAC) and Breast International Group (BIG) 1-98 studies,^{2,3} sequentially after 2 to 3 years of tamoxifen as in the International Exemestane Study (IES), the Italian Tamoxifen Anastrozole (ITA) and Arimidex-Nolvadex (ARNO) 95/Austrian Breast and Colorectal Study Group (ABCSG) 8 trials⁴⁻⁶ or after 5 years of tamoxifen as in the MA.17 data.⁷

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2015 meta-analyses comparing a 5-year course of an AI versus tamoxifen, a 5-year course of an AI versus 2 to 3 years of tamoxifen, then an AI to year 5, and 2 to 3 years of tamoxifen followed by an AI to year 5 versus 5 years of tamoxifen demonstrated that AIs gave a 30%

Address for Correspondence: Dr Tan Sing Huang, Department of Haematology-Oncology, National University Cancer Institute, Singapore, 1E Kent Ridge Road, NUHS, Tower Block, Level 7, Singapore 119228.
Email: sing_huang_tan@nuhs.edu.sg

proportionate reduction in recurrence rates compared with tamoxifen while treatments differed but not thereafter. Additionally, 5 years of an AI reduced the 10-year breast cancer mortality rates by about 15% compared with 5 years of tamoxifen.⁸

However, a common side effect of AIs is bone loss resulting in increased risk of osteoporotic fractures, due to their action of inhibiting the conversion of peripheral androgens to estrogen and causing a decline in estrogen levels. This is an especially pertinent issue in Singapore as since the 1960s, osteoporotic hip fractures have increased 5-fold in women over the age of 50, the age group in which AIs will potentially be used.

Bisphosphonates, although introduced as bone protective agents in osteoporosis management, now form an integral part of the treatment armamentarium to reduce cancer therapy-induced bone loss in breast cancer patients. Bisphosphonates are specific inhibitors of osteoclast-mediated bone resorption consisting of 2 major groups: non-nitrogen containing (clodronate and etidronate) and nitrogen containing or aminobisphosphonates (alendronate, risedronate, pamidronate and zoledronate).⁹ While oral bisphosphonates are generally well tolerated by most women, some have upper gastrointestinal tract adverse effects such as nausea (~4% to 11%), vomiting ($\leq 1\%$ to 3%), abdominal pain (~1% to 12%) and dyspepsia (~1% to 11%).¹⁰⁻¹³ There are some less common but potentially serious side effects of intravenous bisphosphonates including hypocalcaemia ($\leq 3\%$ to 17%), renal toxicity (~8% to 20%) and osteonecrosis of the jaw [ONJ] (~1% to 2%).^{10,14,15} Because of the risk of ONJ especially with intravenous bisphosphonates, and the attendant debilitating consequences, early screening and initiation of appropriate dental care are recommended before commencing bisphosphonate therapy.¹⁶ Patients should inform the dentist of their use of bisphosphonates before undergoing dental procedures.

In addition to bone protective effects, preclinical models have revealed an antitumour effect of bisphosphonates,^{17,18} leading to several clinical trials investigating their adjuvant use to improve cancer outcome in early breast cancer. Some data including a meta-analysis showed promising clinical outcomes¹⁹⁻²¹ while benefit was not demonstrated in some other studies.²² The exact mechanism for a possible antitumour effect of bisphosphonates remains unclear. In light of the complexity of this issue, guidelines are needed to aid the decision-making process with regard to using bisphosphonates to influence breast cancer outcomes.

The SCAN Guidelines for Bisphosphonate Use in the Adjuvant Breast Cancer Setting

The SCAN Guidelines are clinical practice guidelines for bisphosphonate use in early breast cancer patients.

This includes 1) women who may need bisphosphonates to preserve bone health when initiating AI therapy, or 2) women with primary breast cancer who may be considered for bisphosphonates as adjuvant therapy to improve breast cancer outcomes irrespective of their bone health.

These first edition guidelines are intended to serve as treatment recommendations by members of this working group reflecting their views on current existing international guidelines for these management issues. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

Target Users of the Guidelines

The guidelines will be of interest to oncologists, oncology nurse specialists, pharmacists, allied health workers and general practitioners involved in the management of women with breast cancer.

Guideline Recommendations/Development

The SCAN breast cancer workgroup comprises a panel of 11 medical oncologists and 1 oncology pharmacist from Singapore with special subspecialty interest in the management of breast cancer. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead with input from the workgroup members. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework²³ was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, specific breast cancer-related issues of relevance were identified and the scope and distribution of tasks was finalised. High quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. The guidelines were chosen based on their high quality, currency and applicability to

our patient population. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to address the 2 main management issues which were selected for this topic:

1. Use of bisphosphonates to preserve bone health in postmenopausal women initiating adjuvant AIs in breast cancer.
2. Use of adjuvant bisphosphonates to improve breast cancer outcomes.

For the first management issue, 5 international guidelines were selected for review (Supplementary Table 1):

- “NCCN Guidelines for Breast Cancer Version 3.2015” (v3.2015) by the National Cancer Comprehensive Network (NCCN, USA)²⁴
- “Bone Health in Cancer Patients: ESMO Clinical Practice Guidelines”, April 2014²⁵
- “Early and Locally Advanced Breast Cancer: Diagnosis and Treatment” by the National Institute for Clinical Evidence (NICE), February 2009²⁶ Last reviewed on April 2012 and decision made not to update pre-existing guidelines at that time.
- “SIGN 134. Treatment of Primary Breast Cancer” by the Scottish Intercollegiate Guidelines Network (SIGN); September 2013²⁷
- “Aromatase Inhibitors and Bone Health in Women with Breast Cancer”—Treatment Algorithm Based on the National Osteoporosis Foundation Guidelines²⁸

For the second management issue, guideline availability was limited. The following 2 guidelines were considered (Supplementary Table 2):

- “Bone Health in Cancer Patients: ESMO Clinical Practice Guidelines”, April 2014²⁵
- “Breast Cancer Management. Bone Modifying Agents” by the British Columbia (BC) Cancer Agency, January 2013²⁹

Although the following 3 guidelines were screened, 1) and 2) were considered of limited utility as they were released more than 10 years ago (2003, 2004), and 3) did not have a formal recommendation:

1. “Update on the Role of Bisphosphonates and Bone Health Issues in Women with Breast Cancer” by the American Society of Clinical Oncology, 2003³⁰
2. “Use of Bisphosphonates in Women with Breast Cancer” by the Breast Cancer Disease Site Group (DSG), Program in Evidence-Based Care (PEBC) and Cancer Care Ontario (CCO), April 2004.³¹ Reviewed in February 2012 and update in progress.
3. “Early and Locally Advanced Breast Cancer: Diagnosis and Treatment” by NICE, February 2009²⁶

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of breast cancer with regard to bisphosphonate use, it will be reviewed earlier.

1. Use of Bisphosphonates to Preserve Bone Health in Postmenopausal Women Initiating Adjuvant AIs in Breast Cancer

Oral Bisphosphonates

The use of bisphosphonates to reduce therapy-induced bone loss has been investigated in several clinical studies. Earlier studies have evaluated oral bisphosphonates such as clodronate³² and risedronate^{33,34} with 2-year mean differences in lumbar spine (LS) bone mineral density (BMD) ranging from +2.2% to 2.9%, and hip BMD of up to +3.7% in favour of bisphosphonate-containing over no bisphosphonate or placebo arms. The ARIBON trial of oral ibandronate (150 mg/month) versus placebo for 2 years in postmenopausal women with hormone receptor-positive early breast cancer having osteopenia while on anastrozole showed a significant increase in LS and hip BMD of 2.98% and 0.6% respectively in the ibandronate group compared to placebo ($P < 0.01$), with no fragility fractures in either group.³⁵

Intravenous Zoledronate

More recent trials have focused on the efficacy of intravenous zoledronate. In particular, the Austrian Breast and Colorectal Cancer Study Group (ABCSG)-12 bone substudy which randomised premenopausal women with hormone receptor (HR)-positive early breast cancer to receive endocrine therapy (goserelin/anastrozole or goserelin/tamoxifen) alone or with adjuvant zoledronate (4 mg, 6-monthly) for 3 years reported increased LS (+4%, $P = 0.02$) and trochanter (+3.9%, $P = 0.07$) BMD from baseline at 5 years.³⁶ For those not receiving zoledronate, the LS and trochanter BMD remained below baseline even at 5 years. The study was not powered to assess proportion of fractures between groups.

The Z-FAST and ZO-FAST trials studied the efficacy

of zoledronate (4 mg, 6-monthly) given up to a maximum of 5 years, either upfront or in a delayed fashion based on BMD T-scores <-2.0 or non-traumatic fractures, in postmenopausal women receiving adjuvant letrozole. In the Z-FAST study, the mean differences in LS and total hip BMD between upfront versus delayed therapy at 5 years were +8.9% and +6.7% respectively ($P < 0.0001$ for both) in favour of upfront zoledronate, with no significant difference in fracture rates.³⁷ Mean differences at 5 years in LS and total hip BMD between the upfront and delayed groups were +4.3% and -5.4% ($P < 0.0001$) in the ZO-FAST trial, with statistically similar fracture rates in both groups.³⁸

Treatment Algorithm Based on the National Osteoporosis Foundation Guidelines

A useful algorithm based on the National Osteoporosis Foundation (NOF) guidelines was developed by Chien and Goss.²⁸ Under this algorithm, all patients on adjuvant AIs are required to have a thorough history and physical examination focusing on prior fractures, family history of fractures and height decrease and undergo a baseline BMD and annual height measurements, in addition to lifestyle modifications. Lifestyle modifications recommended include the following: total calcium intake of 1200 to 1500 mg/day, vitamin D3 supplementation of 800 U/day, weight-bearing exercises, moderate alcohol consumption (1 to 2 drinks/day) and smoking cessation. Subsequent management is based upon the T-score as follows:

- T-score $>-1 \rightarrow$ rescreen in 1 year. If 1-year T-score >-1.0 , screen every 1 to 2 years.
- T-score between -1.0 and -1.5 $\rightarrow$ annual screening.
- T-score between -1.5 and -2.0 $\rightarrow$ check vitamin D level [25(OH)D]. Consider bisphosphonate therapy depending on risk factors (advanced age, female sex, personal history of fracture as an adult, history of fracture in a first-degree relative, chronic corticosteroid use, immobility and inadequate physical activity, cigarette smoking, excessive alcohol consumption [>2 drinks/day], low body weight, estrogen deficiency [early menopause, menopause, bilateral ovariectomy, prolonged amenorrhea of >1 year], lifelong low calcium intake, vitamin D deficiency, chronic illness [i.e. hyperthyroidism, hyperparathyroidism, inflammatory bowel disease]).
- T-score $<-2.0 \rightarrow$ check vitamin D level [25(OH)D]. Treat with bisphosphonate therapy.

However, it remains unclear whether a particular bisphosphonate is superior.

Cost-effectiveness Analyses

Using a Markov state transition model in a hypothetical cohort of women aged 60 years with hormone receptor-positive early breast cancer starting a 5-year course of adjuvant AI, a policy of baseline and annual BMD screening followed by selective treatment with oral bisphosphonates for those diagnosed with osteoporosis was found to be the most cost-effective use of societal resources. Incremental cost-effectiveness ratio (ICER) for annual BMD screening followed by oral bisphosphonates for those with osteoporosis, annual BMD screening followed by oral bisphosphonates for those with osteopenia, and universal treatment with oral bisphosphonates were US\$87,300, US\$129,300, and US\$283,600 per quality-adjusted life year (QALY) gained, respectively.³⁹ Results were sensitive to age at AI initiation, post-treatment residual effects of oral bisphosphonates, types of bisphosphonates, and a potential adjuvant benefit of intravenous bisphosphonates. Analysis of intravenous bisphosphonates use increased the ICERs for all strategies to more than USD \$100,000 per QALY gained, but if potential of breast cancer recurrence reduction was considered, its use became more cost-effective, regardless of its impact on bone health.

Local data for cost-effectiveness analysis is not available at present.

Recommendations Regarding the Use of Bisphosphonates to Preserve Bone Health in Postmenopausal Women Initiating Adjuvant AIs in Breast Cancer

Systematic Recommendations (Table 1)

The SCAN workgroup voted 10 to 2 in favour of the adoption of the treatment algorithm based on the NOF guidelines as this approach gives a comprehensive recommendation based upon lifestyle modifications, inclusion of osteoporosis risk factors in decision-making, and stratification of management based on T-score.

Two members supported the NCCN recommendations which state that the use of a bisphosphonate is generally a preferred intervention to improve BMD. One agreed that the use of bisphosphonates is generally a preferred intervention to improve BMD in women with early stage breast cancer. However, limited data on their effect on fracture rates in these patients exists, hence the choice of NCCN guidelines to reflect some uncertainties regarding optimal use of bisphosphonates. The other member preferred the flexibility the NCCN guidelines offered, in particular with regard to vitamin D testing, BMD evaluations and treatment. The optimal duration of bisphosphonate has not been established. Factors to consider include BMD, response to therapy, and risk factors for continued bone loss or fracture.

The workgroup acknowledges that there are no guidelines

Table 1. Singapore Cancer Network (SCAN) Guidelines for Bisphosphonate Use in the Adjuvant Breast Cancer Setting

Guideline Recommendations	
Use of Bisphosphonates to Preserve Bone Health in Postmenopausal Women Initiating Adjuvant Aromatase Inhibitors in Breast Cancer	National Osteoporosis Foundation Guidelines: History and physical examination, baseline bone mineral density (BMD) and annual height measurements, lifestyle modifications. T-score >-1: Rescreen in 1 year. If 1-year BMD >-1.0, screen every 1 – 2 years. T-score between -1.0 and -1.5: annual screening. T-score between -1.5 and -2.0: check vitamin D level [25(OH)D]. Consider bisphosphonate therapy depending on risk factors. T-score <-2.0: check vitamin D level [25(OH)D]. Treat with bisphosphonate therapy.
Use of Adjuvant Bisphosphonates to Improve Breast Cancer Outcomes	European Society for Medical Oncology (ESMO) Guidelines: Bisphosphonates reduce the frequency of bone metastases and improve survival in postmenopausal women (natural or induced) with breast cancer (I, A). Bisphosphonates do not improve disease outcomes in premenopausal women (I, A).

on the specific choice of bisphosphonate agent. Of note, the role of denosumab has only been addressed in the ESMO 2014 guidelines as it is a relatively newer agent on the market and hence is not covered in this edition of recommendations.

There are no unsystematic recommendations.

The workgroup acknowledges that local data regarding the use of bisphosphonates to preserve bone health in postmenopausal women initiating adjuvant AIs in breast cancer is lacking.

2. Use of Adjuvant Bisphosphonates to Improve Breast Cancer Outcomes

Evidence on the antitumour effects of adjuvant bisphosphonates has been conflicting. Early trials using adjuvant clodronate for 2 or 3 years in breast cancer patients failed to show a beneficial antitumour effect.^{40,41} The study by Saarto et al showed adjuvant clodronate to result in inferior 10-year DFS compared to control (45% vs 58%, $P = 0.01$);⁴⁰ while the NSABP B-34 trial showed no DFS benefit from adjuvant oral clodronate at a median follow-up of 90 months although interestingly, clodronate appeared to benefit women ≥ 50 years in secondary endpoints such as recurrence-free interval (0.75, $P = 0.045$), bone metastasis-free interval (0.62, $P = 0.027$), and non-bone metastasis-free interval (0.63, $P = 0.014$).⁴¹ Similarly, in the German Adjuvant Intergroup Node-positive (GAIN) trial, there was no reported difference in DFS between early breast cancer patients randomised to oral ibandronate at 50 mg daily versus standard of care for 2 years.⁴²

The ZO-FAST and Z-FAST studies, although not powered to study zoledronate as an adjuvant treatment, found conflicting results for their secondary endpoint of DFS, with the ZO-FAST study reporting a decrease in incidence of 5-year DFS events by 34% in the upfront compared to

the delayed group (HR = 0.66; 95% CI, 0.44 to 0.97; $P = 0.0375$)³⁸ and the Z-FAST study showing similar disease recurrence and deaths between the 2 groups at 5 years of follow-up.³⁷

The AZURE study investigating the role of adjuvant zoledronate over 5 years versus standard care in stage II and III breast cancer patients found no significant difference in the primary endpoint of DFS at a median follow-up of 5 years.^{22,43} Notably, both pre- and postmenopausal women were included. Of interest, a prespecified subgroup analysis showed a possible invasive-DFS benefit (HR = 0.77; 95% CI, 0.63 to 0.96) in those who had undergone menopause >5 years earlier.⁴³ The hazard ratios for overall survival were 0.81 (95% CI, 0.63 to 1.04) for this group compared to 1.04 (95% CI, 0.86 to 1.25) for those who were less than 5 years since menopause.

However, an earlier ABCSG-12 study by Gnant et al using adjuvant zoledronate every 6 months for 3 years in premenopausal women with HR-positive early breast cancer randomised to tamoxifen/goserelin or anastrozole/goserelin with or without zoledronate showed an absolute reduction of 3.2% and a relative reduction of 36% in the risk of disease progression (HR 0.64; $P = 0.01$) but no significant reduction in the risk of death.⁴⁴ This benefit was maintained in a subsequent updated analysis at 62 months follow-up.¹⁹ Only 5% of women in the ABCSG-12 study had prior chemotherapy, compared to about 95% in the AZURE study.

The recent EBCTCG meta-analyses examining the role of adjuvant bisphosphonates in early breast cancer, consisting of 18,766 women, mostly those in trials of 2 to 5 year of bisphosphonates, demonstrated that it produced highly significant reductions in recurrence (RR = 0.86; 95% CI, 0.78 to 0.94; $2P = 0.002$), distant recurrence (0.82; 0.74 to 0.92; $2P = 0.0003$), bone recurrence (0.72; 0.60 to 0.86, $2P = 0.0002$) and breast cancer mortality (0.82; 0.73 to 0.93;

2P = 0.002) among postmenopausal (natural or induced) women when treatment began; the effect of which was not similarly seen in premenopausal women.²¹ Only the preliminary results of the EBCTCG meta-analyses had been incorporated into the ESMO guidelines we reviewed.

The literature is still unclear with regards to the exact choice of bisphosphonates, the optimal dosing and duration of therapy.

Cost-effectiveness Analyses

In a recent cost-effectiveness analysis study of adjuvant bisphosphonates in a simulated cohort of 100,000 postmenopausal women with non-metastatic breast cancer followed over 10 years using available clinical trials and meta-analysis data, alendronate at 70 mg/week and ibandronate at 150 mg/month were cost saving compared to no therapy, while zoledronic acid at 4 mg/6 months had an ICER of USD \$10,317/QALY gained.⁴⁵ High-dose ibandronate at 50 mg/day and high-dose zoledronate (6 doses in the first 6 months, 8 doses in the next 24 months and 5 doses in the final 30 months) were not cost-effective at a willingness-to-pay threshold of \$50,000/QALY gained.

Local data for cost-effectiveness analysis is not available at present.

Recommendations Regarding the Use of Adjuvant Bisphosphonates to Improve Breast Cancer Outcomes

Systematic Recommendations (Table 1)

The SCAN Workgroup voted unanimously in support of the ESMO 2014 guidelines which state that adjuvant bisphosphonates reduce the frequency of bone metastases and improve survival in postmenopausal women (natural or induced) with breast cancer (I, A), but they do not improve disease outcomes in premenopausal women (I, A). The collective opinion from the members was in line with these recommendations that offering adjuvant bisphosphonates is justified in the postmenopausal but not premenopausal setting.

There are no unsystematic recommendations.

The workgroup acknowledges that local data regarding the use of adjuvant bisphosphonates to improve breast cancer outcomes is lacking.

Conflicts of Interest

Dr Dent reports receiving advisory board fees from Roche; Dr Shang, honoraria from Novartis; Dr Ang, Dr Khoo, Dr Lee, Dr Lim, Dr Ng, Dr Shih, Dr Tan, Dr Wong, Dr Wong and Dr Yap have nothing to disclose.

Workgroup Members

The Members of the SCAN Breast Cancer Workgroup are Section Lead: Sing Huang Tan, MBBS (S'pore), MRCP(UK), FAMS (Med Onc), Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore; Workgroup Chairperson: Nan Soon Wong, MBBS (S'pore), MRCP (UK), FAMS (Med Onc), Oncocare Cancer Centre, Singapore; Workgroup Members (Voting): Peter Ang, MBBS (S'pore), MRCP(UK), FAMS (Med Onc), Oncocare Cancer Centre, Singapore; Rebecca Dent, MSc (Canada), MD (Canada), FRCP (Canada), Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Kei Siong Khoo, MBBS (S'pore), FRCP (Edin), FAMS (Med Onc), Medical Oncology, Parkway Cancer Centre, Singapore; Soo Chin Lee, MBBS, MRCP (UK), FAMS (Med Onc), Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore; Siew Eng Lim, MB BCh BAO, ABIM (Int Med), ABIM (Med Oncology), Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore; Raymond Ng, MB ChB (Otago), FRACP (NZ), MPH (NUS), Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Vivianne Shih, Pharm.D, BCOP, Department of Pharmacy, National Cancer Centre Singapore, Singapore; Karmen Wong, MBBS (Adelaide), MRCP (UK), FAMS (Med Onc), Karmen Wong Medical Oncology, Singapore; Yoon Sim Yap, MBBS (Adelaide), FRACP (Med Onc), Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Shang Yeap, MBBS, FRACP, Novena Cancer Centre, Singapore.

Reviewers

Invited reviewers were Ian F Tannock, MD, PhD, DSc, Princess Margaret Cancer Centre, University of Toronto, Canada; Gilberto Lopes, MD, MBA, Oncoclinicas Group, Brazil; Fatima Cardoso, MD, Breast Unit, Champalimaud Clinical Center, Portugal.

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Supplementary Table 1. International Guidelines for the Use of Bisphosphonates for Bone Health When Using Adjuvant Aromatase Inhibitors

Guideline Title	Algorithm Based on Guidelines from National Osteoporosis Foundation	NCCN Clinical Practice Guidelines in Oncology Breast Cancer Version 3.2015	Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	NICE Early and Locally Advanced Breast Cancer: Diagnosis and Treatment Full Guideline	Treatment of Primary Breast Cancer SIGN134	SCAN Systematic Recommendations (Derived from Existing Guidelines, At Least 50% of Group Concur)	SCAN Unsystematic Recommendations (Not Derived from Existing Guidelines, If At Least 2/3rds of Workgroup Concur)
Date Released	November 2006	July 2015	April 2014	February 2009	September 2013	April 2014	April 2014
Guideline Developer	Chien and Goss. JCO 2006; 24:5305	National Cancer Comprehensive Network (NCCN), United States	European Society for Medical Oncology (ESMO)	National Institute of Health and Clinical Excellence (NICE), United Kingdom	Scottish Intercollegiate Guidelines Network (SIGN)	SCAN Breast Cancer Workgroup	SCAN Breast Cancer Workgroup
Description of Method of Guideline Validation	NA	Statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Validation method not specified.	Group decision-making that seeks the consensus of experts and the fulfillment of objectives. Guidelines approved by the ESMO Guidelines Working Group: March 2014.	Guideline development group made up of health professionals, representatives of patient and carer groups, and technical experts assess the available evidence and make recommendations. After the guideline development group finalises the recommendations, the collaborating centre produces the final guideline. NICE formally approves the final guideline and issues its guidance to the NHS.	SIGN guidelines are developed using an explicit methodology. - Development is carried out by multidisciplinary, nationally representative groups. - A systematic review is conducted to identify and critically appraise the evidence. - Recommendations are explicitly linked to the supporting evidence.	Systematic recommendations are derived from existing guidelines with support of at least 50% of voting workgroup members (excluding abstaining individuals). Recommended changes in dosing of established standard drugs may be included under systematic recommendations. Abstaining is not recommended unless the member belongs to a different specialty or has a significant conflict of interest.	Unsystematic recommendations are not derived from existing guidelines, but represent best practice recommendations in Singapore supported by at least two-thirds of voting workgroup members, excluding abstaining individuals. Abstaining is not recommended unless the member belongs to a different specialty or has a significant conflict of interest.
Target Population	Early breast cancer	Early breast cancer	Early breast cancer	Early breast cancer	Early breast cancer	Early breast cancer	Early breast cancer
Bisphosphonates for Osteoporosis Prevention	History and physical examination, baseline BMD and annual height measurements, lifestyle modifications. T-score > -1: rescreen in 1 year. If 1-year BMD > -1: screen every 1 – 2 years. T-score between -1.0 and -1.5: annual screening.	The use of a bisphosphonate is generally a preferred intervention to improve BMD. Optimal duration of bisphosphonate has not been established. Factors to consider include BMD, response to therapy, and risk factors for continued bone loss or fracture.	Bisphosphonates and denosumab prevent bone loss associated with use of ovarian suppression or aromatase inhibitors in early breast cancer (1B).	Qualifying statement: This recommendation is based on evidence from RCTs and guidance produced by Reid et al (2008). Guidance for the management of breast cancer treatment-induced bone-loss: A consensus position statement from a UK Expert Group. Cancer Treatment Reviews. Volume 34 (Suppl 1), S3-S18.	Women who are postmenopausal and on AIs – High risk: T-score < -2 or known vertebral fracture > Bisphosphonates and calcium and vitamin D. Repeat axial DXA after 24 months and/or monitor if desired with biochemical markers after 6 months.	Algorithm based on guidelines from National Osteoporosis Foundation (Chien and Goss. JCO 2006; 24:5305)	NA

AI: Aromatase inhibitors; BMD: Bone mineral density; BMI: Body mass index; DXA: Dual energy X-ray absorptiometry; NA: Non-applicable; RCT: Randomised controlled trials; TH: Total hip

Supplementary Table 1. International Guidelines for the Use of Bisphosphonates for Bone Health When Using Adjuvant Aromatase Inhibitors (Con't)

Guideline Title	Algorithm Based on Guidelines from National Osteoporosis Foundation	NCCN Clinical Practice Guidelines in Oncology Breast Cancer Version 3.2015	Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	NICE Early and Locally Advanced Breast Cancer: Diagnosis and Treatment Full Guideline	Treatment of Primary Breast Cancer SIGN134	SCAN Systematic Recommendations (Derived from Existing Guidelines, At Least 50% of Group Concur)	SCAN Unsystematic Recommendations (Not Derived from Existing Guidelines, If At Least 2/3rds of Workgroup Concur)
				Women who are postmenopausal and on AIs – High risk: T-score ≤ -2 or known vertebral fracture > Bisphosphonates and calcium and vitamin D. Repeat axial DXA after 24 months and/or monitor if desired with biochemical markers after 6 months. Medium risk: T-score between -1 and -2 > Lifestyle advice plus calcium and vitamin D. Repeat axial BMD after 24 months. If annual rate of bone loss $>4\%$ at LS or TH and /or T-score ≤ -2.0 > bisphosphonates and treat under high risk category. Low risk: Both T-scores > -1 . Lifestyle advice. Women ≥ 75 years old with at least 1 major risk factor (previous low trauma fracture >50 years old, parental history of hip fracture, alcohol intake ≥ 4 units/day, diseases associated with secondary osteoporosis, prior corticosteroids for >6 months, BMI <22): Bisphosphonates and calcium and vitamin D.			
	T-score between -1.5 and -2.0 : check vitamin D level [25(OH)D]. Consider bisphosphonate therapy depending on risk factors. T-score ≤ -2.0 : check vitamin D level [25(OH)D]. Treat with bisphosphonate therapy.			Women ≥ 75 years old with at least one major risk factor (previous low trauma fracture >50 years old, parental history of hip fracture, alcohol intake ≥ 4 units/day, diseases associated with secondary osteoporosis, prior corticosteroids for >6 months, BMI <22): Bisphosphonates and calcium and vitamin D.			
Member Votes	10 out of 12 votes	2 out of 12 votes	Nil	Nil	Nil	10 out of 12 votes	NA

AI: Aromatase inhibitors; BMD: Bone mineral density; BMI: Body mass index; DXA: Dual energy X-ray absorptiometry; NA: Non-applicable; RCT: Randomised controlled trials; TH: Total hip

Supplementary Table 2. International Guidelines for the Use of Adjuvant Bisphosphonates to Influence Breast Cancer Outcomes

Guideline Title	Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	BC Cancer Agency: Breast Cancer Management. Miscellaneous Considerations	SCAN Systematic Recommendations (Derived from Existing Guidelines, At Least 50% of Group Concur)	SCAN Unsystematic Recommendations (Not Derived from Existing Guidelines, If At Least Two-thirds of Workgroup Concur)
Date Released	April 2014	January 2013	April 2014	April 2014
Guideline Developer	European Society for Medical Oncology (ESMO)	BC Cancer Agency	SCAN Breast Cancer Workgroup	SCAN Breast Cancer Workgroup
Description of Method of Guideline Validation	Group decision-making that seeks the consensus of experts and the fulfillment of objectives. Guidelines approved by the ESMO Guidelines Working Group: March 2014.	The BC Cancer Agency has prepared these cancer management guidelines, based on the accumulated experiences of this agency together with "best" practice evidence derived from major cancer centres throughout the world. The recommendations have been developed by provincial tumour groups composed of oncologists, radiologists, pathologists, oncology nurses, pharmacists and practitioners from health disciplines contributing to specialised oncology care at the BC Cancer Agency and University of British Columbia.	Systematic recommendations are derived from existing guidelines with support of at least 50% of voting workgroup members (excluding abstaining individuals). Recommended changes in dosing of established standard drugs may be included under systematic recommendations. Abstaining is not recommended unless the member belongs to a different specialty or has a significant conflict of interest.	Unsystematic recommendations are not derived from existing guidelines, but represent best practice recommendations in Singapore supported by at least two-thirds of voting workgroup members, excluding abstaining individuals. Abstaining is not recommended unless the member belongs to a different specialty or has a significant conflict of interest.
Target Population	Early breast cancer	Early breast cancer		
Bisphosphonates as Adjuvant Therapy	Bisphosphonates reduce the frequency of bone metastases and improve survival in postmenopausal women (natural or induced) with breast cancer (I, A). Bisphosphonates do not improve disease outcomes in premenopausal women (I, A).	There is insufficient evidence to routinely recommend bisphosphonate therapy to adjuvant breast cancer patients. Oncologists may recommend intermittent zoledronic acid for three years in selected early breast cancer patients based on existing evidence.	ESMO Clinical Practice Guidelines	NA
Member Votes	12 of 12 votes	Nil	12 of 12 votes	NA

Singapore Cancer Network (SCAN) Guidelines for Systemic Therapy of Colorectal Cancer

The Singapore Cancer Network (SCAN) Colorectal Cancer Systemic Therapy Workgroup

Abstract

Introduction: The SCAN colorectal cancer systemic therapy workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for systemic therapy for colorectal cancer in Singapore. **Materials and Methods:** The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. **Results:** Five international guidelines were evaluated—those developed by the National Comprehensive Cancer Network for colon (2014) and rectal (2014) cancer, the European Society of Medical Oncology for advanced (2012) and early (2013) cancer and the National Institute of Clinical Excellence (2011). Recommendations on systemic therapy in colorectal cancer were produced. **Conclusion:** These adapted guidelines form the SCAN Guidelines 2015 for systemic therapy of colorectal cancer.

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Key words: Treatment recommendations, Multidisciplinary, Malignancy

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Introduction

Globally, colorectal cancer (CRC) is the third most common cancer with 1 million new cases per year. In Singapore, CRC is the most common cancer (8206 new cases, 2006 to 2010),¹ accounting for 18% and 14% of all cancers in males and females respectively. One in 25 male and 1 in 35 female Singaporeans will develop CRC in their lifetime.² Adjuvant postoperative systemic therapy is recommended for patients with stage III CRC and considered for patients with high risk stage II CRC. About half of CRC patients develop metastatic disease (either at diagnosis or as systemic recurrence after initial early stage CRC). Systemic therapy improves quality of life and overall survival (OS) in patients with stage IV CRC.

While several international guidelines for treatment of CRC exist, due to unique differences in patient population, healthcare structure and reimbursement issues, direct application of these international guidelines to the local context is oftentimes not possible. Hence, there exists a need to develop a set of local Singapore guidelines to address this patient population and practice within our healthcare context.

The SCAN Guidelines for the Systemic Therapy of CRC

The SCAN Guidelines are clinical practice guidelines for systemic treatment of CRC patients.

These first edition guidelines are intended to serve as treatment recommendations by members of this working group reflecting their views on current existing international guidelines for the management of CRC. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

Target Users of the Guidelines

The guidelines will be of interest to oncologists, oncology nurse specialists, pharmacists, allied health workers and general practitioners involved in the management of patients with colorectal cancer.

Guideline Recommendations/Development

The SCAN Colorectal Cancer Workgroup is made up of a panel of 11 medical oncologists with special interests in the management of CRC. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and

Address for Correspondence: Dr Iain Tan Bee Huat, Department of Medical Oncology, National Cancer Centre Singapore, 11, Hospital Drive, Singapore 169610.

Email: iain.tan@gmail.com

decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead with input from the workgroup members. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework³ was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, high quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to address the 6 main management issues which were selected for this topic:

1. Adjuvant systemic chemotherapy in colon cancer
2. Adjuvant systemic chemotherapy in rectal cancer
3. Systemic chemotherapy strategies in patients with metastatic CRC
4. First-line systemic chemotherapy in patients with metastatic CRC
5. Duration of therapy and maintenance/intermittent chemotherapy in patients with metastatic CRC
6. Second- and further-line treatment in patients with metastatic CRC

Five international guidelines were selected for review:

- “NCCN Guidelines for Colon Cancer Version 3.2014” by the National Cancer Comprehensive Network (NCCN), USA⁴

- “NCCN Guidelines for Rectal Cancer Version 3.2014” by NCCN, USA⁵
- “ESMO Consensus Guidelines for Management of Patients with Colon and Rectal Cancer. A Personalized Approach to Clinical Decision Making” by the European Society of Medical Oncology (ESMO), 2012⁶
- “Early Colon Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up” by ESMO, 2013⁷
- “Colorectal Cancer: the Diagnosis and Management of Colorectal Cancer” by the National Institute of Health and Clinical excellence (NICE, UK), 2011⁸

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of CRC, it will be reviewed earlier.

1. Adjuvant Systemic Chemotherapy for Colon Cancer

Choices for adjuvant therapy for patients with resected, non-metastatic colon cancer depend on the stage of disease. Patients with stage I disease do not require any adjuvant therapy. Patients with low risk stage II disease can be enrolled in a clinical trial, observed without adjuvant therapy, or considered for capecitabine or 5-FU/leucovorin (LV). The addition of oxaliplatin to 5-FU-based therapy is not considered appropriate adjuvant therapy in patients with stage II disease without high risk features.

Patients with high risk stage II disease, defined as those with poor prognostic features, including T4 tumours (stage IIB/IIC), poorly differentiated histology (exclusive of those cancers that are MSI-high [MSI-H]), lymphovascular invasion, perineural invasion (PNI), bowel obstruction, lesions with localised perforation or close, indeterminate, or positive margins, or inadequately sampled nodes (<12 lymph nodes) can be considered for adjuvant chemotherapy with 5-FU/LV, capecitabine, FOLFOX, capecitabine/oxaliplatin (CapeOx), or bolus 5-FU/LV/oxaliplatin (FLOX). Observation without adjuvant therapy is also an option in this population. The benefit from adjuvant chemotherapy for stage II patients is a modest but significant survival benefit (83.6% vs 80% 5-year mortality, relative risk of death, 0.82; 95% CI, 0.70 to 0.95; $P = 0.008$).

Microsatellite instability (MSI) is a marker of a more favourable outcome. The panel recommends that mismatch repair (MMR) testing be considered to assist decision-making in patients with stage II disease.

For patients with stage III disease, the panel recommends 6 months of adjuvant chemotherapy after primary surgical treatment. The treatment options are FOLFOX (preferred) or CapeOx (preferred) FLOX or single-agent capecitabine or 5-FU/LV in patients for whom oxaliplatin therapy is

believed to be inappropriate. The addition of oxaliplatin to 5-FU/LV conferred an OS benefit compared to 5-FU/LV alone at the 6-year follow-up update (72.9% and 68.7%, respectively (HR = 0.80; 95% CI, 0.65 to 0.97; $P = 0.023$). CapeOx showed an improved 3-year disease-free survival (DFS) rate compared with 5-FU/LV (70.9% vs 66.5%, HR = 0.80; 95% CI, 0.69 to 0.93; $P = 0.0045$).⁹

Overall, the benefit and toxicities of 5-FU-based adjuvant therapy seem to be similar in older and younger patients. In contrast, the panel cautions that a benefit for the addition of oxaliplatin to 5-FU/LV in patients aged 70 years and older has not been proven in stage II or stage III colon cancer. Individualised assessment will assist in decision-making for older patients with CRC.

The panel recommends against the use of bevacizumab, cetuximab, panitumumab, or irinotecan in adjuvant therapy for non-metastatic disease.

Recommendations for Adjuvant Systemic Chemotherapy in Colon Cancer

The workgroup members unanimously support the general adoption of the NCCN guidelines.

The workgroup members unanimously support the following statements as modifications to the NCCN guidelines:

The lack of convincing benefit of adjuvant therapy in stage II colon cancer without any poor prognostic features supports observation alone as the preferred option for the majority of low risk stage II colon cancer patients. The QUASAR trial showed a modest but significant survival benefit for patients treated with 5-FU/LV compared to observation (83.6% vs 80% 5-year mortality, relative risk of death, 0.82; 95% CI, 0.70 to 0.95; $P = 0.008$). However, the trial also included more than 60% of patients who had <12 lymph nodes sampled, and may reflect patients with higher risk features.⁹ Pooled analysis from SEER databases and meta-analysis showed that OS benefit from chemotherapy was statistically significant for stage III patients but not for (unselected) stage II.^{10,11} However, it can be considered if at least 1 high risk clinical feature is present.

The MOSAIC trial did not show a benefit of the addition of oxaliplatin to 5-FU/LV (FOLFOX) for patients with stage II disease, both for DFS and OS, despite accounting for such patients with high risk features as described above (HR = 0.72; 95% CI, 0.50 to 1.02; $P = 0.063$ and HR = 0.91; 95% CI, 0.61 to 1.36; $P = 0.648$, respectively).¹² The 5-year DFS rate was 82.3% for FOLFOX vs 74.6% for 5-FU/LV, while the 6-year OS rate was 85% versus 83.3%. Similar results were seen in the C-07 study comparing FLOX to 5-FU/LV¹³ (absolute benefit of 2% for 5-year DFS and 0.1% for OS, both statistically not significant). Given the potential risk of

long-term peripheral neuropathy among other side effects and the lack of evidence, the routine addition of oxaliplatin to 5-FU/LV is not advised in the adjuvant treatment of most patients with stage II colon cancers.

The efficacy and safety data of randomised trials comparing either FOLFOX or CapeOx to 5-FU-based regimens are more convincing compared to randomised trials comparing FLOX to 5-FU-based regimens. In general, FLOX should not be considered a regimen of choice.

2. Adjuvant Systemic Chemotherapy in Rectal Cancer

Neoadjuvant/adjuvant therapy of clinical stage II (T3-4, node-negative disease with tumour penetration through the muscle wall) or stage III (node positive disease without distant metastasis) rectal cancer often includes locoregional treatment due to the relatively high risk of locoregional recurrence. A total of approximately 6 months of 5-FU-based perioperative treatment is preferred. Preoperative chemoradiotherapy showed fewer local recurrences (relative risk, 0.46; 95% CI 0.26 to 0.82; from 6% to 13%) and less acute and late toxicities.

Patients, with resected stage II or III rectal cancer, who have not received preoperative radiotherapy should be offered postoperative therapy with concurrent chemoradiotherapy in addition to fluoropyrimidine-based chemotherapy. It is recommended that the total duration for perioperative therapy be approximately 6 months.

Although acknowledging that few studies have evaluated the effect of adjuvant chemotherapy in patients with rectal cancer, and that its role is not well defined, NCCN recommends adjuvant chemotherapy for all patients with stage II/III rectal cancer following neoadjuvant chemo-RT/surgery regardless of the surgical pathology results (e.g. NCCN recommends that most patients should receive postoperative chemotherapy even following an apparent complete response (CR)).

The role and optimal duration of treatment with adjuvant oxaliplatin in addition to 5-FU in rectal cancer is still unclear. Oxaliplatin may be added to 5-FU as adjuvant therapy. Most of the support for addition of oxaliplatin to 5-FU as adjuvant chemotherapy in rectal cancer is an extrapolation from the data available for colon cancer. The use of a shorter course of adjuvant oxaliplatin in addition to 5-FU in rectal cancer (i.e. ~ 4 months) is justified when preoperative chemo-RT is administered.

The panel recommends against the use of bevacizumab, cetuximab, panitumumab, or irinotecan in adjuvant therapy for non-metastatic disease.

Recommendations for Adjuvant Systemic Chemotherapy in Rectal Cancer

The workgroup members unanimously support the general adoption of the NCCN guidelines.

The workgroup members unanimously support the following statements as modifications to the NCCN guidelines:

Evidence for the role of adjuvant 5-FU and oxaliplatin in rectal cancer is limited and at times conflicting, nevertheless till more definitive data emerges, adoption of the NCCN guidelines is prudent.

The role of adjuvant therapy in patients with pT3N0 rectal cancer following upfront surgery remains contentious.

3. Systemic Chemotherapy Strategies in Patients with Metastatic CRC

Our panel proposes to adopt the ESMO guidelines as a pragmatic guideline for systemic therapy in metastatic colorectal cancer. The key recommendations are listed below. Patients can be divided into treatment groups. Systemic treatment recommendations are listed based on these groups:

Group 0: Upfront R0 resectable liver $\pm$ lung metastases.
Group 1: Potentially resectable metastatic disease after systemic treatment.

Group 2: Non-resectable, intermediate intensive treatment (e.g. extensive disease, tumour-related symptoms).

Group 3: Non-intensive/sequential treatment.

Upfront R0 Resectable Liver $\pm$ Lung Metastases (Group 0)

When patients undergo upfront resection of metastases (including primary resection in cases of synchronous presentation), postoperative adjuvant FOLFOX for 6 months could be considered. Postoperative chemotherapy with FOLFOX for 6 months is generally recommended. However, adjuvant 5-FU has not shown significant benefit in 2 small randomised trials and no data is available for FOLFOX. The use of FOLFOX in this situation is supported only by the indirect evidence with regard to the potential value of FOLFOX in the perioperative situation.

Upfront resection of metastases followed by adjuvant systemic chemotherapy may be a preferred option in good prognosis patients with a single small (<2 cm) liver metastasis since this lesion may not remain visible during surgery if responding well to chemotherapy.

For initially R0 resectable metastatic disease, perioperative chemotherapy is another option. In this situation 3 months pre and postoperative FOLFOX should be applied analogous to the EORTC 40983 trial.¹⁴

Achieving CR to chemotherapy is of major prognostic importance for liver metastases but should be avoided in

order to enable resection (before complete disappearance). Therefore, close follow-up with imaging and multi-disciplinary discussion is mandatory. If an anatomical resection can be performed, CR is not a major problem, because resection will be based on initial sites of liver metastases. In case of CR on CT and no option for anatomical resection, different imaging methods might be used (MRI, PET scan, contrast-enhanced ultrasound) or resection might be delayed until relapse occurs.

Potentially Resectable Metastatic Disease after Chemotherapy (Group 1)

Although never prospectively proven, it seems evident, that the achievement of a disease-free status after downsizing by induction chemotherapy or enabling secondary surgery is the only means of giving the potential of long-term survival or cure in an otherwise incurable/palliative situation. For this aim, the most active induction chemotherapy which is able to induce downsizing as much as possible in as many patients as possible should be selected upfront.

If metastases become resectable, surgery for the metastases (and the primary) should be performed, followed by postoperative continuation of the same regimen for a total of 6 months of systemic therapy (including preoperative). If metastases remain unresectable, treatment should be continued or switched, depending on quality of response.

Never (Unlikely) Resectable Metastatic Disease (Group 2/3) and Group 1 Patients Not Becoming Resectable

Multiple factors should be considered in determining appropriate frontline chemotherapy in patients with metastatic CRC.

Tumour Biology-related Factors

- Localisation and extent: Liver- or lung-only metastases versus multiple sites; potentially R0-resectable lesions after induction chemotherapy and sufficient downsizing versus massive disease extension; imminent relevant tumour symptoms should be considered.
- Growth dynamics: Aggressive versus indolent growth.
- Asymptomatic versus symptomatic disease: Possibility that patient may not be fit/able to receive second-line therapy following ineffective first-line therapy.
- Prognostic molecular or biochemical markers (e.g. BRAF mutation).

Patient-related Factors

- Biological age.
- Comorbidity.

- Physical capacity to tolerate more intensive treatment.
- Eligibility for potential secondary resection of liver/lung.
- Psychological capacity/willingness to undergo more intensive treatment.

Treatment Factors

- Potential to induce maximal regression of metastases size/number.
- Drug efficacy/toxicity profile of chemotherapy.
- Potential to prolong progression-free survival (PFS) or OS.
- Toxicity profile.
- Drug sensitivity/predictive biomarkers.
- Drug availability and cost.

For Group 2 patients, where there is significant disease bulk or treatment-related symptoms, reliable and rapid regression of metastases is important. In this situation, an escalation strategy (single agent followed by combination) might have the risk that the first-line treatment is not effective, and switching to more effective second-line treatment may not be possible. Therefore, very active first-line treatment that has a high likelihood to induce metastases regression in a short time seems to be appropriate for most of Group 2 patients. It should be noted that there may be individual cases whereby surgery becomes feasible following exceptional response despite initial assessment of unresectability. For the majority of patients, the treatment aim is palliative rather than curative. The duration of any response, time to progression and OS are also relevant in choosing the most optimal regimen.

For Group 3 patients, maximal shrinkage of metastases is not the primary treatment aim. Rather, without present or imminent symptoms and limited risk for rapid deterioration, prevention of tumour progression with symptom disappearance and prolongation of life with minimal treatment burden is the aim. Therefore, an escalation strategy seems to be appropriate, starting with single agent or well tolerated 2-drug combination.

Local ICER analyses were not available for all drugs. While ICER analyses have been performed by NICE,^{15,16} these cannot be extrapolated due to different costs of molecular testing, surgery and infusional therapy. NICE did not provide precise estimates for anti vascular endothelial growth factor (VEGF) first-line or second-line therapy.

Recommendations for Systemic Chemotherapy Strategies in Patients with Metastatic CRC

The workgroup members unanimously support the general adoption of the ESMO guidelines.

The workgroup members unanimously support the following statements as modifications to the ESMO guidelines:

A recent UK study found that addition of cetuximab to chemotherapy and surgery for operable colorectal liver metastases in KRAS exon 2 wild-type colorectal cancer patients results in shorter PFS.¹⁷ (PFS at 12 months 60% in group receiving chemotherapy plus cetuximab vs 72% in group on chemotherapy alone; median PFS 14.1 months (95% CI, 11.8 to 15.9) in the group receiving chemotherapy with cetuximab compared with 20.5 months (95% CI, 16.8 to 26.7) in the chemotherapy alone group (HR = 1.48; 95% CI, 1.04 to 2.12; $P = 0.030$). Cetuximab should be used with caution in patients with upfront resectable CRC.

4. First-line Systemic Chemotherapy in Patients with Metastatic CRC

The selection of the first-line regimen depends on the chosen treatment strategy (Table 1). In the absence of conclusive comparative data, options in Table 1 should be regarded as proposals rather than as strong recommendations, reflecting the available options and the likelihood of efficacy with respect to the specific treatment aim in the different disease groups. They can be modified according to individual patients' situations and experience. The majority of the proposals are not supported by sufficient randomised data but rather by small trials and retrospective subgroup analyses.

For Group 1 patients (Table 1), downsizing by induction chemotherapy (conversion therapy) enabling secondary surgery is the only means of giving the potential of long-term survival or cure in an otherwise incurable/palliative situation. Data emerging from randomised and single-arm trials suggest that the addition of a targeted agent (bevacizumab or epidermal growth factor receptor (EGFR)-antibody) to a doublet or even to a triplet might lead to a higher R0 resection rate in liver limited disease. The combination of a chemodoublet with EGFR-antibodies has led to high overall response rate (ORR) of 75% to 80% of liver metastasis and higher resection rates accordingly (although still low in absolute numbers) in patients with liver limited unresectable metastatic KRAS wild-type CRC. In contrast, the combination of a FU with oxaliplatin and bevacizumab has led to a non-significant trend of an increased resection rate compared with the chemo-backbone alone, although no increase in response rate was shown. FOLFOXIRI could be an alternative to FOLFIRI/FOLFOX combined with EGFR-antibodies, and is the preferred option if targeted drugs, in particular EGFR-antibodies, are not available, and in particular for KRAS mutant tumours.

For Group 2 and 3 patients (Table 1), a retrospective

Table 1. Systemic Therapy Recommendations in Colorectal Cancer (CRC)

Group	KRAS Wild-type	Recommendation*	KRAS Mutant	Recommendation*
1	FOLFIRI + Cet	+++	FOLFOX/XELOX + Bev	+++
	FOLFOX + Pan/Cet	+++	FOLFOXIRI	++(+) [†]
	FOLFOX/XELOX + Bev	++(+)	FOLFIRI/XELIRI + Bev	++(+) [‡]
	FOLFOXIRI	++(+) [†]	FOLFOX/XELOX	+
	FOLFIRI/XELIRI + Bev	++(+) [‡]	FOLFIRI/XELIRI	+
	FOLFOX/XELOX	+	IRIS	+
	FOLFIRI/XELIRI	+	-	-
	IRIS	+	-	-
2	FOLFIRI + Cet	+++	FOLFOX/XELOX + Bev	+++
	FOLFOX + Pan	+++	FOLFIRI/XELIRI + Bev	++(+) [‡]
	FOLFOX/XELOX + Bev	+++	FOLFOX/XELOX	++
	FOLFIRI/XELIRI + Bev	++(+) [‡]	FOLFIRI/XELIRI	++
	FOLFOXIRI	+(+) [†]	FOLFOXIRI	++ [†]
	FOLFOX + Cet	+(+)	IRIS	+
	FOLFOX/XELOX	+	-	-
	FOLFIRI/XELIRI	+	-	-
3	IRIS	+	IRIS	+
	Cet/Pan (mono)	(+)	Watchful waiting	+ Selected pts. [§]
	Watchful waiting	+ Selected pts. [§]	Triplets (±Bev)	+ Option for spec.
	Triplets (+/-Bev or Cet/ Pan)	+ Option for spec.	-	Situations
	-	Situations	-	-
	FUFOL/Cape (mono)	+++	FUFOL/Cape (mono)	+++
	FUFOL/Cape + Bev	+++	FUFOL/Cape + Bev	+++
	XELOX/FOLFOX	++	XELOX/FOLFOX	++
	FOLFIRI/XELIRI	++	FOLFIRI/XELIRI	++
	IRIS	+	IRIS	+
	Cet/Pan (mono)	(+)	Watchful waiting	+ Selected pts. [§]
	Watchful waiting	+ Selected pts. [§]	Triplets (±Bev)	+ Option for spec.
	Triplets (+/-Bev or Cet/ Pan)	+ Option for spec.	-	Situations
	-	Situations	-	-
	-	Situations	-	-
	-	Situations	-	-

XELIRI: capecitabine + irinotecan; IRIS: irinotecan + S1

*Consented recommendation; however decision might be modified based on individual objective and subjective parameters.

[†]FOLFOXIRI: Only 2 (small) phase III trials with contradictory results.[‡]No randomised data for FOL (XEL) IRI + Bev.[§]Option in case of low tumour burden, asymptomatic, indolent disease: close control until definitive progression (not until symptoms).^{||}Patients who are Group 3 but deserve (and tolerate) more intensive treatment due to specific reasons.

pooled analysis revealed a correlation between improved survival and the availability of 5-FU/LV, oxaliplatin and irinotecan at some point during the course of the disease.

In Group 3 patients (Table 1), large trials evaluated different sequential approaches. Although ORR and PFS were improved with upfront combination treatment, OS

was similar for both approaches with a non-significant median difference of 1 month. Comparable results could be shown in an elderly and/or frail population in the FOCUS 2 trial.¹⁸ Upfront single-agent fluoropyrimidine does not have a significant negative impact on final outcome, although these studies reported a lower OS (<20 months), as would

nowadays be expected (>20 months) at least in a patient population mainly from Groups 2 and 3. Patient selection may well explain these differences.

Watchful waiting can be recommended in patients with the following criteria: low tumour burden, but not eligible for secondary resection, indolent disease, asymptomatic, patient is fully informed and agrees to this approach, and the patient is monitored frequently. It should be noted that the 3 pivotal trials from the 5-FU-only era have conflicting outcomes.

Recommendations for First-line Systemic Chemotherapy in Patients with Metastatic CRC

The workgroup members unanimously support the general adoption of the ESMO guidelines.

The workgroup members unanimously support the following statements as modifications to the ESMO guidelines:

Recent data has demonstrated that anti-EGFR therapy should be reserved for patients wildtype for KRAS and NRAS (exons 2, 3 and 4). Testing of KRAS and NRAS mutational status should be performed for patients for whom anti-EGFR therapy is considered. Anti-EGFR therapy should not be used in patients whose tumours are found to have mutation in KRAS or NRAS. In addition, the aggregate data from randomised trials suggests that anti-EGFR therapy added to either FOLFIRI or FOLFOX is efficacious and can confer a DFS and/or OS advantage in RAS wild-type metastatic CRC.

Whilst FOLFOXIRI may be considered in selected Group 1 patients, it should be balanced against the elevated risk of substantial toxicity.

5. Duration of Therapy and Maintenance/Intermittent Chemotherapy in Patients with Metastatic CRC

The treatment duration is dependent on the treatment aim. If the intention of treatment is potential conversion to resectability, induction chemotherapy should be continued until potential resectability might be achieved, ideally at least for 3 to 4 months, with first evaluation after 6 to 8 weeks, to evaluate whether the chosen regimen is active at all, and if resectability is still not achieved, for up to 6 and 8 months. Further treatment (>8 months) with the same regimen is not recommended, since it is unlikely that by continuation of the same treatment, resectability will be achieved. At this point and, in case of insufficient response within 3 to 4 months (again judged by the multidisciplinary team (MDT)), a switch to alternative chemotherapy could be considered. Cumulative liver toxicity with the risk of perioperative morbidity/mortality and delayed recovery

after liver resection will be increased by prolonged treatment duration. However, the potential toxicity of the treatment should be balanced with the potential benefits of achieving a resectable status.

For Group 2 and 3 patients, in clinical trials, the median treatment duration is only 6 months indicating that in many patients (~60% to 70%) treatment is stopped not because of progression but because of other reasons. Re-induction with the same treatment regimen is recommended in cases whereby treatment was discontinued in the absence of cancer progression. Drug-specific toxicity must be taken into account when deciding to re-induce treatment. For example, in case of oxaliplatin limiting toxicity second-line treatment must be started since oxaliplatin might not be applicable any more.

Treatment break is appropriate in a subset of patients. This requires careful patient selection and close monitoring for disease progression. In patients with aggressive disease and poor prognostic features, survival may be impaired if first-line combination treatment with all drugs is not given continuously until progression. In all other patients, induction chemotherapy (without oxaliplatin) might be stopped after 3 to 4 months until progression; in case of progression, the same treatment should be reinstituted if feasible ("stop go"). However, if complete discontinuation of induction chemotherapy is chosen, accurate selection of patients and close monitoring for progression (rather than waiting until progression is clinically evident through symptoms) is strongly recommended.

An alternative to "stop and go" is the preplanned treatment intervals and break duration ("intermittent treatment") of 1 or all drugs resulting in comparable overall outcome in comparison to treatment until progression. However, the 2 approaches, intermittent and "stop and go", have not been prospectively compared yet.

The role of maintenance therapy in bevacizumab and anti-EGFR inhibitors was not established as of 2012, when the ESMO guidelines were developed.

Recommendations for Duration of Therapy and Maintenance/Intermittent Chemotherapy in Patients with Metastatic CRC

The workgroup members unanimously support the general adoption of the ESMO guidelines. The workgroup members support the following statements as modifications to the ESMO guidelines:

Maintenance bevacizumab/capecitabine may lead to a modest PFS benefit in metastatic CRC.¹⁹ Two workgroup members felt that maintenance bevacizumab/capecitabine's benefit came after bevacizumab/capecitabine and oxaliplatin, a regimen which in itself is not convincingly

better than capecitabine/oxaliplatin although widely practised.

There is limited data (COIN-B)²⁰ on the role of intermittent or maintenance scheduling of anti-EGFR inhibitors.

6. Second- and Further-line Treatment in Patients with Metastatic CRC

Second-line is defined as when the first-line chemotherapy backbone has to be changed. The general sequence is either FU/oxaliplatin followed by FU/irinotecan or the reverse sequence, which yields similar results in terms of OS.

5-FU can and should be used again in second- and further-lines, despite proven resistance to first-line combination. Continuation of bevacizumab with changed chemotherapy backbone in second-line increases OS after progression with first-line bevacizumab and chemotherapy [ML18147 study: OS at 12 months 48% vs 42% in bevacizumab plus chemotherapy group vs chemotherapy alone] (ML18147 study: median OS in the bevacizumab plus chemotherapy group was 11.2 months (95% CI, 10.4 to 12.2) vs 9.8 months (8.9 to 10.7) for chemotherapy (HR = 0.81; 95% CI, 0.69 to 0.94; $P = 0.0062$)). 5-FU and bevacizumab could be continued throughout first- and second-line treatment, and solely irinotecan and oxaliplatin will be exchanged by each other.

For EGFR antibodies, there is no clear data on the efficacy of continuing EGFR antibodies beyond progression. After FOLFOX combination chemotherapy (with or without bevacizumab), aflibercept and bevacizumab in combination with FOLFIRI are active with increase in PFS and OS.

Second-line FOLFOX and bevacizumab is superior in terms of ORR, PFS and OS compared with FOLFOX after failure of FU/irinotecan. (E3200: OS at 12 months 58% vs 45% in group receiving bevacizumab in combination with FOLFOX4 vs those treated with FOLFOX4 alone; bevacizumab in combination with FOLFOX4 had a median survival of 12.9 months compared with 10.8 months for those treated with FOLFOX4 alone; HR = 0.75; $P = 0.0011$.)

Second-line treatment with aflibercept plus FOLFIRI is superior in terms of response rate (RR), PFS and OS compared with FOLFIRI after failure of FOLFOX. (Velour study: OS at 12 months 50% vs 44% in aflibercept plus FOLFIRI vs placebo plus FOLFIRI.)

(Velour study: median OS with aflibercept + FOLFIRI vs placebo + FOLFIRI 13.50 vs 12.06 months, HR = 0.817; $P = 0.0032$. Two-year survival rate, 28% vs 18.7%.)

For KRAS wild-type patients not previously treated with anti-EGFR antibodies, cetuximab with or without irinotecan and panitumumab with or without FOLFIRI are possible options.

In patients refractory to FU, oxaliplatin, irinotecan, anti-EGFR antibodies (only KRAS wild-type), bevacizumab, and regorafenib, treatment with fluoropyrimidines and mitomycin or reintroduction of oxaliplatin (and irinotecan) results in very limited improvement in some patients treated last-line. However, despite poor data, these treatment strategies may be appropriate in selected patients.

Last-line salvage treatment with regorafenib is superior to placebo in terms of OS. (CORRECT: OS at 12 months: ~25% in both arms, OS at 6 months 52% vs 48% in regorafenib group vs placebo group.)

(CORRECT: HR for OS was 0.77 for regorafenib vs placebo); 95% CI, 0.64 to 0.94; $P = 0.0052$; median OS was 6.4 months in the regorafenib group and 5.0 in the placebo group. The OS rate was 80.3% in the regorafenib group and 72.7% in the placebo group at 3 months, 52.5% and 43.5%, respectively, at 6 months, 38.2% and 30.8%, respectively, at 9 months, and 24.3% and 24.0%, respectively, at 12 months.

Recommendations for Second- and Further-line Treatment in Patients with Metastatic CRC

The workgroup members unanimously support the general adoption of the ESMO guidelines. The workgroup members unanimously support the following statement as modification to the ESMO guidelines:

Recent data has demonstrated that anti-EGFR therapy should be reserved for patients wild-type for KRAS and NRAS (exons 2, 3 and 4). Testing of KRAS and NRAS mutational status should be performed for patients for whom anti-EGFR therapy is considered. Anti-EGFR therapy should not be used in patients whose tumour is found to have a mutation in KRAS or NRAS.

Conflicts of Interest

Dr Kong reports receiving personal fees from Merck Serono, Roche, Pfizer and Bayer; Dr Soh, receiving conference support and travel and accommodation grants from Merck and Roche; Dr Tan, receiving honoraria from Roche, Bayer, GSK, Amgen and Merck; Dr Yeo, receiving advisory board fees from Bayer and Roche; Dr Yong, receiving fees from Roche as a trial data safety monitoring committee member; Dr Zee, receiving advisory board fees from Bayer and conference support from Roche, Bayer and Merck; Dr Chong, Dr Chua, Dr Chuah, Dr Poon and Dr Toh have nothing to disclose.

Workgroup Members

The Members of the SCAN Colorectal Cancer Systemic Therapy Workgroup are Section Lead (Adjuvant): Thomas Soh, MBBS (Singapore), MRCP (UK), Department of Haematology-Oncology, National University Cancer Institute, Singapore,

Singapore; Section Lead (Metastatic): Clarinda WL Chua, MBBS, MRCP, MMed, Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Workgroup Chairperson: Iain BH Tan, MBBS, MRCP (UK), PhD, Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Workgroup Members (Voting): Dawn Chong, MBBS, MRCP (UK), Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Benjamin Chuah, MBBS, BAO (Ireland), MRCP (UK), Oncocare Cancer Centre, Singapore; Hwai Loong Kong, MBBS, MRCP (UK), FAMS (Med Onc), HL Kong Medical Oncology Centre, Singapore; Donald Poon, MBBS (S'pore), MRCP (UK), MMed (Int Med), Medical Oncology, Raffles Cancer Centre, Singapore; Han Chong Toh, MB ChB (Cambridge), MRCP, Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Wee Lee Yeo, MBBS, MRCP, FAMS, Department of Medical Oncology, Tan Tock Seng Hospital, Singapore; Wei Peng Yong, MB ChB (University of Aberdeen), MRCP (UK), Clinical Pharmacology Fellowship (University of Chicago), Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore; Ying Kiat Zee, MBBS (London), MRCP (UK), FAMS (Med Onc), Medical Oncology, Parkway Cancer Centre, Singapore.

Reviewers

Invited reviewers were Gilberto Lopes, MD, MBA, Oncoclinicas Group, Brazil; Young Suk Park, MD, PhD, Division of Hematology/Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea.

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Singapore Cancer Network (SCAN) Guidelines for Systemic Therapy of Pancreatic Adenocarcinoma

The Singapore Cancer Network (SCAN) Pancreatic Cancer Workgroup

Abstract

Introduction: The SCAN pancreatic cancer workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for systemic therapy for pancreatic adenocarcinoma in Singapore. **Materials and Methods:** The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. **Results:** Five international guidelines were evaluated—those developed by the National Cancer Comprehensive Network (2014), the European Society of Medical Oncology (2012), Cancer Care Ontario (2013), the Japan Pancreas Society (2013) and the British Society of Gastroenterology, Pancreatic Society of Great Britain and Ireland, and the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (2005). Recommendations on the management of resected, borderline resectable, locally advanced and metastatic pancreatic adenocarcinoma were developed. **Conclusion:** These adapted guidelines form the SCAN Guidelines for systemic therapy for pancreatic adenocarcinoma in Singapore.

Ann Acad Med Singapore 2015;44:388-96

Key words: Singapore context, Treatment recommendation

Address for Correspondence: Dr Yeo Wee Lee, Oncology, John Hopkins Singapore, Tan Tock Seng Hospital (Level 1), 11 Jalan Tan Tock Seng, Singapore 308433.

Email: weelee_yeo@ttsh.com.sg

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Introduction

Worldwide, pancreatic cancer is the thirteenth most common adult malignancy and the seventh most common cause of cancer death. In Singapore, it is the eleventh and twelfth most common cancer among Singaporean men and women respectively. Although pancreatic cancer did not feature among the 10 most common cancers in Singapore, it represented the fifth and seventh most common cause of cancer death in Singaporean males and females, respectively.¹ This is because of the late presentation exhibited by most patients.

For early stage pancreatic cancer, surgery is the treatment modality of choice. Adjuvant chemotherapy has been proven to be of benefit for selected patients. For advanced pancreatic cancer, the treatment of choice is chemotherapy. Radiotherapy may be required in selected patients.

While several international guidelines for treatment of pancreatic cancer exist, due to unique differences in patient population, healthcare structure and reimbursement issues, direct application of these international guidelines to the local context is oftentimes not possible. Hence, there exists

a need to develop a set of local Singaporean guidelines to address this patient population and practice within our healthcare context.

The SCAN Guidelines for the Management of Pancreatic Cancer

The SCAN Guidelines are clinical practice guidelines for the adjuvant and palliative management of pancreatic cancer (Table 1).

These first edition guidelines are intended to serve as treatment recommendations by members of this working group reflecting their views on current existing international guidelines for these management issues. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

Target Users of the Guidelines

The guidelines will be of interest to oncologists, oncology nurse specialists, pharmacists, allied health workers and

Address for Correspondence: Dr Yeo Wee Lee, Oncology, John Hopkins Singapore, Tan Tock Seng Hospital (Level 1), 11 Jalan Tan Tock Seng, Singapore 308433.

Email: weelee_yeo@ttsh.com.sg

Table 1. Singapore Cancer Network (SCAN) Guidelines for Systemic Therapy of Pancreatic Adenocarcinoma

Guideline Recommendations	
Adjuvant Therapy for Resected Pancreatic Adenocarcinoma	1. Adjuvant gemcitabine or adjuvant TS-1 are both reasonable options postsurgical resection for PDAC. 2. Adjuvant radiation therapy concurrent with fluoropyrimidine is not recommended routinely for these patients unless resection margin is positive. 3. A full restaging scan should be performed prior to start of adjuvant chemotherapy to rule out any metastases.
Borderline Resectable Pancreatic Adenocarcinoma	1. Neoadjuvant therapy can be considered in patients with borderline resectable pancreatic adenocarcinoma. There is insufficient evidence to recommend a specific regimen. Possible regimens for chemotherapy include FOLFIRINOX or gemcitabine-based combination chemotherapy. Subsequent chemoradiation can be considered after initial chemotherapy. 2. Participation in clinical trials recommended if available.
Locally Advanced Pancreatic Adenocarcinoma (LAPC)	1. Chemotherapy alone or fluoropyrimidine-based chemoradiotherapy are reasonable options. 2. Chemotherapy regimens recommended as per metastatic setting. 3. Upfront chemoradiotherapy can be considered for patients with poorly controlled pain from local disease. 4. Participation in clinical trials recommended if available.
Metastatic Pancreatic Adenocarcinoma (PDAC)	1. Best supportive care ought to be considered for patients with poor performance status. 2. Systemic chemotherapy is recommended for patients with good performance status. First-line chemotherapy with FOLFIRINOX or combination gemcitabine and abraxane is preferred. 3. In the second-line setting, the recommendation is fluoropyrimidine-based chemotherapy if previously treated with gemcitabine-based therapy or gemcitabine-based therapy if previously treated with fluoropyrimidine-based therapy. 4. After second-line therapy, participation in clinical trials is recommended if available.

general practitioners involved in the management of patients with pancreatic cancer.

Guideline Recommendations/Development

The SCAN pancreatic cancer workgroup comprises a panel of 6 medical oncologists from Singapore with special subspecialty interest in the management of pancreatic cancer. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead with input from the workgroup members. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework² was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, specific breast cancer-related issues of relevance were identified and the scope and distribution of tasks were finalised. High quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source

guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. The guidelines were chosen based on their high quality, currency and applicability to our patient population. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to address the 4 main management issues which were selected for this topic:

1. Adjuvant Therapy for Resected Pancreatic Adenocarcinoma
2. Borderline Resectable Pancreatic Adenocarcinoma
3. Locally Advanced Pancreatic Adenocarcinoma (LAPC)
4. Metastatic Pancreatic Adenocarcinoma (PDAC)

Five international guidelines were selected for review (Supplementary Table 1):

- “NCCN Clinical Practice Guidelines in Pancreatic Ductal Adenocarcinoma” (version 1.2014) by the

National Cancer Comprehensive Network (NCCN, USA)³

- “Pancreatic Adenocarcinoma: ESMO-ESDO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up” by the European Society of Medical Oncology (ESMO) 2012⁴
- “Program in Evidence-based Care (PEBC)” by Cancer Care Ontario 2013⁵⁻⁷
- “EBM-based Clinical Guidelines for Pancreatic Cancer (2013) Issued by the Japan Pancreas Society: A Synopsis” by the Japan Pancreas Society⁸
- “Guidelines for the Management of Patients with Pancreatic, Periapillary and Ampullary Cancers” by the British Society of Gastroenterology, Pancreatic Society of Great Britain and Ireland and the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (2005)⁹

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of pancreatic cancer, it will be reviewed earlier.

1. Adjuvant Therapy for Resected Pancreatic Adenocarcinoma

Rationale for Adjuvant Chemotherapy after Resection of PDAC

Gemcitabine or 5-fluorouracil (FU)

Even when R0 resection is achieved in pancreatic adenocarcinoma, relapse rates are still high. Only about 15% to 20% of PDACs are cured by resection alone. Several trials have examined the role of adjuvant chemotherapy given after resection in PDAC. The European ESPAC-1 trial was a large study examining adjuvant chemotherapy alone and chemoradiotherapy in resected PDAC.¹⁰ In this 2x2 factorial design trial, adjuvant chemotherapy conferred better survival benefit compared to no chemotherapy (20.1 months vs 15.5 months, $P = 0.009$). Adjuvant chemoradiotherapy did not improve survival compared to those who did not receive this. The subsequent CONKO-001 trial compared no adjuvant therapy to adjuvant gemcitabine after PDAC resection and showed improved 5-year overall survival (OS) of 11% (21% vs 10%) with addition of 6 months of adjuvant gemcitabine.¹¹ Similarly, a smaller Japanese trial also showed disease-free survival (DFS) benefit with adjuvant gemcitabine over observation.¹²

ESPA-3 trial compared adjuvant gemcitabine with adjuvant bolus leucovorin-modulated 5-FU in resected PDAC and found no differences in survival outcomes between both arms.¹³ However, patients who received fluoropyrimidines had more grade III and IV toxicities like stomatitis and

diarrhea. Similarly, in the RTOG 9704 trial, there were no survival differences between patients who received gemcitabine versus those who received fluoropyrimidines.¹⁴

The NCCN, ESMO and Canadian guidelines all recommend gemcitabine or 5-FU as adjuvant chemotherapy for resected PDAC.

TS-1

More recently, JASPAC-01 trial showed that adjuvant oral TS-1 alone was not inferior to adjuvant gemcitabine in resected PDAC.¹⁵ Two-year survival with TS-1 was 70% and 53% with gemcitabine ($HR = 0.54$, $P < 0.001$). TS-1 was also better tolerated than gemcitabine though the former had more incidences of stomatitis and diarrhea. The NCCN, ESMO and Canadian guidelines do not recommend TS-1 as adjuvant therapy as this drug is not available in some of these countries and TS-1 data in their PDAC populations is lacking.

All patients with resected PDAC should be considered for adjuvant therapy.

Role of Radiation Therapy as Part of Adjuvant Therapy

In the 1980s, the GITSG trial that was conducted in the USA showed that adjuvant bolus 5-FU with radiation therapy (40 Gy) followed by adjuvant 5-FU for 2 years after PDAC resection doubled survival rates over observation alone (2-year OS, 20% vs 10%).¹⁶ This trial was stopped early due to poor recruitment. The Europeans tried to reproduce these results in the EORTC trial done in the late 1990s, comparing continuous infusion 5-FU concurrent with split course radiation (40 Gy) therapy as adjuvant therapy with observation alone in resected PDACs.¹⁷ This trial only showed a trend towards improved survival with chemoradiation and no differences in local recurrence.

The ESPAC-1 trial, which tried to compare adjuvant chemotherapy, adjuvant chemoradiation and observation found that patients who received adjuvant chemoradiation did worse than patients in the other groups.¹⁰ Thus, based on EORTC and ESPAC-1, ESMO guidelines do not recommend adjuvant chemoradiation after PDAC resection. On the other hand, the American guidelines still recommend adjuvant chemoradiation based on the positive results of the GITSG trial and other uncontrolled series and the opinion that the flaws in the European trials preclude any firm conclusions.

Rationale for Postsurgery Imaging

Pancreatic cancer has an extremely high rate of systemic recurrence (>80%) and a very high rate of local recurrence (>20%). Some patients develop recurrence within 8 weeks of surgery, thus it is recommended that imaging scans are

performed prior to initiation of adjuvant therapy. For patients for whom adjuvant chemoradiation is planned after adjuvant chemotherapy is started, an imaging scan is recommended prior to start of chemoradiation phase.

Recommendations Regarding Adjuvant Therapy for Resected Pancreatic Adenocarcinoma

1. Adjuvant gemcitabine or adjuvant TS-1 are both reasonable options postsurgical resection for PDAC.
2. Adjuvant radiation therapy concurrent with fluoropyrimidine is not recommended routinely for these patients unless resection margin is positive.
3. A full restaging scan should be performed prior to start of adjuvant chemotherapy to rule out any metastases.

2. Borderline Resectable Pancreatic Adenocarcinoma

The consensus statement from the American Hepato-Pancreato-Biliary Association (AHPBA)¹⁸ which is also endorsed by NCCN³ and ESMO⁴ considered “borderline resectable pancreatic adenocarcinoma” to include the following:

1. No distant metastases.
2. Venous involvement of the superior mesenteric vein (SMV)/portal vein demonstrating tumour abutment with or without impingement and narrowing of the lumen, encasement of the SMV/portal vein but without encasement of the nearby arteries, or short segment venous occlusion resulting from either tumour thrombus or encasement, but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction.
3. Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct tumour abutment of the hepatic artery, but without extension to the celiac axis.
4. Tumour abutment of the superior mesenteric artery not to exceed $>180^\circ$ of the circumference of the vessel wall.

There is no clear consensus with regard to management of borderline resectable pancreatic adenocarcinoma. NCCN and ESMO guidelines consider neoadjuvant therapy as an acceptable option to upfront resection in patients with borderline resectable pancreatic cancer. There is however insufficient evidence to recommend specific neoadjuvant regimens. PEBC, Cancer Care Ontario (CCO), the Japan Pancreas Society (JPS) and the British Society of Gastroenterology, Pancreatic Society of Great Britain and Ireland and the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS) recommend participation in clinical trials where possible in this instance.

Recommendations for Borderline Resectable Pancreatic Adenocarcinoma

1. Neoadjuvant therapy can be considered in patients with borderline resectable pancreatic adenocarcinoma. There is insufficient evidence to recommend a specific regimen. Possible regimens for chemotherapy include FOLFIRINOX or gemcitabine-based combination chemotherapy. Subsequent chemoradiation can be considered after initial chemotherapy.
2. Participation in clinical trials recommended if available.

3. Locally Advanced Pancreatic Adenocarcinoma (LAPC)

At initial diagnosis, 30% of patients with pancreatic adenocarcinoma present with locally advanced tumour (LAPC).¹⁹ The goals of treatment are to reduce symptoms and prolong life. Treatment recommendation depends on the patient's performance status. Patients with poor performance status would not benefit from aggressive therapy. The following discussion is meant for patients with good performance status.

Chemotherapy versus Chemoradiotherapy

There are differing treatment recommendations. Both NCCN and ESMO guidelines recommend systemic chemotherapy alone, although NCCN does endorse chemoradiotherapy following a course of systemic chemotherapy in selected patients. PEBC, CCO prefers chemoradiotherapy whilst JPS lists chemoradiotherapy as an option.

The utility of adding radiotherapy to chemotherapy is debatable. Two chemoradiotherapy strategies have been employed: 1) upfront chemoradiotherapy and 2) chemoradiotherapy following chemotherapy.

Upfront Chemoradiotherapy

Two recent studies have evaluated the role of upfront chemoradiotherapy in this setting with differing conclusions. Both studies were however terminated early. ECOG 4201 compared gemcitabine alone versus gemcitabine with radiotherapy in patients with LAPC. Despite poor accrual and early termination, median OS of patients who received radiotherapy was longer (9.2 months vs 11.1 months, $P = 0.017$). This study however lacks statistical robustness as the confidence interval of survival between the 2 arms overlap.²⁰

The FFCD-SFRO study randomised 119 patients to receive either gemcitabine alone or intensive chemoradiotherapy with 5-FU plus cisplatin followed by maintenance gemcitabine. This study demonstrated a superior OS at 1 year for gemcitabine alone compared to chemoradiotherapy

(53% vs 32%, HR = 0.54; 95% CI, 0.31 to 0.96; $P = 0.006$). This study was stopped early as interim analysis showed a lower survival rate in combination arm attributable to increased severe toxicities.²¹

Taken together, upfront chemoradiotherapy in patients with LAPC is controversial. Use of upfront chemoradiotherapy however, can be considered in selected cases, for example in patients with poor pain control.

Chemoradiotherapy Following Chemotherapy

The LAP 07 trial attempted to evaluate the additional benefit of chemoradiotherapy after a course of chemotherapy. Preliminary analyses have been presented in abstract form. LAPC patients were first randomised to gemcitabine or gemcitabine plus erlotinib. Patients with controlled disease after 4 months of chemotherapy were then randomised to 2 additional months of chemotherapy or chemoradiotherapy amounting to 54 Gy and concurrent capecitabine. Administration of chemoradiotherapy in patients with LAPC controlled with induction chemotherapy was not superior to continuing chemotherapy alone in terms of overall survival. The OS was not significantly different between the 2 arms (15.2 vs 16.5 months, $P = 0.8$). Even though the OS was not improved in the chemoradiotherapy arm, patients with non-progressive LAPC after 4 months of induction chemotherapy had a longer time without treatment in the chemoradiotherapy arm (159 vs 96 days, respectively, $P = 0.05$) with significantly less local tumour progression (34% vs 65%, $P < 0.0001$).²²

Choice of Chemotherapy

Choice of chemotherapy used in patients with LAPC mirrors the options of systemic chemotherapy in the metastatic setting.

Recommendations for LAPC

1. Chemotherapy alone or fluoropyrimidine-based chemoradiotherapy are reasonable options.
2. Chemotherapy regimens recommended as per metastatic setting.
3. Upfront chemoradiotherapy can be considered for patients with poorly controlled pain from local disease.
4. Participation in clinical trials recommended if available.

4. Metastatic Pancreatic Adenocarcinoma

Front-line Treatment for Metastatic Pancreatic Adenocarcinoma (PDAC)

Patients with poor performance status ought to be offered the best supportive care. In younger patients with good

performance status, options for first-line chemotherapy that have emerged in more recent studies include FOLFIRINOX²³ and gemcitabine in combination with nab-paclitaxel.²⁴ This is based on the PRODIGE²³ and MPACT²⁴ trials respectively, first-line radiochemotherapies (RCTs) showing overall survival benefits when compared to the existing standard of gemcitabine monotherapy.²⁵

FOLFIRINOX has shown an improvement in both median progression-free survival (PFS) (6.4 months vs 3.3 months, $P < 0.001$) and median OS (11.1 months vs 6.8 months, $P < 0.001$). The rates of grade III or IV toxicities were higher in the FOLFIRINOX arm, in particular 45.7% for neutropenia, though there were no toxic deaths reported. In fact, the patients in the FOLFIRINOX arm had an improved quality of life comparatively.²⁵ The toxicities of FOLFIRINOX could be managed with supportive measures such as growth factor support.

The MPACT trial²⁴ showed that the addition of nab-paclitaxel to gemcitabine demonstrated improved median OS (8.5 months vs 6.7 months; $P < 0.0001$), median PFS (5.5 months vs 3.7 months; $P < 0.001$) and improved overall response rate (ORR) (23% vs 7%; $P < 0.001$). The common grade III or IV adverse events attributable to nab-paclitaxel were neutropenia (38%), fatigue (17%), and neuropathy (17%).

For older patients and individuals who are unable to tolerate combination therapy, it is reasonable to consider monotherapy with either gemcitabine or S-1.²⁶⁻²⁷

Addition of Targeted Therapy to Systemic Chemotherapy

There is currently no evidence to support the use of targeted therapy with bevacizumab or cetuximab in combination with chemotherapy in the first-line treatment of metastatic pancreatic carcinoma.

Second-line Treatment

In the second-line setting, for patients with good performance status, fluoropyrimidine-based chemotherapy is recommended for patients who had previously been treated with gemcitabine based therapy^{7-9,28-30} or gemcitabine-based therapy if previously treated with fluoropyrimidine-based therapy.³⁰

A systemic review of clinical trials done in the second-line setting revealed that there is limited data but possible advantage of second-line treatment over best supportive care.³⁰

Third-line Treatment

Patients who have progressed beyond 2 or more lines of treatment are recommended for enrollment in clinical trials if they still have good performance status.

Recommendations for Metastatic Pancreatic Cancer

1. Best supportive care ought to be considered for patients with poor performance status.
2. Systemic chemotherapy is recommended for patients with good performance status. First-line chemotherapy with FOLFIRINOX or combination gemcitabine and abraxane is preferred.
3. In the second-line setting, the recommendation is fluoropyrimidine-based chemotherapy if previously treated with gemcitabine-based therapy or gemcitabine-based therapy if previously treated with fluoropyrimidine-based therapy.
4. After second-line therapy, participation in clinical trials is recommended if available.

All recommendations were unanimously agreed upon.

Conflicts of Interest

Dr Choo reports serving on advisory boards of Bayer, Novartis, Bristol Myers Squibb and Lilly Oncology, receiving advisory or speaker honoraria from SIRTEX, Novartis and Bristol Myers Squibb and travel funding from Merck; Dr Lim, receiving advisory board fees from Pfizer and Bristol Myers Squibb and speaker bureau fees from Novartis; Dr Yeo, serving on advisory boards of Roche and Bayer; Dr Yong, receiving fees from Roche as a trial data safety monitoring committee member; Dr Foo and Dr Tai have nothing to disclose.

Workgroup Members

The Members of the SCAN Pancreatic Cancer Workgroup are Section Lead and Workgroup Chairperson: Wee Lee Yeo, MBBS, MRCP, FAMS, Oncology, John Hopkins Singapore, Singapore; Workgroup Members (Voting): Kian-Fong Foo, MBBS (S'pore), MMed (Int Med), MRCP (UK), Medical Oncology, Parkway Cancer Centre, Singapore; Su Pin Choo, MBBS, MRCP (UK), FAMS, Division of Medical Oncology, Gastrointestinal Oncology Department, National Cancer Centre Singapore, Singapore; Hwee Yong Lim, BmedSci, MB BCh BAO, ABIM Int Med (USA), ABIM Hematology (USA), Medical Oncology, Novena Cancer Centre, Singapore; Angela SL Pang, MBBS (S'pore), MRCP, MMed (Int Med), Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore; David Tai, MBBS, MRCP (UK), Division of Medical Oncology, Gastrointestinal Oncology Department, National Cancer Centre Singapore, Singapore; Wei Peng Yong, MB ChB (Aberdeen), MRCP (UK), Clinical Pharmacology Fellowship (University of Chicago), Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore.

Reviewers

Invited reviewers were Gilberto Lopes, MD, MBA, Oncoclinicas Group, Brazil; John Zalcberg, MBBS, PhD, FRACP, Cancer Research Program, Monash University, Australia; Eileen M O'Reilly, MD, Department of Medicine, Memorial Sloan Kettering Cancer Center, USA; Junji Furuse, MD, PhD, Department of Medical Oncology, Kyorin University School of Medicine, Japan; Takuji Okusaka, MD, PhD, Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Japan.

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Supplementary Table 1. International Guidelines for Systemic Therapy of Pancreatic Adenocarcinoma

Guideline Title	NCCN Clinical Practice Guidelines in Oncology Pancreatic Ductal Adenocarcinoma Cancer Version 1.2014	Pancreatic Adenocarcinoma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	Guidelines for the Management of Patients with Pancreatic Cancer, Periampullary and Ampullary Carcinoma	Program in Evidence-Based Care (PEBC), Cancer Care Ontario	EBM-Based Clinical Guidelines for Pancreatic Cancer 2009 from the Japan Pancreas Society: A Synopsis	Singapore Cancer Network (SCAN) Guidelines
Date Released	1 January 2014	1 October 2012	13 May 2005	2 April 2013	1 July 2009	27 March 2014
Guideline Developer	National Cancer Comprehensive Network (NCCN), United States	European Society for Medical Oncology (ESMO)	Pancreatic section of the British Society of Gastroenterology, Pancreatic Society of Great Britain and Ireland, Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, Royal College of Pathologists, Special Interest Group for Gastro-Intestinal Radiology	Cancer Care Ontario (CCO)	Japan Pancreas Society	Consensus of SCAN Pancreatic Cancer Workgroup
Description of Method of Guideline Validation	Statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment.	Recommendations developed from discussion at consensus conferences. Group decision-making that seeks the consensus of experts and the fulfillment of objectives.	Consensus statement of authors based on available evidence.	Recommendations derived from systematic review of clinical and scientific literature and its interpretation by Disease Site Group (DSG) or Guideline Development Group (GDC) and a formalised external review by Ontario practitioners.	Recommendations derived from systematic review of literature listed on Pubmed and Igakuchuo Zasshi (443 papers).	Recommendations made through adaptation of existing guidelines.
Target Population	Preoperative Panel does not recommend neoadjuvant therapy for resectable patients except on a clinical trial. For selected patients who appear technically resectable but have poor prognostic feature, however, consideration can be given to neoadjuvant therapy after biopsy confirmation though a clinical trial is preferred.	Preoperative In case of resectable pancreatic cancer, neoadjuvant chemotherapy, radiotherapy or chemoradiation should only be performed within clinical trials. Patients should be encouraged to join clinical trials.	Preoperative Neoadjuvant therapies should only be given within the context of a clinical trial.	Preoperative There is insufficient evidence to support the use of preoperative chemotherapy or radiotherapy.	Preoperative There is increasing evidence supporting the efficacy of preoperative treatment: 1) chemoradiation and 2) chemotherapy. However, clinical trials or long-term analyses are required.	Preoperative Patients with resectable pancreatic adenocarcinoma should undergo upfront resection*.
Treatment						

*Resectable – resect first.

†Borderline – consider neoadjuvant, insufficient evidence to recommend specific regimen.

‡Chemotherapy or chemoRT.

§Possible regimens: FOLFIRINOX, GEM-based treatment.

Supplementary Table 1. International Guidelines for Systemic Therapy of Pancreatic Adenocarcinoma (Cont)

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Treatment	Many NCCN member institutions and the panel itself consider neoadjuvant therapy as an acceptable option to upfront resection in patients with borderline resectable pancreatic cancer. There is insufficient evidence to recommend specific neoadjuvant regimens.	Patients with borderline resectable pancreatic cancer may benefit from neoadjuvant chemotherapy or chemoradiotherapy. The optimal neoadjuvant strategy is still under investigation and there is no standard protocol for neoadjuvant chemoradiotherapy in Europe.			Neoadjuvant chemotherapy or chemoradiotherapy can be considered in patients with borderline resectable pancreatic cancer^{†‡}. There is insufficient evidence to recommend a specific regimen. Possible regimens for chemotherapy include FOLFIRINOX or gemcitabine-based combination chemotherapy[§]. Participation in clinical trials recommended if available.	

*Resectable – resect first.

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‡Chemotherapy or chemoradiation.

§Possible regimens: FOLFIRINOX, GEM-based treatment.

Singapore Cancer Network (SCAN) Guidelines for the Management of Advanced Castrate-Resistant Prostate Cancer

The Singapore Cancer Network (SCAN) Genitourinary Cancer Workgroup

Abstract

Introduction: The SCAN genitourinary cancer workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for the management of advanced castrate-resistant prostate cancer. **Materials and Methods:** The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. **Results:** Five international guidelines were evaluated—those developed by the National Comprehensive Cancer Network (2014), the European Society of Medical Oncology (2013), the American Urological Association (2013), the National Institute of Health and Clinical Excellence (2014) and the American Society of Clinical Oncology and Cancer Care Ontario (2014). Recommendations on the management of advanced castrate-resistant prostate cancer were developed. **Conclusion:** These adapted guidelines form the SCAN Guidelines 2015 for the management of advanced castrate-resistant prostate cancer.

Ann Acad Med Singapore 2015;44:397-405

Key words: Abiraterone, Cabazitaxel, Docetaxel, Ketoconazole, Enzalutamide, Radium-223

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Introduction

Prostate cancer is the third most common cancer among the male population in Singapore, and the sixth most frequent cause of cancer death.¹ The age-standardised incidence rate for prostate cancer has increased significantly over the last 40 years from 5.2 per 100,000 in 1973 to 1977 to 28.3 per 100,000 in 2008 to 2012. This may be a result of the increase in use of prostate specific antigen (PSA) testing. Overall, there was also an increase in the age-standardised mortality rate for prostate cancer. Most prostate cancers are diagnosed in the early stages, and about 21% of prostate cancer patients will have stage IV disease at diagnosis. Despite high response rates to initial androgen deprivation therapy, nearly all men with metastatic prostate cancer become castrate-resistant. Metastatic castrate-resistant prostate cancer (mCRPC) is a form of prostate cancer that has spread beyond the prostate and is resistant to medical or surgical treatments that lower testosterone level. In recent years, a number of novel agents that have improved survival in men with this disease have entered the clinic. There is therefore a need to review the available data, especially in the Singapore setting.

The SCAN Guidelines for the Management of Metastatic Castrate-Resistant Prostate Cancer (mCRPC)

The SCAN Guidelines are clinical practice guidelines for the management of mCRPC.

These first edition guidelines are intended to serve as treatment recommendations by members of this working group reflecting their views on current existing international guidelines for the management of mCRPC. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

Target Users of the Guidelines

The guidelines will be of interest to oncologists, urologists, allied health workers and general practitioners involved in the management of patients with mCRPC.

Guideline Recommendations/Development

The SCAN genitourinary cancer workgroup comprises a panel of 7 medical oncologists from Singapore with

Address for Correspondence: Dr Quan Sing Ng, Division of Medical Oncology, National Cancer Centre Singapore, 11 Hospital Drive, Singapore 169610.
Email: Ng.Quan.Sing@singhealth.com.sg

special interests in the management of genitourinary cancers. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead with input from the workgroup members. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework² was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, high quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to address the 4 main management issues which were selected for this topic:

1. Androgen deprivation therapy
2. Hormone therapy
3. Chemotherapy
4. Radium-223

Five international guidelines were selected for review (Supplementary Table 1):

- “NCCN Clinical Practice Guidelines in Oncology Prostate Cancer” (version 1.2014) by the National Cancer Comprehensive Network (NCCN, USA)³
- “Prostate cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up” by the European Society for Medical Oncology (ESMO), 2013⁴
- “Castrate-Resistant Prostate Cancer: AUA Guideline”

by the American Urological Association (AUA), 2013⁵

- “Prostate Cancer: Diagnosis and Treatment (CG175)” by the National Institute of Health and Clinical Excellence (NICE), 2014⁶
- “Systemic Therapy in Men With Metastatic Castration-Resistant Prostate Cancer: American Society of Clinical Oncology and Cancer Care Ontario Clinical Practice Guideline” by the American Society of Clinical Oncology (ASCO) and Cancer Care Ontario (CCO), 2014⁷

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of mCRPC, it will be reviewed earlier.

1. Androgen Deprivation Therapy

Androgen suppression should be continued with luteinizing hormone-releasing hormone (LHRH) agonist or antagonist unless previous bilateral orchidectomy had been performed. Patients who progress on LHRH treatment or orchidectomy, should be started on an anti-androgen such as bicalutamide. Following further disease progression, the anti-androgen should be withdrawn.⁸ As per the Prostate Cancer Working Group 2⁹ consensus, there is no need to wait for a withdrawal response before initiating further therapy if there has been no response to adding anti-androgen to LHRH treatment or orchidectomy. Retrospective studies have also demonstrated limited PSA response when alternative anti-androgens, e.g. bicalutamide, flutamide, nilutamide, are used following progressive disease.¹⁰

2. Hormone Therapy

Abiraterone

Recent research has shown that drugs that target the hormone synthesis pathway can be clinically active in patients with castrate-resistant prostate cancer. Abiraterone is a potent and irreversible inhibitor of CYP17 that has shown clinical activity in patients. In patients who had disease progression after docetaxel chemotherapy, overall survival was significantly longer in patients who received abiraterone-prednisone compared to the placebo-prednisone group (14.8 months vs 10.9 months; hazard ratio (HR) = 0.65; 95% confidence interval (CI), 0.54 to 0.77; $P < 0.001$).¹¹ All secondary endpoints, including time to PSA progression (10.2 vs 6.6 months; $P < 0.001$), progression-free survival (PFS) (5.6 months vs 3.6 months; $P < 0.001$), and PSA response rate (29% vs 6%, $P < 0.001$), favoured the treatment group. In addition, there were significant benefits compared with prednisone alone in terms of pain relief, delayed pain progression, prevention of skeletal-related events, and patient reported health-related quality of

life.^{12,13} In chemotherapy-naïve patients, radiographic PFS was significantly increased with abiraterone-prednisone compared with placebo-prednisone (median 16.5 vs 8.2 months, HR = 0.52; 95% CI, 0.45 to 0.61).¹⁴ At a median follow-up of 49.2 months (IQR 47.0 to 51.8), overall survival was increased with abiraterone-prednisone compared to the placebo-prednisone group (median 34.7 vs 30.3 months, HR = 0.81; 95% CI, 0.70 to 0.93; $P = 0.0033$).¹⁵

There have been no cost-effectiveness analyses on abiraterone performed using local cost data and Singaporean societal norms. Based on NICE appraisal,¹⁶ the manufacturer's base-case incremental cost-effectiveness ratio (ICER) for abiraterone plus prednisolone compared with prednisolone alone is USD \$71,756 per quality-adjusted life-year (QALY) gained for the one prior chemotherapy subgroup. The NICE committee determined that the most plausible ICER was likely to be higher than the manufacturer's base-case estimate for the one prior chemotherapy subgroup, but would be less than USD \$76,645 per QALY gained.

Enzalutamide

Enzalutamide is a novel anti-androgen agent that has significant antitumour activity in patients with castrate-resistant prostate cancer who have progressed after previous chemotherapy. In the AFFIRM study, patients who had previously received docetaxel chemotherapy were randomised to enzalutamide or placebo.¹⁷ The median overall survival was 18.4 months (95% CI, 17.3 to not yet reached) in the enzalutamide group versus 13.6 months (95% CI, 11.3 to 15.8) in the placebo group (HR for death in the enzalutamide group = 0.63; 95% CI, 0.53 to 0.75; $P < 0.001$). Treatment was well tolerated. However, seizures were reported in 0.6% of patients who received enzalutamide and none with placebo. In addition, there was improvement in time to first skeletal-related event, time to pain progression, and quality of life in patients who received enzalutamide.^{18,19} The role of enzalutamide in chemotherapy-naïve patients was evaluated in the PREVAIL study.²⁰ Eligible patients had not received cytotoxic chemotherapy, ketoconazole or abiraterone. At the planned interim analysis, there was a median duration of follow-up of 22 months. At that point, overall survival was significantly increased with enzalutamide compared with placebo (estimated median 32.4 vs 30.2 months, HR = 0.71; 95% CI, 0.60 to 0.84). An updated analysis of overall survival with 116 additional deaths showed that 82% of patients in the enzalutamide group and 73% of those in the placebo group were alive at 18 months. There was a significant decrease in the risk of radiographic progression with enzalutamide compared with placebo (12 month PFS 65 vs 14%, HR = 0.19; 95% CI, 0.15 to 0.23). One patient in each study group experienced

a seizure. Patients who received enzalutamide also reported significantly improved patient-related outcomes, with delays in the occurrence of first skeletal-related event.²¹

There have been no cost-effectiveness analyses on enzalutamide performed using local cost data and Singaporean societal norms. On 23 July 2014, NICE recommended enzalutamide for the treatment of metastatic hormone-relapsed prostate cancer that has progressed during or after docetaxel-containing chemotherapy.²² The NICE Committee determined a probable pairwise ICER of USD \$22,213 per QALY for enzalutamide versus abiraterone and USD \$78,391 per QALY for enzalutamide versus best supportive care. For patients who had received 2 or more previous courses of cytotoxic chemotherapy, the NICE Committee's estimated ICER for enzalutamide compared with best supportive care was USD \$73,600 per QALY gained.

Ketoconazole

Ketoconazole is an imidazole antifungal agent that inhibits adrenal androgen synthesis, although it does have a direct cytotoxic effect on prostatic cancer cells in vitro. Ketoconazole is less specific than abiraterone. In a phase III trial conducted by the Cancer and Leukemia Group B (CALGB 9583), a subgroup of patients who had progressed on androgen deprivation therapy were assigned to anti-androgen withdrawal alone.⁸ Upon PSA progression, patients were treated with ketoconazole plus hydrocortisone. Thirty-two percent had a PSA response, and 7% with measurable disease had an objective response.

A retrospective study of 32 patients given ketoconazole at 200 mg thrice daily at 2 tertiary cancer centres in Singapore demonstrated a PSA response rate (defined as at least 50% decrease in PSA level from baseline) of 38% and a median duration of response of 6.75 months.²³ The median time to reach PSA nadir was 3.5 months (range, 1.5 to 11 months).

3. Chemotherapy

Docetaxel

Docetaxel was the first chemotherapy to demonstrate improvement in survival in patients with mCRPC. In the TAX 327 study, patients received 5 mg of prednisone twice daily and were randomly assigned to receive 12 mg of mitoxantrone per square metre of body-surface area every 3 weeks, 75 mg of docetaxel per square metre every 3 weeks, or 30 mg of docetaxel per square metre weekly for 5 of every 6 weeks.²⁴ The median survival was 16.5 months in the mitoxantrone group, 18.9 months in the group given docetaxel every 3 weeks, and 17.4 months in the group given weekly docetaxel. As compared with the survival rate in the mitoxantrone group, the survival rate was significantly

higher ($P = 0.009$) in the group given docetaxel every 3 weeks but not in the group given weekly docetaxel ($P = 0.36$). With an extended follow-up that included death of 86% of the patients, the 3-year survival rates were higher in those treated with the 2 docetaxel schedules (18.6 and 16.6 vs 13.5% with mitoxantrone, respectively).²⁵ Apart from cardiac events, which were more frequent in the mitoxantrone group, other adverse events were more frequent among patients receiving docetaxel, and there was no trend toward a lower frequency with weekly docetaxel than with docetaxel given every 3 weeks. The addition of estramustine to docetaxel has been shown to increase side effects without enhancing efficacy.²⁶

A retrospective study of 89 patients with castrate-resistant prostate cancer treated at the National Cancer Centre Singapore evaluated the efficacy and tolerability of 2 attenuated regimens—60 mg of docetaxel per square metre every 3 weeks, and weekly docetaxel (20 to 35 mg per square metre) (unpublished data). The use of 60 mg of docetaxel per square metre every 3 weeks had similar efficacy and an acceptable toxicity profile compared to the standard 75 mg of docetaxel per square metre every 3 weeks. Weekly docetaxel had significant palliative benefits among symptomatic patients despite lower overall survival.

Cabazitaxel

Cabazitaxel is a semi-synthetic novel tubulin-binding taxane drug with antitumour activity in docetaxel-resistant cancers. In the phase III open label randomised TROPIC trial, men with mCRPC who had received previous hormone therapy, but whose disease had progressed during or after treatment with a docetaxel-containing regimen were enrolled.²⁷ Patients were treated with 10 mg of oral prednisone daily, and were randomly assigned to receive either 12 mg of mitoxantrone per square metre of body-surface area intravenously over 15 to 30 min or 25 mg per square metre of cabazitaxel intravenously over 1 h every 3 weeks. Men treated with cabazitaxel plus prednisone had a better overall survival compared with those treated with mitoxantrone plus prednisone (HR = 0.70; 95% CI, 0.59 to 0.83; median survival 15.1 vs 12.7 months). PFS was also significantly prolonged (2.8 vs 1.4 months, HR = 0.74; 95% CI, 0.64 to 0.86). With additional follow-up, the 2-year estimated survival was greater than 2 years in 27% of patients treated with cabazitaxel versus 16% in those treated with mitoxantrone.²⁸ The most common clinically significant grade III or higher adverse events were neutropenia (cabazitaxel, 303 [82%] patients vs mitoxantrone, 215 [58%]) and diarrhoea (23 [6%] vs 1 [<1%]). Twenty-eight (8%) patients in the cabazitaxel group and 5 (1%) in the mitoxantrone group had febrile neutropenia. About 5% of patients treated with cabazitaxel

died within 30 days of the last infusion and the most frequent cause of death in the cabazitaxel group was neutropenia and its clinical consequences. In this heavily pretreated, high risk population, current guidelines for prophylactic white blood cell growth factor use should be adhered to.

There have been no cost-effectiveness analyses on cabazitaxel performed using local cost data and Singaporean societal norms. The NICE Committee considered that the most plausible ICER would be above USD \$134,183 per QALY gained.²⁹ The Committee further noted that there remains considerable uncertainty in the robustness of this ICER because the utility values that were used in the model were based on unpublished data from an interim analysis of a small number of patients from the TROPIC study, and the costs associated with managing febrile neutropenia were underestimated.

4. Radium-223

Radium-223 dichloride is a targeted alpha emitter that selectively binds to areas of increased bone turnover in bone metastases and emits high-energy alpha particles of short range (<100 μm). As a bone-seeking calcium mimetic, radium-223 is bound into newly formed bone stroma, especially within the microenvironment of osteoblastic or sclerotic metastases. In the phase III ALSYMPCA trial, all patients had castrate-resistant prostate cancer with multiple bone metastases and had either progressed on docetaxel chemotherapy or were not candidates for docetaxel chemotherapy.³⁰ Patients were required to have 2 or more bone metastases and no known visceral metastases. Overall survival, the primary endpoint, was significantly improved compared with placebo (median 14.9 vs 11.3 months, HR = 0.70; 95% CI, 0.58 to 0.83). The 18-month survival was estimated to be 39% for the radium-223 group versus 29% for placebo. The time to first symptomatic skeletal event (which included the first use of external beam radiation therapy (RT) for symptom relief, new pathologic fracture, spinal cord compression, or tumour-related orthopaedic surgery intervention) was also significantly increased (median 15.6 vs 9.8 months, HR = 0.66; 95% CI, 0.52 to 0.83).

There have been no cost-effectiveness analyses on radium-223 performed using local cost data and Singaporean societal norms. The NICE Committee noted that the manufacturer's base case ICER for radium-223 compared with best supportive care was USD \$85,118 per QALY gained and that the Committee's adjustments to the model increased the base-case ICER to USD \$88,008 per QALY gained (National Institute for Health and Care Excellence, Appraisal consultation document—Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases; issue date: December 2014). However, it concluded that it was not possible to determine whether

radium-223 could be considered a cost-effective use of National Health Service (NHS) resources, because the appropriate comparison with docetaxel and abiraterone had not been presented. At the time of publication of these guidelines, NICE has yet to publish their final recommendation on the use of radium-223 in patients with castrate-resistant prostate cancer.

Recommendations for Metastatic Castrate-Resistant Prostate Cancer (mCRPC)

The workgroup voted unanimously to adopt the AUA guidelines (Supplementary Table 1) and made the following adaptations (Table 1):

1. The workgroup recommends that participation in clinical trials should be strongly encouraged.
2. Best supportive care and referral to palliative medicine should be recommended when appropriate.
3. There was consensus that Sipuleucel-T should not be recommended as part of local treatment practice. Sipuleucel-T is currently not licensed for use in Singapore. The Immunotherapy Prostate

Adenocarcinoma Treatment (IMPACT) phase III trial reported a statistically significant 4.1-month median overall survival advantage with sipuleucel-T versus placebo (HR = 0.78; 95% CI, 0.61 to 0.98).³¹ However, the workgroup has considered several issues that have been raised about the registration trial.³² In particular, there was concern that the overall survival benefit may be a result of the detrimental effect of repeated depletion of circulating mononuclear cells in the placebo group.

4. There is lack of evidence demonstrating superiority between abiraterone and enzalutamide. In addition, the workgroup acknowledged that there are several retrospective studies indicating that either using abiraterone after enzalutamide or enzalutamide after abiraterone in castrate-resistant disease has limited activity. The workgroup accepts that there is insufficient data for specific recommendations on the sequencing of hormonal therapy.
5. The workgroup acknowledges that there is lack of definitive phase III trial data showing benefit of ketoconazole, although PSA responses have been observed. Clinicians may continue to recommend the

Table 1. Singapore Cancer Network (SCAN) for the Management of Metastatic Castrate-Resistant Prostate Cancer

Guideline Recommendations (Adapted from AUA Guidelines)	
Androgen Deprivation Therapy	- Androgen suppression should be continued with LHRH agonist or antagonist unless previous bilateral orchidectomy had been performed - Patients who progress on LHRH treatment or orchidectomy, should be started on an anti-androgen such as bicalutamide. Following further disease progression, the anti-androgen should be withdrawn - Alternative anti-androgen may be considered
Chemo-naïve, Asymptomatic or Minimally Symptomatic	- Clinical trial participation - Abiraterone + prednisolone - Ketoconazole + hydrocortisone - Enzalutamide - Observation - Androgen withdrawal and alternative anti-androgen therapy
Chemo-naïve, Symptomatic, Good Performance Status	- Clinical trial participation - Docetaxel (chemotherapy may be preferred if the patient failed to achieve a good response to initial hormonal therapy) - Abiraterone + prednisolone - Ketoconazole + hydrocortisone (clinicians may continue to recommend the use of ketoconazole on the basis of lower cost) - Enzalutamide - Radium-223 (in patients who decline chemotherapy and do not have visceral metastases)
Postchemo, Symptomatic, Good Performance Status	- Clinical trial participation - Abiraterone + prednisolone - Ketoconazole + hydrocortisone (clinicians may continue to recommend the use of ketoconazole on the basis of lower cost) - Enzalutamide - Cabazitaxel - Re-challenge docetaxel - Radium-223 (in patients without visceral metastases)

AUA: American Urological Association; LHRH: Luteinising hormone-releasing hormone

use of ketoconazole on the basis of lower cost.

6. Docetaxel chemotherapy is the first-line chemotherapy of choice. The workgroup acknowledged that a lower dose (less than 75 mg/m² every 3 weeks) may have a better toxicity profile with comparable efficacy based on the Singapore study. When starting at a lower dose of docetaxel, clinicians should consider dose escalation up to 75 nmg/m² in the absence of significant toxicity with the lower dose.
7. Based on the results of the ALSYMPCA study, the workgroup agreed that radium-223 may be used for the treatment of castrate-resistant prostate cancer patients with symptomatic bone metastases and no known visceral metastatic disease. However, the agent is not recommended if the patient is concurrently receiving chemotherapy. Clinicians should follow instructions in the Food and Drug Administration (FDA) label on haematologic evaluation before each injection.
8. The workgroup agreed that specific recommendations for castrate-sensitive prostate cancer, and bone metastases and bone health be deferred to subsequent editions of the guidelines.

Conflicts of Interest

Dr Kanesvaran reports receiving advisory board fees from Pfizer, GSK and Bayer and speaker bureau fees from Pfizer and GSK; Dr Ng, receiving advisory board fees from Bayer and Astra Zeneca; Dr Tan, receiving grant support from Pfizer and holding the following pending patents: "A Multigene Assay for Prognosis and Drug Response Prediction in Clear-Cell Renal Cell Carcinoma Patients That Identifies Distinct Biological Subtypes", "Method for Predicting Clinical Toxicities and Outcomes in Patients Receiving Sunitinib Using Gene Polymorphisms", "Self-Assembled Micellar Nanocomplexes Comprising Polyethylene Glycol-Epigallocatechin-3-Gallate Conjugates and Anticancer Drugs", "Antibody specific for Parafibromin, a New Marker of Parathyroid Carcinoma", licensed to Santa Cruz Biotechnology, and "Method for Determining Mutation Status in Colorectal Cancer Patients Using Allele-Specific PCR", licensed to AIT Biotech; Miss Cheng, Dr Tan, Dr Tay, Dr Toh and Dr Wong have nothing to disclose.

Workgroup Members

The Members of the SCAN Genitourinary Cancer Workgroup are Section Lead: Quan Sing Ng, MBBS, MD, MRCP, Division of Medical Oncology, National Cancer Centre Singapore, Singapore; Workgroup Chairperson: Ravindran Kanesvaran, MD, MRCP, FAMS, Division of Medical Oncology, National Cancer Centre Singapore, Singapore; Workgroup Members (Voting): Min-Han Tan, MBBS, FRCP, PhD, Division of Medical Oncology, National Cancer Centre Singapore, Singapore; Yew Oo Tan, MBBS, FAMS, Singapore Oncology Consultants, Singapore; Miah Hiang Tay, MBBS, MRCP, FAMS, Onco-Care Cancer Centre, Gleneagles Hospital, Singapore; Chee-Keong Toh, MBBS, MRCP, Division of Medical Oncology, National Cancer Centre Singapore, Singapore; Alvin Wong, MBBS, MRCP, Department of

Haematology-Oncology, National University Health System, Singapore; Workgroup Members (Non-Voting): Ruijun Cheng, BSc (Hons), Clinical Trials and Epidemiological Sciences Department, National Cancer Centre Singapore, Singapore.

Reviewers

Invited reviewers were Ian F Tannock, MD, PhD, DSc, Princess Margaret Cancer Centre, University of Toronto, Canada; Brian Rini, MD, Taussig Cancer Institute, USA; Daniel Heng, MD, MPH, FRCP, Department of Oncology, University of Calgary and Tom Baker Cancer Center, Canada. An additional invited reviewer chose to be anonymous.

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Supplementary Table 1. International Guidelines Reviewed

Guideline Title	NCCN Clinical Practice Guidelines in Oncology Prostate Cancer Version 1.2014	Prostate Cancer: Diagnosis and Treatment (CG175)	Prostate Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	Castration-Resistant Prostate Cancer: AUA Guideline	Systemic Therapy in Men with Metastatic Castrate-Resistant Prostate Cancer: American Society Clinical Oncology and Cancer Care Ontario Clinical Practice Guideline
Date Released	27 November 2013	8 January 2014	27 June 2013	April 2013	8 September 2014
Guideline Developer	National Cancer Comprehensive Network (NCCN), United States	National Institute of Health and Clinical Excellence (NICE), United Kingdom	European Society for Medical Oncology (ESMO)	American Urological Association (AUA)	American Society of Clinical Oncology (ASCO) and Cancer Care Ontario (CCO)
Description of Method of Guideline Validation	Statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Validation method not specified.	Guideline development group made up of health professionals, representatives of patient and carer groups and technical experts assesses the available evidence and makes recommendations. After the guideline development, group finalises the recommendations, the collaborating centre produces the final guideline. NICE formally approves the final guideline and issues its guidance to the NHS.	Recommendations developed from discussion at consensus conferences (CCs). Group decision-making that seeks the consensus of experts and the fulfillment of objectives. Guidelines are endorsed by the Japanese Society of Medical Oncology (JSMO).	This document was written by the Castration-Resistant Prostate Cancer Guidelines Panel of the American Urological Association Education and Research, Inc. Members of the Practice Guidelines Committee (PGC) included urologists, oncologists and other clinicians with specific expertise on this disorder. Guideline was approved by AUA Board of Directors in April 2013.	The ASCO Clinical Practice Guidelines Committee and CCO Program in Evidence-Based Care convened an expert panel with multidisciplinary representation in medical oncology, urologic oncology, radiation oncology, community oncology, patient advocacy, health services, implementation research, and guideline methodology. All ASCO guidelines are reviewed and approved by the ASCO Clinical Practice Guideline Committee on behalf of the ASCO Board before publication. All CCO guidelines are reviewed and approved by the CCO Report Approval Panel and a topic specific disease site group.
Target Population	Metastatic prostate cancer	Metastatic prostate cancer	Metastatic prostate cancer	Castrate-resistant prostate cancer	Metastatic castrate-resistant prostate cancer
mCRPC Recommendations	mCRPC: - maintain serum levels of testosterone 1. Asymptomatic: - sipuleucel-T - secondary hormone therapy: - anti-androgen - anti-androgen withdrawal - abiraterone acetate - enzalutamide - ketoconazole - corticosteroids	mCRPC: - anti-androgen - androgen deprivation - dexamethasone (0.5 mg daily) as third-line - abiraterone (post-docetaxel) - DES - corticosteroids	mCRPC: - continue androgen suppression - secondary hormonal therapy: - antiandrogen - ketoconazole - corticosteroids - abiraterone (post-docetaxel) - enzalutamide (post-docetaxel) - DES or other estrogen - CYP17 inhibitors	mCRPC: - continue androgen deprivation indefinitely 1. Survival and quality of life benefit: - abiraterone + prednisolone - enzalutamide - radium-223 for those with bone metastases - docetaxel chemotherapy	
mCRPC: Metastatic castration-resistant prostate cancer; PS: Performance status					

Supplementary Table 1. International Guidelines Reviewed (Con't)

Guideline Title	NCCN Clinical Practice Guidelines in Oncology Prostate Cancer Version 1.2014	Prostate Cancer: Diagnosis and Treatment (CG175)	Prostate Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	Castration-Resistant Prostate Cancer: AUA Guideline	Systemic Therapy in Men with Metastatic Castrate-Resistant Prostate Cancer: American Society Clinical Oncology and Cancer Care Ontario Clinical Practice Guideline
	- diethylstilboestrol or other estrogen - clinical trials 2. Symptomatic: - chemotherapy - abiraterone acetate - enzalutamide - clinical trial - best supportive care		- those with poor initial hormone response or severe symptoms, chemotherapy preferable	- ketoconazole/mitoxantrone/radiotherapy (for those unwilling to above 2) Chemo-naïve, symptomatic, poor PS: - abiraterone + prednisolone - ketoconazole/radiotherapy (for those unwilling to above two) - chemo in selected cases Postchemo, symptomatic, good PS: - abiraterone + prednisolone - enzalutamide - cabazitaxel - ketoconazole (if all 3 above unavailable) - rechallenge docetaxel Postchemo, symptomatic, poor PS: - palliative care - may offer abiraterone, enzalutamide, ketoconazole or radiotherapy 7 of 7 votes	2. Survival benefit but unclear quality of life benefit: - sipuleucel-T (asymptomatic or minimally symptomatic) - cabazitaxel chemotherapy (post-docetaxel) 3. No survival benefit and quality of life benefit: - mitoxantrone 4. Biological activity, unknown survival, unknown quality of life: - anti-androgens - ketoconazole - low-dose corticosteroid - palliative care should be offered to all patients.
Member Votes	-	-	-	-	-

mCRPC: Metastatic castration-resistant prostate cancer; PS: Performance status

Singapore Cancer Network (SCAN) Guidelines for Systemic Therapy of Metastatic Renal Cell Carcinoma (mRCC)

The Singapore Cancer Network (SCAN) Genitourinary Cancer Workgroup

Abstract

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Ann Acad Med Singapore 2015;44:406-14

Key words: Kidney cancer, Recommendations, Singapore

Address for Correspondence: Dr Ravindran Kanesvaran, Department of Medical Oncology, National Cancer Centre Singapore, 11, Hospital Drive, Singapore 169610.

Email: Ravindran.Kanesvaran@nccs.com.sg

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Introduction

Kidney cancer accounts for less than 1% of all cancers. There are over 200,000 new cases diagnosed with renal cell carcinoma (RCC) and over 100,000 deaths a year worldwide. It is slightly more common in men than in women, and is mainly detected in people in their middle age. In Singapore, kidney cancer (together with other urothelial cancers) ranks as the 9th most common cancer in males.¹

Since 2005, a number of new targeted agents have come into the local market for the treatment of this disease. With many of these therapies showing promising outcomes with improved progression-free survival (PFS) and overall survival (OS), it is important to discuss the timing, and sequencing of these drugs, specifically in the local setting.

The SCAN Guidelines for Systemic Therapy of Metastatic Renal Cell Carcinoma

The SCAN Guidelines are clinical practice guidelines for the front-line systemic treatment of newly diagnosed metastatic renal cell carcinoma (mRCC).

These first edition guidelines are intended to serve as treatment recommendations by members of this working group regarding their views on current existing international guidelines for the management of mRCC. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

Target Users of the Guidelines

The guidelines will be of interest to oncologists, oncology nurse specialists, pharmacists, allied health workers and general practitioners involved in the management of men and women with mRCC.

Guideline Recommendations/Development

The SCAN Genitourinary Cancer Workgroup comprises a panel of 7 medical oncologists from Singapore with special interests in the management of kidney cancer. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope.

Address for Correspondence: Dr Ravindran Kanesvaran, Department of Medical Oncology, National Cancer Centre Singapore, 11, Hospital Drive, Singapore 169610.

Email: Ravindran.Kanesvaran@nccs.com.sg

Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead with input from the workgroup members. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework² was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, high quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to address the 3 main management issues which were selected for this topic:

1. First-line Treatment of mRCC
2. Second-line Treatment of mRCC
3. Third-line Treatment of mRCC

Six international guidelines were selected for review (Supplementary Table 1):

- “NCCN Clinical Practice Guidelines Version 2.2014 Kidney Cancer” by the National Comprehensive Cancer Network (NCCN, USA)³
- “Guidelines on Renal Cell Carcinoma” by the European Association for Urology (EAU), 2013⁴
- “Renal Cell Carcinoma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up” by the European Society for Medical Oncology (ESMO), 2012⁵

- “Management of Advanced Kidney Cancer: Canadian Kidney Cancer Forum 2013 Consensus Update” from the Canadian Kidney Cancer Forum, 2013⁶
- National Institute for Health and Care Excellence (NICE) Guidance:
 - Technology Appraisal Guidance 169. Sunitinib for the First-line Treatment of Advanced and/or Metastatic Renal Cell Carcinoma⁷
 - Technology Appraisal Guidance 178. Bevacizumab (First-line), Sorafenib (First- and Second-line), Sunitinib (Second-line) and Temsirolimus (First-line) for the Treatment of Advanced and/or Metastatic Renal Cell Carcinoma⁸
 - Technology Appraisal Guidance 215. Pazopanib for the First-line Treatment of Advanced Renal Cell Carcinoma⁹
 - Technology Appraisal Guidance 219. Everolimus for the Second-line Treatment of Advanced Renal Cell Carcinoma¹⁰
- “Management of Kidney Cancer in Asia: Resource-stratified Guidelines” from the Asian Oncology Summit, 2012¹¹

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of mRCC, it will be reviewed earlier.

1. First-line Treatment of mRCC

First-line Treatment for Clear Cell mRCC

A number of first-line treatments have been approved and endorsed in many of the above international guidelines for use in clear cell mRCC patients based mainly on the Memorial Sloan Kettering Cancer Centre (MSKCC) prognostication criteria.¹² Here is the list of drugs approved and data to support its use. We have also included the NICE Incremental Cost Effectiveness Ratio (ICER) data to give an idea about the estimated relative cost-effectiveness of such drugs in the United Kingdom as there are no equivalent data in the local setting.

Sunitinib

Sunitinib was approved for use in the first-line based on the study by Motzer et al comparing it to interferon-alpha (IFN- α).¹³ It is indicated for patients with good and intermediate MSKCC prognostic risk.¹² Median OS was greater in the sunitinib group than in the IFN- α group (26.4 vs 21.8 months, respectively; hazard ratio [HR] = 0.821; 95% CI, 0.673 to 1.001; $P = 0.051$) per the primary analysis of unstratified log-rank test ($P = 0.013$ per unstratified Wilcoxon test). By stratified log-rank test, the HR was 0.818

(95% CI, 0.669 to 0.999; $P = 0.049$).¹⁴ The true benefit of sunitinib was likely more if not for the crossover allowed for in the study for patients who had progressed on IFN- α .

Pazopanib

Pazopanib was approved for use in the first-line in patients with MSKCC good and intermediate risk based on the study by Sternberg et al, comparing it to placebo.¹⁵ The difference in final OS between pazopanib- and placebo-treated patients was not statistically significant (22.9 vs 20.5 months, respectively; HR = 0.91; 95% CI, 0.71 to 1.16; one-sided $P = 0.224$). Early and frequent crossover from placebo to pazopanib and prolonged duration of crossover treatment confounded the OS analysis.¹⁶ In a recent study comparing sunitinib and pazopanib, pazopanib was found to be non-inferior to sunitinib.¹⁷

The base-case ICERs for pazopanib (including a 12.5% discount on the list price) compared with best supportive care, IFN- α and sunitinib were USD \$50,702, \$59,767 and \$2750 per quality-adjusted life year (QALY) gained, respectively.⁹

Temsirolimus

Temsirolimus was approved for use in the first-line setting specifically for MSKCC poor risk patients as defined by the poor risk criteria set by Hudes and team in that study.¹⁸ Patients who received temsirolimus alone had longer OS (HR = 0.73; 95% CI, 0.58 to 0.92; $P = 0.008$) and PFS ($P < 0.001$) than did patients who received interferon alone. OS in the combination-therapy group did not differ significantly from that in the interferon group (HR = 0.96; 95% CI, 0.76 to 1.20; $P = 0.70$). Median OS in the interferon group, the temsirolimus group, and the combination-therapy group were 7.3, 10.9, and 8.4 months, respectively.¹⁸ The indirect comparison of temsirolimus with best supportive care produced an ICER of USD \$124,781 per QALY gained.⁸

Bevacizumab and Interferon

Bevacizumab and interferon combination have been approved in the first-line setting for MSKCC good and intermediate risk patients.^{19,20} A total of 732 patients were enrolled. The median OS was 18.3 months (95% CI, 16.5 to 22.5) for bevacizumab plus IFN- α and 17.4 months (95% CI, 14.4 to 20.0) for IFN- α monotherapy (unstratified log-rank $P = 0.097$). Adjusting on stratification factors, HR was 0.86 (95% CI, 0.73 to 1.01; stratified log-rank $P = 0.069$) favouring bevacizumab plus IFN- α .²⁰

The comparison of bevacizumab plus IFN- α with IFN- α plus placebo produced a base-case ICER of USD \$115,241 per QALY gained.⁸ In Singapore, this combination is rarely used in view of the cost and toxicities related to its use.

High-dose Interleukin-2 (IL-2)

High-dose IL-2 can be used in a selected group of fit clear cell mRCC patients postnephrectomy with limited disease burden.^{21,22} Median duration for all complete responses has not yet been reached, but was at least 80 months (range, 7-131 months) at the time of this analysis. Median duration for all partial responses remains 20 months (range, 3-126 months). Median survival time for all 255 patients remains 16.3 months, with 10% to 20% of patients estimated to be alive 5 to 10 years after treatment with high-dose IL-2.²²

Active Surveillance

Observation after cytoreductive nephrectomy is an option that can be considered in a selected group of asymptomatic clear cell mRCC patients.²³ In this local study, 15 patients were put on active surveillance. At a median follow-up of 18 months, 80% of patients had progressed. However, a third of the patients had at least 6 months of progression-free interval, and 3 of 15 patients had not progressed at prolonged follow-up durations of 18, 23, and 46 months. A third of the patients remained alive and the median survival for the cohort was 25 months. Preoperative predictive factors for non-progression after debulking nephrectomy included absence of abnormal laboratory indices, single organ system metastases, and good performance status. A recent study of 52 patients by Rini et al also showed that a selected group of mRCC patients can be safely observed before any treatment is started.²⁴

First-line Treatment of Non-Clear Cell mRCC

No standard treatment is available and the patient should be treated in the framework of clinical trials if available. A number of recent randomised studies have shown that vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors (TKI) like sunitinib may be better than everolimus in treating these patients and are hence a reasonable option for these patients.^{25,26} Best supportive care can be offered as a reasonable option if the patient is not fit to receive further treatment.

Recommendations for First-line Treatment of mRCC

All the committee members who voted expressed preference for the Canadian guideline (Supplementary Table 1) because they listed clinical trials as the first option, followed by patient stratification by MSKCC, and they included observation as an option for first-line. All committee members agreed that tivozanib should not be a part of the local guidelines as data did not support its use.

For MSKCC Poor Risk Patients

It was noted that temsirolimus and sunitinib have both demonstrated their effectiveness in poor risk patients in clinical trials. Majority in the group (86%) held the opinion that pazopanib can be given to poor risk patients because of its better tolerability. One member (14%), however, disagreed, in view of the poor data supporting its use in poor risk patients. The member further elaborated that low-dose sunitinib²⁷ has a higher evidence of efficacy in poor risk patients. In the end, the majority (86%) voted to list pazopanib as a first-line option for poor risk patients, with an indication to mention the lack of strong level of evidence to it, and that pazopanib should only be used as an alternative to sunitinib. All members (100%) agreed everolimus should not be recommended as a first-line drug in poor risk patients. There was a unanimous vote to leave out the Asian resource-stratified guideline as it was broad and not relevant to our local setting (Table 1).

For Non-Clear Cell RCC (CCRCC) Patients

The committee noted that the Canadian guideline did not comment on non-CCRCC, NCCN included all drugs for non-CCRCC, and ESMO indicated the lack of standard therapy for non-CCRCC. The committee also discussed on the inclusion of temsirolimus, sunitinib and IFN- α for non-CCRCC. In view of the limited evidence on these drugs, all members who voted (100%) agreed to indicate 'no standard therapy', 'clinical trial preferred' and 'best

supportive care' for non-CCRCC, much like the EAU guidelines. The members agreed that they would treat the mixed histology group as CCRCC as long as there is a predominant clear cell component in the histology, except with regard to the use of high-dose IL-2, where they would only use it on pure clear cell patients. The group emphasised that best supportive care should be added as an option in the local guideline for first-line mRCC management (Table 1).

2. Second-line Treatment for mRCC

Cytokine Refractory

Sorafenib

Sorafenib has been approved for the treatment of mRCC patients after failure of cytokine therapy.²⁸ The median PFS was 5.5 months in the sorafenib group and 2.8 months in the placebo group (HR = 0.44; 95% CI, 0.35 to 0.55; $P < 0.01$). The first interim analysis of OS in May 2005 showed that sorafenib reduced the risk of death, as compared with placebo (HR = 0.72; 95% CI, 0.54 to 0.94; $P = 0.02$), although this benefit was not statistically significant according to the O'Brien-Fleming threshold. The comparison of sorafenib with best supportive care produced a base-case ICER of USD \$139,182 per QALY gained for the combined group.⁸

Sorafenib was also found to be superior to temsirolimus in the INTORSECT study which enrolled patients who had failed VEGF TKI.²⁹

Table 1. Singapore Cancer Network (SCAN) Guidelines for the Treatment of mRCC (Canadian Kidney Cancer Forum 2013 Guidelines)

First-line	Second-line	Third-line
<u>CCRCC</u> First Option: Clinical trials Good/Intermediate Risk: Sunitinib Bevacizumab + IFN- α Pazopanib High-dose IL-2 Active surveillance Poor Risk: Temsirolimus Sunitinib Pazopanib* Best supportive care	First Option: Clinical trials Cytokine Refractory: Sorafenib Pazopanib Axitinib Sunitinib Bevacizumab + IFN- α Best supportive care Prior VEGF Therapy: Everolimus Axitinib Anti-VEGF therapy not previously used Best supportive care	Anti-VEGF therapy not previously used† Best supportive care
<u>Non-CCRCC</u> No standard treatment available, patient should be treated in the framework of a clinical trial if available. Best supportive care is an option.	Prior MTOR: Anti-VEGF targeted therapy Best supportive care	

CCRCC: Clear cell renal cell carcinoma; VEGF: Vascular endothelial growth factor

*No strong supporting evidence, to be used only as an alternative to sunitinib.

†Patient should be educated of the lack of data guiding third-line treatment for mRCC.

Axitinib

Axitinib has been approved for the treatment of mRCC patients after cytokine failure.³⁰ Median OS was 20.1 months (95% CI, 16.7 to 23.4) with axitinib and 19.2 months (95% CI, 17.5 to 22.3) with sorafenib (HR = 0.969; 95% CI, 0.800 to 1.174; one-sided $P = 0.3744$). Median investigator-assessed PFS was 8.3 months (95% CI, 6.7 to 9.2) with axitinib and 5.7 months (95% CI, 4.7 to 6.5) with sorafenib (HR = 0.656; 95% CI, 0.552 to 0.779; one-sided $P < 0.0001$).

Pazopanib

Pazopanib was approved for use in the second-line after cytokine failure based on the study by Sternberg et al, comparing it to placebo.¹⁵

Prior VEGF TKI

Axitinib

Axitinib has been approved for the treatment of mRCC patients after VEGF TKI failure.³⁰

Everolimus

Everolimus has been approved for the treatment of mRCC patients after VEGF TKI failure.³¹ The median PFS was 4.9 months (everolimus) versus 1.9 months (placebo) (HR = 0.33; $P < 0.001$) by independent central review and 5.5 months (everolimus) versus 1.9 months (placebo) (HR = 0.32; $P < 0.001$) by investigators' review.³² The base-case ICER of everolimus versus best supportive care alone was reported as £89,547 per QALY gained.¹⁰

Recommendations for Second-line Treatment of mRCC

The workgroup voted 5 to 2 in support of the adaptation of the Canadian guideline (Supplementary Table 1), with the exclusion of tivozanib. The group suggested using the word anti-VEGF targeted therapy to make it clearer that drugs like 5-fluorouracil (5-FU) and tamoxifen should not be used. Besides the treatment options listed in the Canadian guidelines, it was also decided that best supportive care and clinical trials should be considered as part of the local treatment practice (Table 1).

3. Third-line Treatment of mRCC

No data is available. If the patient is physically fit to receive further treatment, there can be a discussion regarding the pros and cons of using a targeted therapy in the above list that has not been used before.

Recommendations for Third-line Treatment of mRCC

It was unanimously decided (100%) that the Canadian

guideline can be adapted (Supplementary Table 1). In addition, the group agreed that it should be made clear to patients of the lack of data guiding treatment in third-line. Similar to that of first- and second-line, best supportive care will be listed as an option for third-line (Table 1).

Conflicts of Interest

Dr Kanesvaran reports receiving advisory board fees from Pfizer, GSK and Bayer and speaker bureau fees from Pfizer and GSK; Dr Ng, receiving advisory board fees from Bayer and Astra Zeneca; Dr Tan, receiving grant support from Pfizer; and holding the following pending patents: "A Multigene Assay for Prognosis and Drug Response Prediction in Clear-Cell Renal Cell Carcinoma Patients that Identifies Distinct Biological Subtypes", "Method for Predicting Clinical Toxicities and Outcomes in Patients Receiving Sunitinib Using Gene Polymorphisms", "Self-Assembled Micellar Nanocomplexes Comprising Polyethylene Glycol-Epigallocatechin-3-Gallate Conjugates and Anticancer Drugs", "Antibody Specific for parafibromin, a New Marker of Parathyroid Carcinoma", licensed to Santa Cruz Biotechnology, and "Method for Determining Mutation Status in Colorectal Cancer Patients Using Allele-Specific PCR", licensed to AIT Biotech; Dr Tan, Ms Tan, Dr Tay, Dr Toh and Dr Wong have nothing to disclose.

Workgroup Members

The Members of the SCAN Genitourinary Cancer Workgroup are Section Lead and Workgroup Chairperson: Ravindran Kanesvaran, MD, MRCP, FAMS, Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Workgroup Members (Voting): Quan Sing Ng, MBBS, MD, MRCP, Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Min-Han Tan, MBBS, FRCP, PhD, Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Yew Oo Tan, MBBS, FAMS, Singapore Oncology Consultants, Singapore; Miah Hiang Tay, MBBS, MRCP, FAMS, Onco-Care Cancer Centre, Gleneagles Hospital, Singapore; Chee-Keong Toh, MBBS, MRCP, Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Alvin Wong, MBBS, MRCP, Department of Haematology-Oncology, National University Health System, Singapore; Workgroup Members (Non-Voting): Hui Shan Tan, BSc, MPH, Department of Medical Oncology, National Cancer Centre Singapore, Singapore.

Reviewers

Invited reviewers were Ian F Tannock, MD, PhD, DSc, Princess Margaret Cancer Centre, University of Toronto, Canada; Brian Rini, MD, Taussig Cancer Institute, USA; Daniel Heng, MD, MPH, FRCP, Department of Oncology, University of Calgary and Tom Baker Cancer Center, Canada. An additional invited reviewer chose to be anonymous.

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Supplementary Table 1. International Guidelines for the Treatment of mRCC

Guideline Title	NICE Guidance				Management of Kidney Cancer in Asia: Resource-Stratified Guidelines from the Asian Oncology Summit 2012
	1. Renal Cell Carcinoma-Sunitinib (TA169)	2. Renal Cell Carcinoma (TA178)	3. Renal Cell Carcinoma (First-line Metastatic)-Pazopanib (TA215)	4. Everolimus for the Second-line Treatment of Advanced Renal Cell Carcinoma (TA219)	
	Renal Cell Carcinoma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	Management of Advanced Kidney Cancer: Canadian Kidney Cancer Forum 2013 Consensus Update	Guidelines on Renal Cell Carcinoma (EAU)	Guidelines on Renal Cell Carcinoma (EAU)	
	NCCN Guidelines Version 2.2014 Kidney Cancer				
Date Released	2 December 2013	March 2013	7 October 2012	19 August 2013	November 2012
Guideline Developer	National Cancer Comprehensive Network (NCCN), United States	European Association of Urology (EAU)	European Society for Medical Oncology (ESMO)	Kidney Cancer Research Network of Canada (KCRNC)	NUHS, NCCS, SGH, Gleneagles Singapore, Christian Medical College India, University of Indonesia
Description of Method of Guideline Validation	Statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Validation method not specified.	Guidelines were developed through internal peer review. Appraisal of Guidelines for Research and Evaluation (AGREE) instrument was used to analyse and assess a range of specific attributes contributing to the validity of a specific clinical guideline. No formal external review prior to publication.	Recommendations developed from discussion at Consensus Conferences (CCs). Group decision-making that seeks the consensus of experts and the fulfilment of objectives.	Consensus statement was prepared on the basis of evidence from data published in peer-reviewed journals/texts/abstracts from renowned international congresses, such as AUA, ASCO, ESMO and EAU.	Statement was formulated by a panel of urologists, medical oncologists, and clinical oncologists from Asian countries, at a consensus session on kidney cancer that was held as part of the 2012 Asian Oncology Summit in Singapore.
Target Population	Metastatic RCC	Metastatic RCC	Metastatic RCC	Metastatic RCC	Metastatic RCC

AUA: American Urological Association; ASCO: American Society of Clinical Oncology; CCRCC: Clear cell renal cell carcinoma; mRCC: Metastatic renal cell carcinoma; NCCS: National Cancer Centre Singapore; NUHS: National University Hospital Singapore; PS: Performance status; RCC: Renal cell carcinoma; SGH: Singapore General Hospital; TKI: Tyrosine kinase inhibitor; VEGF: Vascular endothelial growth factor

Supplementary Table 1. International Guidelines for the Treatment of mRCC (Con't)

Guideline Title	NCCN Guidelines Version 2.2014 Kidney Cancer	Guidelines on Renal Cell Carcinoma (EAU)	Renal Cell Carcinoma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	Management of Advanced Kidney Cancer: Canadian Kidney Cancer Forum 2013 Consensus Update	NICE Guidance	
					1. Renal Cell Carcinoma– Sunitinib (TA169)	2. Renal Cell Carcinoma (TA178)
						Management of Kidney Cancer in Asia: Resource- Stratified Guidelines from the Asian Oncology Summit 2012
						3. Renal Cell Carcinoma (First-line Metastatic)- Pazopanib (TA215)
						4. Everolimus for the Second-line Treatment of Advanced Renal Cell Carcinoma (TA219)
Systemic Therapy	First-line (CCRCC): - Clinical trial - Sunitinib - Temsirolimus* - Bevacizumab + IFN- α - Pazopanib - High dose IL-2† - Sorafenib - Best supportive care	First-line (CCRCC, Good/Intermediate Risk): - Sunitinib - IFN α + bevacizumab - Pazopanib - IFN- α † - High-dose IL-2* First-line (CCRCC, Poor risk) - Temsirolimus	First-line (CCRCC, Good/Intermediate risk): - Sunitinib [§] - Bevacizumab + IFN- α [§] - Pazopanib [§] - Cytokines (including high-dose IL2)† - Sorafenib† First-line (CCRCC, Poor Risk): - Temsirolimus [§] - Sunitinib† - Sorafenib†	First Option: - Clinical trials First-line (Good/Intermediate Risk): - Sunitinib - Bevacizumab + IFN- α - Pazopanib - Tivozanib - High-dose IL-2* - Sorafenib* - Observation† First-line (Poor Risk): - Temsirolimus - Sunitinib*	TA169: Sunitinib: - Recommended as first-line treatment option for advanced mRCC who are suitable for immunotherapy and have ECOG PS of 0 or 1 TA178: Bevacizumab, Sorafenib, Temsirolimus: - Not recommended as first-line treatment options for advanced mRCC Sorafenib, Sunitinib: - Not recommended as second-line treatment options for advanced mRCC	According to Resource Level: 1. Basic First-line: - Best supportive care Second-line: Nil 2. Limited First-line: - IFN- α - Targeted therapy with assistance programme - Clinical trials Second-line: - Clinical trials 3. Enhanced First-line: - Most cost-effective approved first-line therapy - Clinical trials Second-line: - Most cost-effective second-line therapy - Clinical trials
	Second- & Subsequent-line (CCRCC): - Clinical trial Second- & Subsequent-line (Cytokine Refractory, CCRCC): - Axitinib	Second-line (CCRCC, Cytokine Refractory): - Sorafenib - Axitinib - Pazopanib Second-line (CCRCC, Cytokine Refractory): - Sorafenib - Axitinib - Pazopanib - Axitinib** - Sunitinib**	Second-line (CCRCC, Cytokine Refractory): - Sorafenib [§] - Pazopanib [§] - Axitinib [§] - Sunitinib** - Axitinib	Second-line (Cytokine Refractory): - Sorafenib - Pazopanib - Tivozanib - Axitinib	TA215: Pazopanib: - Recommended as first-line treatment option for advanced RCC without prior cytokine	
Member Votes						
7 of 7 votes						

AUA: American Urological Association; ASCO: American Society of Clinical Oncology; CCRCC: Clear cell renal cell carcinoma; mRCC: Metastatic renal cell carcinoma; NCCS: National Cancer Centre Singapore; NUHS: National University Hospital Singapore; PS: Performance status; RCC: Renal cell carcinoma; SGH: Singapore General Hospital; TKI: Tyrosine kinase inhibitor; VEGF: Vascular endothelial growth factor

Supplementary Table 1. International Guidelines for the Treatment of mRCC (Con't)

Guideline Title	NCCN Guidelines Version 2.2014 Kidney Cancer	Guidelines on Renal Cell Carcinoma (EAU)	Renal Cell Carcinoma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	Management of Advanced Kidney Cancer: Canadian Kidney Cancer Forum 2013 Consensus Update	NICE Guidance 1. Renal Cell Carcinoma– Sunitinib (TA169) 2. Renal Cell Carcinoma (TA178) 3. Renal Cell Carcinoma (First-line Metastatic)- Pazopanib (TA215) 4. Everolimus for the Second-line Treatment of Advanced Renal Cell Carcinoma (TA219)	Management of Kidney Cancer in Asia: Resource- Stratified Guidelines from the Asian Oncology Summit 2012
	- Sorafenib - Sunitinib - Pazopanib - Temsirolimus - Bevacizumab	Second-line (CCRCC, Prior TKI Therapy): - Axitinib - Sorafenib - Everolimus	Second-line (CCRCC, Prior TKI Therapy): - Everolimus[#] - Axitinib[#] - Sorafenib^{**}	- Sunitinib ^{††} - Bevacizumab + IFN- α ^{††} Second-line (Prior VEGF Therapy): - Everolimus - Axitinib - Targeted therapy not previously used^{††}	therapy and have ECOG PS of 0 or 1, and if the manufacturer provides 12.5% discount on the list price as agreed in the patient access scheme. TA219: Everolimus: - Not recommended for the second-line treatment of advanced RCC	4. Maximum First-line: - High-dose IL-2 in carefully selected patients - Any approved first-line therapy - Clinical trials
Member Votes	Second- & Subsequent-line (Prior TKI Therapy, CCRCC): - Everolimus - Axitinib - Sorafenib - Sunitinib - Temsirolimus - Bevacizumab - Pazopanib	Second-line (Non-CCRCC): - No standard treatment available	Second-line (Non-CCRCC) -no standard therapy -clinical trial -Temsirolimus^{**} -Sunitinib^{**} -Sorafenib^{**}	Second (Prior MTOR): - VEGF TKI^{††}		
	Second- & Subsequent-line (Others): - IL-2 - Best supportive care	Third-line (CCRCC Prior TKI Therapy): - Everolimus	Third-line (CCRCC, Prior 2 TKIs): - Everolimus[#]	Third-line (Any): - Targeted therapy not previously used		Second-line: - Any approved second-line therapy - Clinical trials
Member Votes	Second- & Subsequent-line (Non-CCRCC): - No specific recommendations	Third-line (Non-CCRCC): - No standard treatment available	Third-line (Non-CCRCC) -No standard therapy -Temsirolimus^{§§} -Sunitinib^{§§} -Sorafenib^{§§}	7 of 7 votes		

AUA: American Urological Association; ASCO: American Society of Clinical Oncology; CCRCC: Clear cell renal cell carcinoma; mRCC: Metastatic renal cell carcinoma; NCCS: National Cancer Centre Singapore; NUHS: National University Hospital Singapore; PS: Performance status; RCC: Renal cell carcinoma; SGH: Singapore General Hospital; TKI: Tyrosine kinase inhibitor; VEGF: Vascular endothelial growth factor
^{*}for poor prognosis patients; [†]for excellent PS and normal organ function; [‡]in selected patients; [§]standard; ^{||}option; ^{††}Less than level 1 evidence; ^{‡‡}standard; ^{§§}option; ^{||}Less than level 1 evidence

Singapore Cancer Network (SCAN) Guidelines for Neoadjuvant and Adjuvant Chemotherapy for Muscle-invasive Bladder Cancer

The Singapore Cancer Network (SCAN) Genitourinary Cancer Workgroup

Abstract

Introduction: The SCAN genitourinary cancer workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for neoadjuvant and adjuvant chemotherapy for muscle-invasive bladder cancer (MIBC). **Materials and Methods:** The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. **Results:** Three international guidelines were evaluated—those developed by the National Comprehensive Cancer Network (2014), the European Society of Medical Oncology (2011) and the European Association of Urology (2013). Recommendations on the use of neoadjuvant and adjuvant chemotherapy in MIBC were developed. **Conclusion:** These adapted guidelines form the SCAN Guidelines 2015 for neoadjuvant and adjuvant chemotherapy in MIBC.

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Introduction

In Singapore, bladder cancer is the ninth most common cancer in men. It is less frequent among women. A total of 675 new cases of bladder cancer were diagnosed between 2003 and 2007, with an estimated male to female ratio of 3:1.¹

At initial diagnosis, about 30% of patients present with muscle-invasive bladder cancer (MIBC). MIBC may be locally controlled with cystectomy or radiotherapy but up to 50% of patients ultimately die of distant metastases. These systemic relapses are due to occult micrometastases which may be eliminated by the use of chemotherapy in the perioperative or periradiotherapy period.

There is consistent Level I evidence demonstrating the efficacy of neoadjuvant chemotherapy (NACT) in MIBC. As for adjuvant chemotherapy (ACT) in MIBC, there is convergence of evidence of benefit, but not Level I data. Despite the demonstration of efficacy, the use of NACT and ACT is surprisingly low in the clinical setting.² Thus, there is a need to review the evidence for NACT and ACT for MIBC before or after cystectomy or radiotherapy in order to make recommendations for clinical practice.

The SCAN Guidelines for the Use of NACT or ACT for MIBC

The SCAN Guidelines are clinical practice guidelines for the use of NACT or ACT for MIBC.

These first edition guidelines are intended to serve as treatment recommendations by members of this working group reflecting their views on current existing international guidelines for the management of MIBC. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

Target Users of the Guidelines

The guidelines will be of interest to oncologists, urologists, allied health workers and general practitioners involved in the management of patients with MIBC.

Guideline Recommendations/Development

The SCAN Genitourinary Cancer Working Group comprises a panel of 7 medical oncologists from Singapore

Address for Correspondence: Dr Chee-Keong Toh, Department of Medical Oncology, National Cancer Centre Singapore, 11 Hospital Drive, Singapore 169610.

Email: toh.chee.keong@nccs.com.sg

with special interests in the management of genitourinary cancer. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICJME) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead with input from the workgroup members. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework³ was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, high quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to address the 2 main management issues which were selected for this topic:

1. Use of NACT for MIBC
2. Use of ACT for MIBC

Three international guidelines were selected for review (Supplementary Table 1):

- “NCCN Clinical Practice Guidelines in Oncology for Bladder Cancer Version 2.2014” by the National Cancer Comprehensive Network (NCCN, USA)⁴
- “Bladder Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up” by the European Society for Medical Oncology (ESMO), October 2011⁵
- “Guidelines on Muscle-Invasive and Metastatic Bladder Cancer: EAU Guideline” by the European Association of Urology (EAU), March 2013⁶

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of MIBC, it will be reviewed earlier.

1. Use of NACT for MIBC

The use of NACT has several advantages, including better tolerability of chemotherapy prior to surgery, assessment of chemosensitivity of primary tumour prior to resection, and chemotherapy is given when the burden of metastases is low. However, there are disadvantages and these include delayed surgery, which might compromise outcome in patients who do not respond to chemotherapy and overtreatment, which is a possibility as clinical staging has an accuracy of only 70%. Another problem with regard to the use of NACT is that its uptake is low as surgeons and urologists do not consistently refer to medical oncologists for NACT to be given.

Randomised controlled trials⁷⁻¹⁰ and meta-analyses^{11,12} have demonstrated the efficacy of NACT in MIBC. The MRC/EORTC randomised trial of neoadjuvant cisplatin/methotrexate/vinblastine (CMV) chemotherapy showed a survival benefit, with a reduction of risk of death by 16% (HR = 0.84; 95% CI, 0.72 to 0.99; $P = 0.037$, corresponding to an increase in 10-year survival from 30% to 36%) from CMV.^{9,10} The SWOG/Intergroup trial also showed improved survival for patients given NACT.⁷ After approximately 8.5 years of follow-up, there was a 25% reduction in the risk of death for patients treated with methotrexate/vinblastine/doxorubicin/cisplatin (MVAC) prior to cystectomy (HR = 0.75; 95% CI, 0.57 to 1.00; $P = 0.06$). Another randomised trial, the Nordic Cystectomy 1 trial, using NACT with doxorubicin and cisplatin, found a statistically significant effect of chemotherapy in patients with stages T3-T4a (5-year survival, 52% vs 37% for chemotherapy and control, $P = 0.03$).⁸

In the most recent meta-analysis with updated independent patient data published in 2005, there was a significant survival benefit associated with platinum-based combination chemotherapy (HR = 0.86; 95% CI, 0.77 to 0.95; $P = 0.003$), equivalent to a 5% absolute improvement in survival at 5 years. There was also a significant disease-free survival (DFS) benefit associated with platinum-based combination chemotherapy (HR = 0.78; 95% CI, 0.71 to 0.86; $P < 0.0001$), equivalent to a 9% absolute improvement at 5 years.¹³

The randomised trials that have shown survival benefit utilise cisplatin-based combination chemotherapy which mainly included CMV or MVAC for 3 cycles. Thus, the regimens of CMV or MVAC should be considered standards. Newer less toxic regimens (gemcitabine/cisplatin or dose-dense MVAC) have been shown to be equivalent in the more advanced metastatic setting^{14,15} but further

data on them are still unavailable and are unlikely to be available in the neoadjuvant setting. Although it is unlikely that there will be Level I data on the use of gemcitabine/cisplatin in the neoadjuvant setting, the ease of use and the better tolerability of this regimen make it a suitable alternative chemotherapy combination. In addition, the use of carboplatin in substitution for cisplatin is not advocated.

There is no data on cost-effectiveness of these recommendations, but an unsystematic estimate has suggested that NACT is associated with an increased cost of USD \$6000/quality-adjusted life year (QALY) gained.¹⁶

Recommendations for NACT in MIBC

The SCAN workgroup has voted 5 to 2 in support of the adoption of the EAU guidelines (Supplementary Table 1). Two of the workgroup members support the use of the ESMO guidelines.

There is unanimous agreement among the working group members that cisplatin-based chemotherapy is the standard of care for NACT. The EAU guidelines recommend cisplatin-based combination chemotherapy, without specifying specific regimens. Although there is no evidence to suggest that the newer chemotherapy regimens are as effective as the older ones in the neoadjuvant setting, the workgroup members do not exclude the use of the newer chemotherapy regimens due to better toxicity profiles.

The majority of the workgroup members agree with the EAU guidelines that NACT is not recommended for patients with poor performance status and/or impaired renal function.

2. Use of ACT for MIBC

Despite the fact that there is not enough evidence in favour of ACT, it is still much in use as some clinicians prefer the adjuvant approach. The advantages of ACT include more accurate pathological staging postsurgery, avoidance of overtreatment in patients with earlier stage disease and no delay in surgery, especially for patients who do not respond well to chemotherapy. The disadvantages include delay of chemotherapy due to prolonged postoperative recovery and difficulty in monitoring chemosensitivity of primary tumour as there is no measurable disease. As such, the panel feels the need to review the data and make recommendations.

To date, few published randomised trials have been performed comparing ACT and observation.^{17–20} In addition, these trials had a small sample size and methodological limitations including early termination of trials, poor patient accrual and lack of recommendations regarding salvage chemotherapy for relapse or metastases. Chemotherapy regimens also differed among the trials and a substantial number of patients randomised to the chemotherapy arm

did not receive chemotherapy or had less than 2 courses of chemotherapy.

There was no statistically significant improvement in overall survival (OS) in the trials that reported statistical comparisons between trial arms.^{17–20} DFS defined as the time from cystectomy until evidence of disease recurrence, was significantly prolonged in the ACT groups compared with controls.^{17,18,20} Results of the trials found that patients with more involved nodes were at higher risk of recurrence or death.^{17,19} Only one of the trials found, on subgroup analysis, that chemotherapy has benefit in time to progression and survival in patients with 1 lymph node involved.¹⁷ A meta-analysis based on 491 patients from 6 trials found an overall hazard ratio (HR) for survival of 0.75 (95% CI, 0.60 to 0.96; $P = 0.019$), suggesting a 25% relative reduction in the risk of death for chemotherapy compared to that of control.²¹ However, the impact of trials that stopped early, of patients not receiving allocated treatments or not receiving salvage chemotherapy on the results of this meta-analysis is not clear. Although there is unlikely to be any Level I evidence supporting the use of ACT, there is other evidence of benefit in health outcomes.²²

It is unclear, at the moment, whether immediate ACT is superior to chemotherapy at the time of relapse. Although there are a few long-term survivors with chemotherapy at relapse, this is very rare. In the largest trial to date, which involved 284 patients but was unfortunately stopped early due to poor accrual, immediate adjuvant cisplatin-based combination chemotherapy led to a statistically significant improvement in the secondary endpoint of progression-free survival (PFS) but a non-significant decrease in the primary endpoint of death.²³ The estimated absolute difference in 5-year PFS and OS was 17.3% (46.8% vs 29.5%) and 5.9% (53.6% vs 47.7%) between the 2 arms respectively.

Although there is no Level I evidence to support the routine use of ACT in patients with MIBC, there is data that suggests consistent benefit, including large community-based health outcome research studies.² In addition, as there is some evidence of a statistically significant benefit with regard to DFS, it is reasonable to discuss with patients for whom an improvement of DFS is important, especially for patients with extravesical extension and/or nodal involvement. Patients should be well informed of the scarce data available and the possible benefits and risks of chemotherapy must be discussed.

There is also no evidence that more modern or carboplatin-containing chemotherapy combinations are as effective in the adjuvant setting and that patients ineligible for cisplatin should not receive adjuvant chemotherapy.

There is no data on cost-effectiveness of these recommendations.

Table 1. Singapore Cancer Network (SCAN) Guidelines for NACT and ACT Chemotherapy for MIBC

Guideline Recommendations	
Use of NACT for MIBC	EAU Guidelines: Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival (Level Ia, Grade A). Neoadjuvant chemotherapy is not recommended in patients with PS >2 and/or impaired renal function (Grade B). Although there is no evidence to suggest that the newer chemotherapy regimens are as effective as the older ones in the neoadjuvant setting, the SCAN workgroup members do not exclude the use of the newer chemotherapy regimens due to better toxicity profiles.
Use of ACT for MIBC	ESMO Guidelines: Platinum-based combination not recommended for routine use (Level Ia, Grade A) but can be considered for node positive patients. There is unanimous agreement among the workgroup members that cisplatin-based chemotherapy is not recommended for routine use due to its limited clinical data and evidence. However, as many patients are referred only after surgery, ACT should be considered in patients with high risk of relapse, namely, those with extravesical extension and/or node positive disease due to the possible improvement in DFS.

ACT: Adjuvant chemotherapy; DFS: Disease-free survival; EAU: European Association of Urology; ESMO: European Society for Medical Oncology; MIBC: Muscle-invasive bladder cancer; NACT: Neoadjuvant chemotherapy; PS: Performance status

Recommendations for ACT in MIBC

The SCAN Workgroup voted 4 to 3 in support of the adoption of the ESMO guidelines⁵ (Supplementary Table 1). Two workgroup members support the use of EAU guidelines while 1 member preferred case by case individualised discussion for high risk patients.

There is unanimous agreement among the workgroup members that cisplatin-based chemotherapy is not recommended for routine use due to its limited clinical data and evidence. However, as many patients are referred only after surgery, ACT should be considered in patients with high risk of relapse, namely, those with extravesical extension and/or node positive disease due to the possible improvement in DFS (Table 1).

Conflicts of Interest

Dr Kanesvaran reports receiving advisory board fees from Pfizer, GSK and Bayer and speaker bureau fees from Pfizer and GSK; Dr Ng, receiving advisory board fees from Bayer and Astra Zeneca; Dr Tan, receiving grant support from Pfizer and holding the following pending patents: "A Multigene Assay for Prognosis and Drug Response Prediction in Clear-Cell Renal Cell Carcinoma Patients That Identifies Distinct Biological Subtypes", "Method for predicting Clinical Toxicities and Outcomes in Patients Receiving Sunitinib Using Gene Polymorphisms", "Self-Assembled Micellar Nanocomplexes Comprising Polyethylene Glycol-Epigallocatechin-3-Gallate Conjugates and Anticancer Drugs", "Antibody Specific for Parafibromin, a New Marker of Parathyroid Carcinoma", licensed to Santa Cruz Biotechnology, and "Method for Determining Mutation Status in Colorectal Cancer Patients Using Allele-Specific PCR", licensed to AIT Biotech; Dr Tan, Ms Tan, Dr Tay, Dr Toh and Dr Wong have nothing to disclose.

Workgroup Members

The Members of the SCAN Genitourinary Cancer Workgroup are Section Lead: Chee-Keong Toh, MBBS, MRCP, Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Workgroup Chairperson: Ravindran Kanesvaran, MD, MRCP, FAMS, Department of Medical Oncology,

National Cancer Centre Singapore, Singapore; Workgroup Members (Voting): Quan Sing Ng, MBBS, MD, MRCP, Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Min-Han Tan, MBBS, FRCP, PhD, Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Yew Oo Tan, MBBS, FAMS, Singapore Oncology Consultants, Singapore; Miah Hiang Tay, MBBS, MRCP, FAMS, Onco-Care Cancer Centre, Gleneagles Hospital, Singapore; Alvin Wong, MBBS, MRCP, Department of Haematology-Oncology, National University Health System, Singapore; Workgroup Members (Non-voting): Hui Shan Tan, BSc, MPH, Department of Medical Oncology, National Cancer Centre Singapore, Singapore.

Reviewers

Invited reviewers were Ian F Tannock, MD, PhD, DSc, Princess Margaret Cancer Centre, University of Toronto, Canada; Daniel YC Heng, MD, MPH, FRCPC, Department of Oncology, University of Calgary, Canada; Brian Rini, MD, Taussig Cancer Institute, USA. An additional invited reviewer chose to be anonymous.

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Supplementary Table 1. International Guidelines for the Treatment of Metastatic Bladder Cancer

Guideline Title	NCCN Clinical Practice Guidelines in Oncology Bladder Cancer Version 2.2014	Bladder Cancer: ESMO Clinical Practice Guidelines	Guidelines on Muscle-invasive and Metastatic Bladder Cancer: EAU Guidelines
Date Released	May 2014	October 2011	March 2013
Guideline Developer	National Cancer Comprehensive Network (NCCN), United States	European Society for Medical Oncology (ESMO)	European Association of Urology (EAU)
Description of Method of Guideline Validation	Guidelines are statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. All recommendations are Category IIA unless specified.	Guidelines are endorsed by the Japanese Society of Medical Oncology (JSMO).	Specialist multidisciplinary team. Comprehensive literature searches in the Cochrane Database of Systematic Reviews, Cochrane Database of Controlled Clinical Trials, and Medline and Embase on the Dialog/DataStar platform.
Target Population	Muscle-invasive bladder cancer, cT2 to T4.	Clinical stage II to III	T2-T4A muscle-invasive bladder cancer.
Neoadjuvant Chemotherapy	Cisplatin-based chemotherapy (Category I) • Dose-dense methotrexate, vinblastine, doxorubicin, cisplatin (MVAC) • Gemcitabine/cisplatin • Cisplatin, methotrexate, and vinblastine (CMV)	Platinum-based combination chemotherapy (Level I, Grade A)	Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival (Level Ia, Grade A). Neoadjuvant chemotherapy is not recommended in patients with PS >2 and/or impaired renal function (Grade B).
Member Votes	NIL	2 of 7 votes	5 of 7 votes
Adjuvant Chemotherapy	Cisplatin-based combination chemotherapy (Category IIB) based on pathologic risk (pT3-4 or positive nodes) if neoadjuvant chemotherapy was not given.	Platinum-based combination not recommended for routine use (Level I, Grade A) but can be considered for node-positive patients.	Adjuvant chemotherapy is under debate. Neither randomised trials nor a meta-analysis have provided sufficient data to support the routine use of adjuvant chemotherapy (Level Ia). Adjuvant chemotherapy is advised within clinical trials, but not as a routine therapeutic option (Grade A).
Member Votes	NIL	4 of 7 votes	2 of 7 votes
PS: Performance status			

Singapore Cancer Network (SCAN) Guidelines for Front-Line Systemic Therapy of Newly Diagnosed Advanced Epithelial Ovarian Cancer

The Singapore Cancer Network (SCAN) Gynaecological Cancers Systemic Therapy Workgroup

Abstract

Introduction: The SCAN gynaecological cancers systemic therapy workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for front-line systemic therapy of advanced epithelial ovarian cancer. **Materials and Methods:** The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. **Results:** Five international guidelines were evaluated—those developed by the National Comprehensive Cancer Network (2013), the European Society of Medical Oncology (2013), the National Institute of Health and Clinical Excellence (2011), the Scottish Intercollegiate Guidelines Network (2011) and the Greater Metropolitan Clinical Taskforce (2009). Recommendations on the role of systemic therapy with intravenous chemotherapy, intraperitoneal chemotherapy, anti-angiogenic agents and neoadjuvant chemotherapy in newly diagnosed advanced epithelial ovarian cancer were developed. **Conclusion:** These adapted guidelines form the SCAN Guidelines 2015 for front-line systemic therapy of advanced epithelial ovarian cancer.

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Introduction

Epithelial ovary cancer (EOC) is one of the most challenging cancers to treat and remains the most lethal of all gynaecological cancers worldwide.

Ovarian cancer is the fifth most common cancer and the seventh most common cause of cancer mortality amongst females in Singapore. Over the last 40 years, the incidence of ovarian cancer has climbed continuously from 6.2 per 100,000 (1973 to 1977) to 12.4 per 100,000 (2008 to 2012). A total of 1587 new cases of ovarian cancer were diagnosed between 2008 and 2012. The majority of women (70%) present with advanced disease (International Federation of Gynecology and Obstetrics (FIGO) stage III or IV) due to the lack of effective screening and “silent presentation”. Prognosis for advanced stage disease is poor—the 5-year age-standardised overall survival (OS) was 30.5% and 11.5% for stage III and stage IV disease, respectively.¹

Treatment of advanced EOC involves a 2-pronged

approach, with cytoreductive surgery and chemotherapy as the mainstays of primary therapy.

Cytoreductive surgery aims to remove all macroscopic disease as resection has consistently been shown by retrospective studies to be associated with improved progression-free survival (PFS) and OS.^{2,3} However, prospective randomised studies are lacking and whether or not diseases amenable to complete resection are biologically different from those which cannot be completely resected remains a controversial question.

For the last 15 years, the gold standard of care has been to administer platinum-taxane chemotherapy intravenously every 3 weeks postdebulking surgery. However, the optimal method of administering platinum-taxane chemotherapy remains to be determined. In recent years, variables such as the scheduling (dose-dense vs 3-weekly), route of drug administration (intraperitoneal (IP) vs intravenous (IV)) and the timing of chemotherapy (neoadjuvant vs frontline)

Address for Correspondence: Dr Lim Sheow Lei, Department of Gynaecological Oncology, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899.
Email: lim.sheow.lei@kkh.com.sg

have challenged the conventional platinum-taxane regimen. Targeted therapy is also making inroads into the front-line treatment of advanced EOC.

The SCAN Guidelines for Front-line Systemic Therapy of Advanced EOC

The SCAN Guidelines are clinical practice guidelines for the front-line systemic treatment of newly diagnosed advanced EOC. It includes guidelines for the treatment of FIGO stage II, III or IV EOC (based on the 1997 FIGO staging for ovary cancer) but excludes carcinosarcoma and non-epithelial cancer of the ovary.

These first edition guidelines are intended to serve as treatment recommendations by members of this working group reflecting their views on current existing international guidelines for the management of advanced EOC. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

Target Users of the Guidelines

The guidelines will be of interest to oncologists, oncology nurse specialists, pharmacists, allied health workers and general practitioners involved in the management of women with ovarian cancer.

Guideline Recommendations/Development

The SCANGynaecological Cancers Workgroup comprises a panel of 8 medical oncologists and 1 oncology pharmacist from Singapore with special interests in the management of gynaecological cancers. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead with input from the workgroup members. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework⁴ was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, high quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the

extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to answer the following questions pertaining to front-line systemic therapy for women with newly diagnosed advanced EOC:

1. What is the optimal IV chemotherapy regimen for advanced EOC following primary cytoreductive surgery?
2. What is the role of IP chemotherapy in women with optimally debulked advanced EOC?
3. What is the role of front-line bevacizumab?
4. What is the role of neoadjuvant chemotherapy in advanced EOC?

Five international guidelines were selected for review (Supplementary Table 1):

- “NCCN Guidelines for Ovarian Cancer Version 2.2013” by the National Cancer Comprehensive Network (NCCN, USA)⁵
- “Newly Diagnosed and Relapsed Epithelial Ovarian Carcinoma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up” by the European Society of Medical Oncology (ESMO), 2013⁶
- “SIGN 135. Management of Epithelial Ovarian Cancer. A National Clinical Guideline” by the Scottish Intercollegiate Guidelines Network (SIGN, UK), November 2013⁷
- “Ovarian Cancer: the Recognition and Initial Management of Ovarian Cancer (CG122)” by the National Institute of Health and Clinical Excellence (NICE, UK), 2011⁸
- “Best Clinical Practice. Gynaecological Cancer Guidelines 2009” by the Greater Metropolitan Clinical Taskforce (GMCT, Australasia)⁹

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of advanced EOC, it will be reviewed earlier.

1. What is the Optimal IV Chemotherapy Regimen for Advanced EOC Following Primary Cytoreductive Surgery?

Platinum-taxane Chemotherapy

As advanced EOC has a high risk of recurrence when treated with debulking surgery alone, chemotherapy following surgery is recommended. Platinum-paclitaxel has been the standard of care for the last 15 years, a consequence of 2 high quality landmark phase III randomised controlled trials (RCTs), the GOG 111 and EORTC-NCIC OV10. These trials demonstrated that cisplatin-paclitaxel combinations yield significant improvements in PFS and OS in women with advanced EOC following primary cytoreductive surgery as compared to cisplatin-cyclophosphamide chemotherapy.^{10,11}

Cisplatin versus Carboplatin

The combination carboplatin-paclitaxel has demonstrated similar efficacy as cisplatin-paclitaxel but has advantages such as a more favourable toxicity profile and added convenience due to it being administered in an outpatient setting. These advantages have been demonstrated in 2 non-inferiority phase III RCTs.^{12,13}

Carboplatin-paclitaxel has since become the worldwide standard of care in front-line treatment of EOC. The most commonly used schedule is carboplatin (AUC 5-6) in combination with paclitaxel (175 mg/m²), both administered intravenously every 3 weeks. Typically, 6 cycles of chemotherapy are given. There is no evidence to suggest that improved outcomes will be obtained with more than 6 cycles of chemotherapy.

Paclitaxel Intolerance

For women who are allergic to or intolerant of paclitaxel, carboplatin-pegylated liposomal doxorubicin (PLD) can be considered as an alternative, based on a single phase III RCT, the MITO-2 study.¹⁴ PLD (30 mg/m²) in combination with carboplatin (AUC 5) given every 3 weeks yielded similar PFS and OS as the paclitaxel (175 mg/m²) and carboplatin (AUC 5) combination.

Patients Unfit for Combination Chemotherapy

Women who are unfit for combination chemotherapy can be given single-agent carboplatin, as indicated by the International Collaborative Ovarian Neoplasm (ICON) 3 findings.¹⁵

Adding in a Third Cytotoxic Drug

To date, there have been at least 5 good quality phase III RCTs involving more than 6000 patients that investigate the

addition of a third cytotoxic drug to the standard platinum and paclitaxel combination, either as triplet therapy¹⁶⁻¹⁹ or as sequential doublets.²⁰ Not only did the addition of a third drug not improve survival outcomes, it also enhanced toxicities, in particular haematological toxicities.

Chemotherapy Scheduling: Dose-dense Chemotherapy

The rationale for dose-dense chemotherapy comes from the Norton-Simon hypothesis, which states that increasing the dose density of chemotherapy reduces the chance of emergence of resistant clones and improves efficacy by reducing the regrowth of tumour cells between treatment cycles.²¹

This concept was tested in a single large phase III RCT in Japan (NOVEL-JGOG 3062). In this trial, IV paclitaxel (80 mg/m²) given weekly in combination with IV carboplatin (AUC 6) given every 3 weeks resulted in significant improvement in PFS and OS in women with advanced EOC as compared to those of the standard IV carboplatin and paclitaxel regimen.²² Long-term follow-up results showed that at a median follow-up of 76.8 months, the median PFS was 28.2 months in the dose-dense arm (vs 17.5 months in the conventional group; HR = 0.76; 95% CI, 0.61 to 0.91; *P* = 0.0037) and the median OS was 100.5 months (vs 62.2 months in the conventional group; HR = 0.79; 95% CI, 0.63 to 0.99; *P* = 0.039). However, the dose-dense carboplatin-paclitaxel combination was associated with greater haematological toxicities leading to greater dose-delays and lower completion rates. Less than half of the patients completed treatment according to study protocol and 38% of patients stopped this regimen prematurely (vs 21% in the conventional group). Incidence of grade III or IV anaemia was significantly higher in the dose-dense arm (69% vs 44%; *P* < 0.001). Dose-dense chemotherapy is also more inconvenient due to the weekly treatment schedule. The overall quality of life (QoL) did not differ significantly between the 2 treatment groups.²³ However, according to the taxane subscale, QoL was significantly lower in the dose-dense group, a consequence of the increased neurotoxicity (*P* = 0.02).

A second dose-dense study, the MITO-7, was a recently published²⁴ phase III RCT that used a different chemotherapy schedule from the JGOG 3062. It administered IV carboplatin (AUC 2) in combination with paclitaxel (80 mg/m²) weekly in the treatment of EOC following primary debulking surgery. Although the weekly regimen has a more favourable toxicity profile compared with the conventional 3-weekly chemotherapy, contrary to the JGOG 3062, there was no difference in PFS between the 2 treatment arms. The OS data was immature. The findings of 2 other dose-dense studies, the GOG 262 (NCT 00951496) and the ICON 8 (NCT 01654146), are yet to be published.^{25,26}

Cost-effectiveness Analyses for Dose-dense Chemotherapy

An actual cost data collection was not performed by the JGOG 3062. However, a cost-effectiveness analysis using the Markov economic decision model found that dose-dense paclitaxel administered weekly is a cost-effective treatment option for advanced ovarian cancer.²⁷ The incremental cost-effectiveness ratio was USD \$4859 per progression-free life-year saved for the dose-dense weekly regimen as compared to the conventional 3-weekly regimen.

Recommendations for Front-line IV Chemotherapy Following Primary Cytoreductive Surgery

The SCAN workgroup has voted 6 to 2 in favour of the adoption of the SIGN guidelines⁷ for front-line IV chemotherapy following cytoreductive surgery (Table 1 and Supplementary Table 1) due to its comprehensive nature. The workgroup also recommends the discussion of dose-dense chemotherapy as a treatment option with patients.

There is unanimous agreement amongst the working

Table 1. Singapore Cancer Network (SCAN) Guidelines for Front-line Systemic Treatment for Advanced Epithelial Ovary Cancer

Guideline Recommendations	
What is the Optimal IV Chemotherapy Postprimary Cytoreductive Surgery?	SIGN Guidelines: Carboplatin is the platinum drug of choice in both single and combination therapy (A).
	Paclitaxel is recommended in combination therapy with platinum in the first-line postsurgery treatment of EOC where the potential benefits justify the toxicity of the therapy.
	In those unable to tolerate paclitaxel, pegylated liposomal doxorubicin or gemcitabine in combination with carboplatin can be used as an alternative (A).
	Patients who are unfit for combination therapy should be offered single-agent carboplatin (A).
	A third cytotoxic agent should not be added to carboplatin and paclitaxel (A).
What is the Role of IP Chemotherapy in Optimally Debulked Advanced EOC?	Dose-dense chemotherapy: Carboplatin AUC 6 (day 1 q21) and paclitaxel 80 mg/m ² (days 1, 8, 15 q21) may be considered for the treatment of first-line ovarian cancer. The increased toxicity and frequency of visits need to be discussed with the patient (B).
	ESMO Guidelines: IP treatment has not been adopted as standard of care in view of its greater toxicity and difficulty delivering all the planned treatment.
	Lack of current standard intravenous chemotherapy in the standard arms of the IP trials has made the interpretation of the results difficult.
What is the Role of Upfront Bevacizumab in Advanced EOC?	Recommends IP chemotherapy in the context of clinical trial.
	ESMO Guidelines: Bevacizumab is recommended for patients with poor prognostic features (as defined in ICON7 Trial):
	• stage IV • suboptimal debulking (I,B)
	Bevacizumab should be given with paclitaxel and carboplatin with a treatment duration of 1 year.
What is the Role of Neoadjuvant Chemotherapy in Advanced EOC?	Bevacizumab has been licensed by the EMA at 15 mg/kg for use with carboplatin and paclitaxel for ≤15 months or until progression.
	NCCN Guidelines: Consider neoadjuvant chemotherapy/primary interval cytoreduction (diagnosis by fine needle aspiration, biopsy or paracentesis) for patients with bulky stage III/IV who are poor surgical candidates due to high-risk comorbidity conditions or disease factors (Category I).
	Published data demonstrates that primary assessments and debulking by a gynaecologic oncologist results in a survival advantage. Patients being evaluated for neoadjuvant chemotherapy should be seen by a fellowship-trained gynaecologic oncologist prior to being considered a poor surgical candidate.

EMA: European Medicines Agency; EOC: Epithelial ovary cancer; ESMO: European Society for Medical Oncology; IP: Intraperitoneal; IV: Intravenous; NCCN: National Comprehensive Cancer Network; SIGN: Scottish Intercollegiate Guidelines Network

group members that platinum-taxane is the standard of care for front-line chemotherapy and that the SIGN guidelines are the most comprehensive of all guidelines reviewed as it recommends:

- Single-agent carboplatin in patients who are unable to tolerate combination chemotherapy.
- Carboplatin-pegylated liposomal doxorubicin in cases of taxane-intolerance.
- Against the addition of a third cytotoxic agent to platinum-taxane.

The role of dose-dense chemotherapy was more contentious. Two working group members felt that based on the JGOG 3062 data,²² there is sufficient evidence to support the use of dose-dense chemotherapy as a standard treatment. They therefore voted for the NCCN guidelines⁵ (Table 1) which endorses this mode of treatment as a Category 1 treatment. Six working group members felt that although the JGOG 3062 is a potentially practice-changing study, there exists a possibility that the results may be a chance finding or could be due to pharmacogenomics differences between the Japanese and Caucasian populations. In the absence of confirmatory trial data and in view of the increased toxicities and increased hospital visits associated with dose-dense treatment, they opined that pending the results of other dose-dense studies, dose-dense chemotherapy can only be considered an option and not a standard of care. Hence, they endorsed the SIGN guidelines which recommend dose-dense chemotherapy as a treatment option to be discussed with patients.

The workgroup acknowledges that there is no local data regarding front-line IV chemotherapy for advanced EOC.

2. What is the Role of IP Chemotherapy in Optimally Debulked Advanced EOC?

The natural history of ovarian cancer is transcoelomic spread and the disease is frequently confined to the peritoneal compartment at diagnosis and relapse. The benefit of administering chemotherapy directly into the peritoneal compartment is supported by pharmacokinetic data showing a multifold higher concentration of drug in the abdominal cavity. In 2006, the National Cancer Institute (NCI) published a meta-analysis of 8 randomised studies evaluating the benefit of IP chemotherapy. In the combined analysis of 6 of the 8 randomised studies, the hazard ratio (HR) for OS for IP versus IV therapy was 0.79 (95% CI, 0.70 to 0.89). The latest study by Armstrong et al comparing IP cisplatin and IP paclitaxel with the standard IV cisplatin and IV paclitaxel (GOG 172) was included. Although only 42% of patients on the IP chemotherapy arm completed all 6 cycles of therapy, on an intention-to-treat analysis, IP chemotherapy extended median OS by 16 months (66 months vs 50 months) in a

comparison with standard IV paclitaxel and IV cisplatin.²⁸ The most common toxicities were related to port catheter complications, increased nausea, vomiting and abdominal pain, and higher haematologic, metabolic and neurotoxicity.

Consequently, the NCI issued a clinical announcement in January 2006 regarding their position on the preferred treatment for optimally debulked stage III ovarian cancer.²⁹ This stated that, “Based on the results of 8 phase III clinical trials, the NCI is encouraging doctors to follow surgery with a combination of 2-drug delivery methods: IV and IP. The combined approach, though more toxic, extends OS for women with advanced ovarian cancer by about a year compared to IV drip alone.”

The NCCN guideline,⁵ in line with NCI, has recommended that stage II and III optimally debulked (<1 cm) patients with ovarian cancer who are eligible for chemotherapy should be informed of the option of IP chemotherapy versus IV chemotherapy (or be considered for participation in a clinical trial). The guideline recommends for all women to be counselled about the benefit of IP chemotherapy prior to surgery.

In contrast, the 2011 NICE guidelines⁸ were explicit in their recommendation against the use of IP chemotherapy except in the context of a clinical trial. While the NICE guideline development group placed importance on the improvements in disease-free survival (DFS) and OS associated with IP chemotherapy, they also recognised that IP chemotherapy was more toxic, complex to administer and expensive. The ESMO 2013 guidelines has also highlighted that IP chemotherapy has not been adopted as a standard of care in the majority of institutions and countries due to its greater toxicity and the difficulty in delivering the entirety of the planned treatment.⁶ The guidelines further recognise that much of the IV chemotherapy used in the control arms of reported IP chemotherapy trials are no longer considered current IV treatment standards.

In 2013, SIGN emphasised that IP chemotherapy may be considered as a first-line therapy for eligible women with advanced ovarian cancer, provided that it is delivered in a centre with appropriate expertise and that the potential for toxicities is fully explained.⁷ In contrast, the Australian 2009 GMCT guidelines indicate that IP chemotherapy is not recommended for patients who have significant intra-abdominal adhesions at the conclusion of their surgery as these adhesions may limit the distribution of the chemotherapy drug within the abdomen.⁹

Ongoing trials such as PETROC/OV21 (NCT00993655),³⁰ JGOG 3109 (NCT01506856)³¹ and GOG 252 (NCT00951496)³² are seeking to evaluate the benefit of IP chemotherapy against standard arms that incorporate weekly IV paclitaxel, bevacizumab and the use of IP carboplatin vis-à-vis cisplatin for the reduction of toxicity.

Cost-effectiveness Analyses

No cost-effectiveness analyses using local cost data and societal norms in Singapore have been performed. An analysis performed by the GOG based on an American perspective showed that compared to the IV paclitaxel and carboplatin regimen, the IP paclitaxel and cisplatin combination has an incremental cost-effectiveness ratio of USD \$180,022 per quality-adjusted life year (QALY) saved (using a 7-year time horizon).³³

Recommendations for IP Chemotherapy in Optimally Debulked Advanced EOC

The SCAN workgroup has voted 5 to 3 in favour of the adoption of the 2013 ESMO guidelines.⁶ The workgroup recognises that there exists no local efficacy and toxicity data on IP chemotherapy. The workgroup agreed that the current evidence-based schedule for IP chemotherapy as described in GOG 172 is associated with excess toxicity, more complex to administer and also that there is a lack of experience and familiarity with the procedure locally. In Singapore, the most commonly used regimen is the JGOG dose-dense chemotherapy which has been shown to be superior to the standard 3-weekly IV paclitaxel and carboplatin regimen.²² As such, the SCAN workgroup has voted in support of the adoption of the 2013 ESMO guidelines⁶ for local patients (Supplementary Table 1).

3. What is the Role of Front-line Bevacizumab in Advanced EOC?

Bevacizumab is a humanised monoclonal antibody that binds vascular endothelial growth factor (VEGF) and prevents it from binding to its receptor. This blocks the growth and maintenance of tumour-associated blood vessels. In women with newly diagnosed EOC, postsurgical chemotherapy is given with a curative intent. Unfortunately, the vast majority of women still relapse. The incorporation of bevacizumab as part of the upfront treatment programme was evaluated in 2 randomised studies.

The first study conducted by GOG 0218 was a phase III randomised placebo-controlled study involving 1873 women with stage III or IV EOC who had undergone surgical cytoreduction.³⁴ At a median follow-up of 17 months, there was a significant increase in the median PFS in patients receiving upfront followed by maintenance bevacizumab as compared to when chemotherapy-alone is administered (14.1 vs 10.3 months, $P < 0.001$). This translates into a significant reduction in the risk of disease progression or death (HR = 0.72, 95% CI, 0.63 to 0.82). There was no improvement in OS (39.7 vs 39.3 months for the maintenance bevacizumab and chemotherapy-alone group respectively). PFS was not significantly increased

in patients who did not receive maintenance bevacizumab (they received upfront with placebo maintenance) when compared with the chemotherapy-alone group.

The second study by the ICON7 randomly assigned 1528 previously untreated women with high-risk early stage (I or IIA, clear cell or grade III) or advanced EOC to standard chemotherapy for 6 cycles with or without bevacizumab during chemotherapy, followed by maintenance treatment for 12 additional cycles.³⁵ Compared to standard chemotherapy, the incorporation of bevacizumab resulted in a significant improvement of the median PFS by 1.7 months at a follow-up of 42 months. For women with a high risk of progression (stage III with >1.0 cm residual disease at the end of surgery or stage IV), bevacizumab was associated with significant improvement in PFS (18.1 vs 14.5 months) and OS (36.6 vs 28.8 months). However, this analysis was a posthoc subgroup analysis. In the final survival analysis at a median follow-up of 49 months, there was no difference in median OS (58 months for both arms using restricted means analysis). Women with high risk of progression experienced a lengthening of survival by 4.8 months from 34.5 months to 39.3 months.

In both studies, bevacizumab-containing treatments were associated with greater toxicities. There were higher incidences of grade III and IV adverse events (66% vs 56% in control group),³⁵ hypertension and gastrointestinal-wall disruption.³⁴⁻³⁵ Global QoL was not improved by the addition of bevacizumab.³⁴⁻³⁷

Cost-effectiveness Analyses

Actual cost data was not collected in GOG 0218 or ICON 7. However, independent modelled cost-effectiveness analyses using available data on PFS and OS report that without improvement in OS, the use of bevacizumab as part of the front-line therapy for ovarian cancer is not cost effective.^{8,38-41} These analyses include an analysis by the UK NICE appraisal committee which reported a range of incremental cost-effectiveness ratios from £128,000 to £161,000 per QALY for the use of bevacizumab at its licensed dose of 15 mg/kg body weight with a treatment duration of 15 months or time horizon of 25 years or both.⁸ Treatment with maintenance bevacizumab leads to improved PFS but is associated with both direct and indirect costs.

Recommendations for Front-line Bevacizumab

The SCAN workgroup has voted in favour of the adoption of the ESMO guidelines. ESMO guidelines recommend the use of upfront bevacizumab with chemotherapy followed by maintenance bevacizumab for patients with poor prognostic features as defined in the ICON 7 trial.⁶ Bevacizumab is currently licensed by the European Medicines Agency

(EMA) at a dosage of 15 mg/kg for use with carboplatin and paclitaxel for less than 15 months or until progression.

The NCCN guidelines listed upfront bevacizumab with chemotherapy followed by maintenance therapy as a Category III recommendation as there were major disagreements within the NCCN Panel. Less than 50% of panel members agreed with the recommendation. It was felt that data from GOG 0218 and ICON 7 had not shown a statistically significant increase in OS and/or improved QoL.

Four out of 8 SCAN workgroup members concurred with the ESMO guidelines as it defined the role of bevacizumab comprehensively. However, while bevacizumab is licensed at a dose of 15 mg/kg in the European Union, SCAN workgroup members unanimously agreed that a dose of 7.5 mg/kg based on the ICON7 regimen is preferable due to the lower toxicities and cost involved. Three members expressed disagreement with regard to the NCCN guidelines, endorsing the widely differing opinions regarding the use of bevacizumab. One member agreed with the recommendation by the SIGN guidelines against upfront bevacizumab as cost-effectiveness analyses have shown that the treatment's cost does not justify its health benefits.

The workgroup acknowledges that there is currently no local data on upfront bevacizumab. The diverse views of the SCAN workgroup are reflected in the NCCN guidelines. The workgroup has voted in favour of the ESMO guidelines (Supplementary Table 1) but recommends the careful selection of patients when considering the use of upfront bevacizumab. Only patients with poor prognostic features as defined in ICON7 should be considered for upfront bevacizumab. The preferred dose of bevacizumab is 7.5 mg/kg as defined by the ICON7 regimen.

4. What is the Role of Neoadjuvant Chemotherapy in Advanced EOC?

There are 2 phase III trials on neoadjuvant chemotherapy in advanced EOC. The EORTC 55971⁴² randomised 718 women with stage III or IV ovarian cancer to neoadjuvant chemotherapy followed by interval debulking surgery or primary debulking surgery. There were no significant differences between the study groups with regards to OS (HR = 0.98; 95% CI, 0.82 to 1.18) or PFS (HR = 1.01; 95% CI, 0.86 to 1.17). In the EORTC 55971 study, there was increased debulking rate and reduced surgical complications in the neoadjuvant chemotherapy group. In the CHORUS study, a phase III randomised trial to investigate the timing of initial surgery in ovarian cancer,⁴³ patients with clinical stage III or IV ovarian cancer were randomised to primary surgery followed by 6 cycles of platinum-based chemotherapy or 3 cycles of neoadjuvant chemotherapy followed by surgery before another 3 cycles of platinum-based chemotherapy.

CHORUS was designed to demonstrate non-inferiority of neoadjuvant chemotherapy based on a 3-year survival of 50% with primary debulking surgery. A total of 550 women were randomised. Median tumour size was 8 cm, 25% FIGO IV and 19% World Health Organization (WHO) performance status 2. At a median follow-up of 3 years, the OS is superior for the neoadjuvant chemotherapy group (24.5 months vs 22.8 months; HR = 0.87; 80% CI, 0.76 to 0.98).

No cost-effectiveness analysis was done.

With regard to the EORTC trial, we are mindful of the fact that the accrued patients have very extensive and bulky disease as 73% had tumours of >5 cm and 47% had tumours of >10 cm at randomisation. Similarly, the median size of tumour in the CHORUS trial was 8 cm. Hence, the results of the trials on the role of neoadjuvant chemotherapy cannot be extrapolated to patients with less bulky disease. Furthermore, in a posthoc analysis in the EORTC trial, amongst patients with metastatic disease <5 cm in diameter at randomisation, the OS was slightly longer in the primary surgery group than in the neoadjuvant chemotherapy group (HR = 0.64; 95% CI, 0.45 to 0.93). Hence, rather than recommending neoadjuvant chemotherapy as an alternative for ovarian cancer patients with any stage or disease bulk, it is preferable to reserve neoadjuvant chemotherapy for selected patients with bulky stage III or IV disease, at the same time taking into account the resectability, age, stage, histology and performance status.⁴⁴

SCAN Workgroup Recommendations for Neoadjuvant Chemotherapy in Advanced EOC

All members of the workgroup unanimously voted for the NCCN guidelines as it endorses the use of neoadjuvant chemotherapy in patients who are poor surgical candidates due to comorbidities and disease factors. The NCCN recommends the involvement of gynaecologic oncologists in deciding if neoadjuvant chemotherapy should be given. As it does not specify the neoadjuvant chemotherapy regimen, it accommodates for the treating oncologist to make the judgement that best suits the patient's interests as some patients may not be able to tolerate standard combination chemotherapy.

Conflicts of Interest

Dr Chia reports receiving advisory board fees from GSK, Astra Zeneca and Bayer; Dr Lim, receiving travel support from Roche; Dr See, receiving accommodation and travel grants from GSK, conference support from GSK and Sirtex and advisory fees from Roche; Ms Foo, Dr Lim, Dr Lim, Dr Ngo, Dr Soh and Dr Tan have nothing to disclose.

Workgroup Members

The Members of the SCAN Gynaecological Cancers Systemic Therapy Workgroup are Section Lead and Workgroup Chairperson: Sheow Lei Lim, MBBS (Hons, Aust), MRCP (UK), MD (UK), Department of Gynaecological Oncology, KK Women's and Children's Hospital, Singapore; Workgroup Members (Voting): John WK Chia, MBBS, MRCP (UK), FAM (S'pore), Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Siew Eng Lim, MBBCh, Medl Onco (ABIM), Med Onco (FAMS), Department of Haematology-Oncology, National University Cancer Institute, Singapore; Yi Wan Lim, MBBChir, MRCP (UK), Department of Haematology-Oncology, National University Cancer Institute, Singapore; Lynette Ng, MBBS (S'pore), MMed (Int Med), MRCP (UK), Department of Medical Oncology, Raffles Cancer Centre, Singapore; Hui Ti See, MB ChB (Leicester), MRCP, FAMS (Med Oncology), Department of Medical Oncology, Parkway Cancer Centre, Singapore; Lay Tin Soh, MBBS (S'pore), FRCP (UK), FAMS, Department of Medical Oncology, National Cancer Centre Singapore, Singapore; David SP Tan, MRCP (UK) (Medical Oncology), PhD, Department of Haematology-Oncology, National University Cancer Institute, Singapore; Non-Voting Member: Koon Mian Foo, BSc (Pharmacy), BCOP, Department of Pharmacy, KK Women's and Children's Hospital, Singapore.

Reviewers

Invited reviewers were Peter Ang, MBBS (S'pore), MRCP (UK), M Med (Int Med), OncoCare Cancer Centre, Singapore; Xiaohua Wu, MD, PhD, Department of Gynecologic Oncology, Fudan University Shanghai Cancer Center, People's Republic of China. An additional invited reviewer chose to be anonymous.

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Supplementary Table 1. International Guidelines for the Systemic Treatment of Advanced Epithelial Ovarian Cancer

Guidelines Title	NCCN Clinical Practice Guidelines in Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Version 2.2013	Newly Diagnosed and Relapsed Epithelial Ovarian Carcinomas: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	SIGN - Management of Epithelial Ovarian Cancer. A National Clinical Guideline. SIGN Publication No. 135	Ovarian Cancer: The Recognition and Initial Management of Ovarian Cancer (CG122)	Best Clinical Practice Gynaecological Cancer Guidelines 2009, GMCT
Date Released	13 June 2013	July 2013	November 2013	May 2013	2009
Guideline Developer	National Cancer Comprehensive Network (NCCN), United States	European Society for Medical Oncology (ESMO)	Scottish Intercollegiate Guidelines Network (SIGN), United Kingdom	National Institute of Health and Clinical Excellence (NICE), United Kingdom	Greater Metropolitan Clinical Taskforce (GMCT)
Description of Method of Guideline Validation	Statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Validation method not specified.	Recommendations developed from discussion at consensus conferences. Group decision-making that seeks the consensus of experts and the fulfillment of objectives. Guidelines are endorsed by the JSMO.	SIGN is a collaborative network of clinicians, healthcare professionals and patient organisations that develops guidelines using a standard methodology based on a systematic review of the evidence for the NHS in Scotland. Recommendations are explicitly linked to the supporting evidence. NHS evidence has accredited the process used by SIGN to develop guidelines.	Guideline development group made up of health professionals, representatives of patient and carer groups and technical experts assesses the available evidence and makes recommendations. After the guideline development group finalises the recommendations, the collaborating centre produces the final guideline. NICE formally approves the final guideline and issues its guidance to the NHS.	Guidelines development working group that consists of gynaecological oncologists, radiation oncologists, medical oncologists, gynaecological pathologists, palliative medicine consultants, nurse oncologists from Australia's New South Wales, Queensland, Tasmania and New Zealand. The workgroup was tasked by the GMCT to review the Gynaecological Oncology Clinical Practice Guidelines that were originally published in 2004, using updated references and are intended to be evidence-based wherever possible.
Target Population	Advanced epithelial ovarian cancer.	Advanced epithelial ovarian cancer.	Advanced epithelial ovarian cancer.	Advanced epithelial ovarian cancer.	Advanced epithelial ovarian cancer.
Front-line Postoperative Chemotherapy	Carboplatin (AUC 5 – 7.5)/paclitaxel 175 mg/m² q3wk 6 cycles (Category I) Carboplatin (AUC 5 – 6)/docetaxel 60 – 75 mg/m² q3wk 6 cycles (Category I) <u>Dose-dense Chemotherapy:</u> Carboplatin AUC 6 (Day 1)/paclitaxel 80 mg/m² (Days 1, 8, 15); q3wk 6 cycles (Category I)	<u>Standard Chemotherapy:</u> Paclitaxel 175 mg/m² and carboplatin AUC 5 – 6, administered intravenously q3wks (1,A) Patients who develop an allergy to or do not tolerate paclitaxel – alternative regimen: • Carboplatin/docetaxel or • Carboplatin/pegylated liposomal doxorubicin (11,A)	Carboplatin is the platinum drug of choice in both single and combination therapy (A). Paclitaxel is recommended in combination therapy with platinum in the first line postsurgery treatment of epithelial ovarian cancer where the potential benefits justify the toxicity of the therapy. In those unable to tolerate paclitaxel, pegylated liposomal doxorubicin or gemcitabine in combination with carboplatin can be used as an alternative (A).	Paclitaxel in combination with a platinum-based therapy (cisplatin or carboplatin) should be the standard chemotherapy: • Paclitaxel 175 mg/m² in a 3-hour intravenous infusion, followed by a platinum every 3 weeks	Current recommendation is carboplatin/paclitaxel q3wks for 6 cycles.

EMA: European Medicines Agency; IP: Intraperitoneal; JSMO: Japanese Society of Medical Oncology; NHS: National Health Service; QOL: Quality of life; RCT: Randomised controlled trial

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		<u>Dose-dense chemotherapy:</u> In the absence of confirmatory data, dose-dense administration of paclitaxel currently can only be considered an option, and not as a standard of care (1,B). <u>Dose-dense chemotherapy:</u> Carboplatin AUC 6 (day 1) and paclitaxel 80 mg/m² (days 1, 8, 15) q3wk may be considered for the treatment of first-line ovarian cancer. The increased toxicity and frequency of visits need to be discussed with the patient (B). Recommendation: Where possible, patients should be enrolled in ongoing clinical trials in order to establish if this regime should become the standard of care. There are several ongoing studies that assess the efficacy of dose-dense paclitaxel (ICON8, GOG262, MITO7) and results are awaited.	Patients who are unfit for combination therapy should be offered single-agent carboplatin (A). A third cytotoxic agent should not be added to carboplatin and paclitaxel (A).		
Member Votes	6 of 8 votes				
Front-line Bevacizumab – Chemotherapy	Option to use bevacizumab-containing regimens per ICON-7 and GOG-218: Carboplatin AUC 6 /paclitaxel 175 mg/m²/bevacizumab 7.5 mg/kg q3wk x 5 – 6 cycles → continue bevacizumab for up to 12 additional cycles (Category III).	Recommended for patients with poor prognostic features: - stage IV, - suboptimal debulking (as defined in ICON7 trial) (1,B). Bevacizumab should be given with paclitaxel and carboplatin with a treatment duration of 1 year.	Not recommended – cost-effectiveness analysis has shown that the treatment's cost in relation to its health benefits is not sufficient.	Not recommended – bevacizumab does not provide benefit to justify its high cost.	Nil

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	Carboplatin AUC 6/paclitaxel 175 mg/m²/bevacizumab 15 mg/kg q3wk x 6 cycles. Bevacizumab started on Day 1 of cycle 2 q3wk for up to 22 cycles (Category III). Major disagreements among panel members, therefore Category 3. Recommendation: (data from the 2 phase III RCTs have not shown a statistically significant increase in overall survival and/or improved QOL) Encourage participation in ongoing clinical trials involving anti-angiogenesis agents.	Bevacizumab has been licensed by the EMA at 15 mg/kg for use with carboplatin and paclitaxel for ≤15 months or until progression.			
Member Votes	4 of 8 votes (majority)				
Front-line IP Chemotherapy	Stage II and III optimally debulked to <1 cm: - All women should be counselled regarding benefit of IP chemotherapy prior to surgery. - Day 1: IV paclitaxel 135 mg/m² over 3 or 24 hours; Day 2: IP cisplatin 75 – 100 mg/m²; Day 8: IP paclitaxel 60 mg/m²; q3wk 6 cycles. (Category I for stage III)	IP treatment has not been adopted as standard of care in view of its greater toxicity and difficulty delivering all the planned treatment. Lack of current standard intravenous chemotherapy in the standard arms of the IP trials has made the interpretation of the results difficult. Recommends IP chemotherapy in the context of clinical trial.	Chemotherapy which includes an IP element can be considered for women with a new diagnosis of epithelial ovarian cancer and residual disease ≤1 cm after primary surgery provided a regimen of proven benefit in a clinical trial compared to intravenous therapy is used, it is delivered in a centre with appropriate expertise and the potential toxicities are fully explained (B). Where possible, women receiving IP chemotherapy should be enrolled into ongoing clinical trials.	Toxicity +++, complex and expensive. Do not offer IP chemotherapy except in clinical trial.	IP chemotherapy is an option supported by Phase III trials for patients with low volume residual disease following surgery. However the reported benefits need to be balanced against the drawbacks of catheter-related morbidity, infection, and discomfort associated with treatment. IP chemotherapy is not recommended for patients who have significant intra-abdominal adhesions at the conclusion of their surgery as the adhesions may limit the distribution of chemotherapy within the abdomen.
Member Votes	5 of 8 votes				

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Supplementary Table 1. International Guidelines for the Systemic Treatment of Advanced Epithelial Ovarian Cancer (Cont)

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Front-line Neoadjuvant Chemotherapy	Consider neoadjuvant chemotherapy/primary interval cytoreduction (diagnosis by fine needle aspiration, biopsy or paracentesis) for patients with bulky stage III/IV who are poor surgical candidates due to high-risk comorbidity conditions or disease factors (Category I). Published data demonstrate that primary assessment and debulking by a gynaecologic oncologist results in a survival advantage. Patients being evaluated for neoadjuvant chemotherapy should be seen by a fellowship-trained gynaecologic oncologist prior to being considered a poor surgical candidate.	The use of chemotherapy with interval surgery is becoming more widely accepted and is offered to patients with poor performance status, low albumin levels and in those with very extensive tumour dissemination. Validation of this approach may come from further trials that are ongoing.	The use of neoadjuvant chemotherapy in women with stage IIIC or IV ovarian cancer may be considered as an alternative to primary debulking surgery (A). Good practice points: With regard to selecting who will benefit from neoadjuvant chemotherapy, treatment should be individualised to the patient taking into account resectability, age, histology, performance status and after ruling out the possibility of other primary tumours and full discussion at multidisciplinary meetings.	If performing surgery for women with ovarian cancer, whether before chemotherapy or after neoadjuvant chemotherapy, the objective should be complete resection of all macroscopic disease. NIL	
Member Votes	8 of 8 votes				

EMA: European Medicines Agency; IP: Intraperitoneal; JSMO: Japanese Society of Medical Oncology; NHS: National Health Service; QOL: Quality of life; RCT: Randomised controlled trial

Singapore Cancer Network (SCAN) Guidelines for the Systemic Therapy of Endometrial (Uterine) Cancer

The Singapore Cancer Network (SCAN) Gynaecological Cancers Systemic Therapy Workgroup

Abstract

Introduction: The SCAN gynaecological cancers systemic therapy workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for the systemic therapy of endometrial (uterine) cancer. **Materials and Methods:** The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. **Results:** Three international guidelines were evaluated—those developed by the National Cancer Comprehensive Network (2015), the European Society of Medical Oncology (2013) and the Cancer Council Australia (2011). Recommendations on the role of chemotherapy following surgery in women diagnosed with endometrial cancer, the chemotherapeutic options for women with advanced or recurrent endometrial cancers and the role of chemotherapy in women with uterine papillary serous carcinoma or clear cell carcinoma were developed. **Conclusion:** These adapted guidelines form the SCAN Guidelines 2015 for the systemic therapy of endometrial (uterine) cancer.

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Key words: ADAPTE, Chemotherapy, Evidence-based, Review

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Key words: ADAPTE, Chemotherapy, Evidence-based, Review

Introduction

Endometrial (uterine) cancer is the fourth most common cancer in women in Singapore and the most common cancer of the female genital tract. It accounts for 6.2% of all cancers in women.¹ The age standardised incidence rate for endometrial cancer has increased significantly over the last 40 years from 4.1 per 100,000 in 1973 to 1977 to 13.1 per 100,000 in 2008 to 2012.¹ Amongst the ethnic groups, the age standardised incidence rate was highest among the Indians.¹ The Singapore cancer registry estimates there will be 350 new cases this year.¹ Endometrial cancer which is usually diagnosed in early stage has a high curative rate. Despite the rising incidence, endometrial cancer is associated with a lower mortality, and is the eleventh most common cause of cancer death in females in Singapore. There were 203 deaths from endometrial cancer for the period 2008 to 2012.¹ The majority of cases diagnosed are in women under the age of 50 years. The peak age at diagnosis is 50 to 59 years of age. The majority of cases are stage I cancers.¹

There are several histological types of endometrial cancer. Among the subtypes endometrioid endometrial cancers

have a favourable prognosis and typically present at an early stage. Other histologic types (e.g. serous, clear cell) are associated with a poorer prognosis.

The management of endometrial cancer has traditionally consisted mainly of surgery and radiation therapy. However a recent randomised controlled trial showed improved outcomes from treatment with chemotherapy in patients with high risk disease.² Other studies on the role of chemotherapy with more diverse patient selection and treatment protocols showed more variable outcomes for chemotherapy. To reflect evolving standards of care and practice, there is a need to systematically review existing high quality expert guidelines and to formulate a set of clinical practice guidelines to best suit our patients and resources in Singapore.

The SCAN Guidelines for the Systemic Therapy of Endometrial (Uterine) Cancer

The SCAN Guidelines are clinical practice guidelines for the management of endometrial cancer. The guideline applies to women with endometrial (uterine) cancer, including uterine carcinosarcoma. The guideline does not

Address for Correspondence: Dr Lim Siew Eng, Department of Haematology-Oncology, National University Cancer Institute, Singapore, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074.
Email: siew_eng_lim@nuhs.edu.sg

apply to uterine leiomyosarcoma and endometrial stromal sarcoma.

These first edition guidelines are intended to serve as treatment recommendations by members of this working group regarding their views on current existing international guidelines for the management of endometrial cancer. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

Target Users of the Guidelines

The guidelines will be of interest to oncologists, oncology nurse specialists, pharmacists, allied health workers and general practitioners involved in the management of women with endometrial (uterine) cancer.

Guideline Recommendations/Development

The SCAN gynaecological cancers workgroup comprises a panel of 8 medical oncologists and one oncology pharmacist with special interests in the management of endometrial cancer. Membership of the workgroup was based on invitation of relevant Singapore medical oncology subspecialists. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by all members of the group. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework³ was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, high quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority

for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

The panel felt that the following questions regarding systemic treatment of endometrial cancer should be addressed in these guidelines given that they are commonly encountered scenarios for medical oncologists treating patients with these cancers in clinical practice. As such, these guidelines set out to answer the following questions pertaining to systemic therapy of endometrial (uterine) cancer (Table 1):

1. What is the role of chemotherapy following surgery in women diagnosed with endometrial cancer?
2. What are the chemotherapeutic options for women with advanced or recurrent endometrial cancers?
3. What is the role of chemotherapy in women with uterine papillary serous carcinoma or clear cell carcinoma?

Only guidelines that were updated in the last 2 years were reviewed. Three international guidelines were selected for review (Supplementary Table 1):

- “NCCN Clinical Practice Guidelines in Uterine Neoplasms” (version 2.2015) by the National Cancer Comprehensive Network (NCCN, USA)⁴
- “Endometrial Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up” by the European Society of Medical Oncology (ESMO) – 2013⁵
- “Clinical Practice Guidelines for the Treatment and Management of Endometrial Cancer” by Cancer Council Australia – 2014⁶

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of endometrial cancer, it will be reviewed earlier.

1. What is the Role of Chemotherapy Following Surgery in Women Diagnosed with Endometrial Cancer?

It was unanimously agreed by all members of the workgroup that the NCCN guidelines version 2.2015, regarding the use of adjuvant chemotherapy in endometrial (uterine) carcinoma (EC), were sufficiently comprehensive and evidence-based for it to be adopted in Singapore.

In the specific context of endometrioid EC, all members agreed that all FIGO (International Federation of Gynecology and Obstetrics) stage II (although rare), III and IV patients who have had their disease resected should be offered adjuvant chemotherapy. This is based on the results from the pooled analysis of 2 randomised clinical trials

Table 1. Singapore Cancer Network (SCAN) Guidelines for the Systemic Therapy of Endometrial (Uterine) Cancer

Guideline Recommendations	
What is the Role of Chemotherapy Following Surgery in Women Diagnosed with Endometrial Cancer?	NCCN Guidelines: It was unanimously agreed by all members of the workgroup that the NCCN guidelines version 2.2015, regarding the use of adjuvant chemotherapy in endometrial (uterine) carcinoma (EC), were sufficiently comprehensive and evidence-based for it to be adopted in Singapore. Adjuvant chemotherapy should be offered to patients with endometrial cancer stage III/IV. Chemotherapy could be offered to women with stage 1B or II, grade III, with adverse risk factors, due to higher risk of extrapelvic relapse and possible benefit.
What are the Chemotherapeutic Options for Women with Advanced or Recurrent Endometrial Cancers?	ESMO Guidelines: The group unanimously endorsed the ESMO guidelines 2013 on the treatment of advanced endometrial cancer as it was felt to be the most comprehensive among the 3 chosen guidelines. The use of taxane - platinum-based chemotherapy should be considered as standard of care (in comparison to platinum-non-taxane combination); while the use of hormones can be considered. There is data to support the role of mTOR inhibitors in patients with metastatic/recurrent endometrioid endometrial cancer following failure of first-line chemotherapy.
What is the Role of Chemotherapy in Women with Uterine Papillary Serous Carcinoma or Clear Cell Carcinoma?	NCCN Guidelines: The group unanimously endorsed the NCCN guidelines version 2.2015 on the treatment of uterine papillary serous carcinoma or clear cell carcinoma. All the members agree that chemotherapy should be recommended for all stages of UPSC/clear cell, including stage I disease. NCCN recommendations were considered to be the most comprehensive and to best represent the current evidence.

ESMO: European Society of Medical Oncology; NCCN: National Cancer Comprehensive Network; UPSC: Uterine papillary serous carcinoma

(NSGOEC-9501/EORTC-55991 and MaNGO ILIAD-III) that were undertaken to clarify if sequential combination of chemotherapy and radiotherapy improves progression-free survival (PFS) in high risk endometrial cancer.⁷ In the NSGO/EORTC study, combined modality treatment was associated with a 36% reduction in the risk for relapse or death (HR = 0.64; 95% CI, 0.41 to 0.99; $P = 0.04$). The result from the MaNGO-study pointed in the same direction (HR = 0.61), but was not significant. In combined analysis, the estimate of risk for relapse or death was similar but with narrower confidence limits (HR = 0.63; CI, 0.44 to 0.89; $P = 0.009$). Neither study showed significant differences in overall survival (OS). However, in combined analysis, OS approached statistical significance (HR = 0.69; CI, 0.46 to 1.03; $P = 0.07$) and cancer-specific survival was significant (HR = 0.55; CI, 0.35 to 0.88; $P = 0.01$). The results of these 2 studies suggest that addition of adjuvant chemotherapy to radiation improves PFS in endometrial cancer patients following surgical resection with no residual tumour and a high risk profile. However, it remains unclear if the addition of radiotherapy to chemotherapy improves the results.

There was, however, initially a difference in opinion regarding the role of adjuvant chemotherapy for patients with stage IA and IB fully staged uterine endometrioid cancer with grade III disease. Three workgroup members were not in favour of routinely offering chemotherapy to patients with stage IA/IB grade III endometrioid uterine carcinoma while 3 other members were of the opinion that these patients (especially those who are younger and/or who have additional risk factors for distant and/or vaginal recurrence e.g. lymphovascular and myometrial invasion)

should be offered adjuvant chemotherapy together with a detailed discussion on the lack of high quality clinical data regarding its risks and potential benefit or lack thereof for PFS and OS in this context. One member had no comments on the issue and 2 members were absent from the discussion. Two members quoted the results of a retrospective data analysis of patient outcomes with endometrioid uterine cancer from KK Women's and Children's Hospital (KKWCH) showing that patients with IC (i.e. new FIGO 2009 stage IB) grade III uterine cancers without adjuvant chemotherapy had a 5-year OS of 89% (unpublished data), hence suggesting that there is likely to be minimal OS benefit for the addition of chemotherapy. One member proffered the opinion that the KKWCH data was not a randomised controlled study of adjuvant chemotherapy in early stage uterine cancer and it would therefore be inappropriate to infer too much from this single retrospective unpublished study of a small number of patients as a basis to define guidelines for practice in Singapore. Furthermore, 64% of patients in the NSGOEC-9501/EORTC-55991 and MaNGO ILIAD-III pooled analysis who showed benefit for adjuvant chemotherapy had stage I disease (IC n = 190 [36%], IB n = 109 [20%], IA n = 44 [8.2%]),⁷ which would support the use of adjuvant chemotherapy in this subgroup of patients. Additionally, while the local data from KKWCH would suggest that OS outcomes for local patients with stage IB grade III are generally very good even without adjuvant chemotherapy, published data from other groups have also demonstrated improved disease-free survival and OS outcomes following adjuvant chemotherapy in early stage high risk endometrial cancer

(i.e. grade II-III, stage IB or II cancers with more than 50% myometrial invasion).⁸ In view of published data suggesting that the addition of chemotherapy may improve outcomes for women considered to be at the highest risk of distant and/or vaginal recurrence (i.e. outer one-third myometrial invasion, grade II-III, and the presence of lymphovascular invasion LVSI), one member felt cautious about adopting the practice of not offering chemotherapy to stage IB uterine cancers as a standard of care on the basis of this single retrospective study. In reply, a member mentioned further data collection would be performed to update this series and to further delineate the effect of adjuvant treatment in patients with stage IB uterine cancer in Singapore. Until then, the group endorses the NCCN version 2.2015 guidelines in its entirety, including the use of adjuvant chemotherapy in combination with radiotherapy in patients with stage IB disease with high risk features, which have been defined in the NCCN guidelines as age, positive lymphovascular invasion, tumour size, and lower uterine segment or surface cervical glandular involvement. For patients with high risk stage IA disease, 3 members were not in favour of routinely offering chemotherapy to patients with high risk features, while 4 were of the opinion that these patients (especially those who are younger and/or who have additional risk factors for distant and/or vaginal recurrence e.g. lymphovascular and myometrial invasion) should be offered adjuvant chemotherapy together with a detailed discussion on the lack of high quality clinical data regarding its risks and potential benefit or lack thereof for PFS and OS in this context.

In terms of the choice of adjuvant chemotherapy regimen, the working group would suggest 4 to 6 cycles of 3-weekly carboplatin and paclitaxel to be used as the regimen of choice in this setting. Our preference for carboplatin plus paclitaxel in the adjuvant setting is based on the results of GOG 209 (currently unpublished), which was presented at the 2012 Society of Gynecologic Oncology Annual Meeting.⁹ This trial compared carboplatin plus paclitaxel to the 3-drug regimen of paclitaxel, doxorubicin and cisplatin (TAP) in 1300 women with chemotherapy-naïve advanced uterine cancer, including women with stage III disease, and demonstrated that carboplatin and paclitaxel results in an equivalent overall response rate and similar PFS, but is also less toxic.⁹

There are currently no cost-benefit/cost-effectiveness analyses available with regard to the NCCN guidelines/recommendations on adjuvant chemotherapy of uterine cancer.

2. What are the Chemotherapeutic and Hormonal Therapy Options for Women with Advanced or Recurrent Endometrial Cancer?

The group unanimously endorsed the ESMO guidelines 2013⁵ on the treatment of advanced endometrial cancer as it was felt to be the most comprehensive among the 3 chosen guidelines.

Paclitaxel and platinum-based combination chemotherapy (carboplatin/paclitaxel) is the preferred first-line chemotherapy regimen for patients with advanced or recurrent endometrial cancer. In non-randomised trials, paclitaxel with carboplatin/cisplatin demonstrated a response rate of more than 60% and prolonged survival compared with historical non-paclitaxel based combination therapy. The results of GOG 2099 showed that the carboplatin and paclitaxel combination is non-inferior to the triple drug regimen in response rate and PFS, and is also less toxic.

The use of hormonal therapy can also be considered in certain circumstances. Hormonal therapy, mainly progestins, and less commonly tamoxifen or aromatase inhibitors, are recommended for endometrioid-type histology only. The predictors of response include well differentiated tumours, a long disease-free interval and site of disease (pulmonary metastases). The overall response rate to progestin is about 25%.

Endometrial cancer recurring after first-line chemotherapy is usually chemo-resistant. Various agents have been tested in small phase II trials. The PI3K/Akt/mTOR pathway is frequently upregulated in endometrial cancer because of the loss of the tumour suppression gene *PTEN*. There is emerging phase II data to support the role of mTOR inhibitors in patients with metastatic or recurrent endometrioid endometrial cancer following failure of first-line chemotherapy.¹⁰ The mTOR inhibitor temsirolimus has been reported to have a 24% response rate in chemotherapy-naïve patients. In previously treated patients, the response rate to temsirolimus is 4% with 46% disease stabilisation.¹⁰ Predictive factors of response to mTOR inhibitors have not yet been identified.

Our recommendation is to first treat with hormonal therapy for patients with endometrioid-type histology who are asymptomatic with low volume disease. Symptomatic disease or high-grade/large volume disease should be treated with platinum and taxane combination chemotherapy.

3. What is the Role of Chemotherapy in Women with Uterine Papillary Serous Carcinoma or Clear Cell Carcinoma?

The group unanimously endorsed the NCCN guidelines 2015 on the treatment of uterine papillary serous carcinoma (UPSC) or clear cell carcinoma. All the members agree that chemotherapy should be recommended for all stages of UPSC/clear cell, including stage I disease.

In comparison with endometrioid adenocarcinomas, uterine serous and clear cell carcinomas are more aggressive histologic types and are considered high risk endometrial cancers. There is a paucity of data to help inform treatment recommendations for this group of patients, and they should be encouraged to participate in clinical trials. Most of the data on chemotherapy in these subtypes are largely retrospective or derived from randomised trials that included patients with all histologies. Treatment options include radiation therapy, adjuvant chemotherapy or a combined approach (chemotherapy plus radiation therapy). There is considerable evidence from retrospective series that platinum-based adjuvant chemotherapy for early (stage I and II) disease improves PFS and OS.^{11,12} Platinum-based chemotherapy is recommended in patients with stage III or IV. The same chemotherapy regimens usually employed for epithelial ovarian cancer can be considered in women with advanced or recurrent serous or clear cell uterine cancer. Historically, serous endometrial carcinomas have not been considered to be hormone responsive.

Conflicts of Interest

Dr Chia reports receiving advisory board fees from GSK, Astra Zeneca and Bayer; Dr Lim, receiving travel support from Roche; Dr See, receiving accommodation and travel grants from GSK, conference support from GSK and Sirtex and advisory fees from Roche; Ms Foo, Dr Lim, Dr Lim, Dr Ngo, Dr Soh and Dr Tan have nothing to disclose.

Workgroup Members

The Members of the SCAN Gynaecological Cancers Systemic Therapy Workgroup are Section Lead: Siew Eng Lim, MBBS, BAO, LRCPSI, Department of Haematology-Oncology, National University Cancer Institute, Singapore; Workgroup Chairperson: Sheow Lei Lim, MBBS (Hons, Aust), MRCP (UK), MD (UK), Department of Gynae-oncology, KK Women's and Children's Hospital, Singapore; Workgroup Members (Voting): John WK Chia, MBBS, MRCP (UK), FAM (S'pore), Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Koon Mian Foo, BSc (Pharmacy), BCOP, Department of Pharmacy, KK Women's and Children's Hospital, Singapore; Yi Wan Lim, MBBS, MRCP (UK), Department of Haematology-Oncology, National University Cancer Institute, Singapore; Lynette Ng, MBBS (S'pore), MMed (Int Med), MRCP (UK), Department of Medical Oncology, Raffles Cancer Centre, Singapore; Hui Ti See, MB ChB (Leicester), MRCP (UK), FRCP (Edin), Department of Medical Oncology, Parkway Cancer Centre, Singapore; Lay Tin Soh, MBBS (S'pore), FRCP (UK), FAMS, Department of Medical Oncology, National Cancer Centre Singapore, Singapore; David SP Tan, BSc (Hons), MBBS (Hons, London), PG Dip (Oncology), Department of Haematology-Oncology, National University Cancer Institute, Singapore.

Reviewers

Invited reviewers were Peter Ang, MBBS (S'pore), MRCP (UK), M Med (Int Med), OncoCare Cancer Centre, Singapore; Xiaohua Wu, MD, PhD, Department of Gynecologic Oncology, Fudan University Shanghai Cancer Center, People's Republic of China.

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Supplementary Table 1. International Guidelines for the Treatment of Endometrial Cancer

Guideline Title	Endometrial Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	Clinical Practice Guidelines for the Treatment and Management of Endometrial Cancer	NCCN Clinical Practice Guidelines in Uterine Neoplasms (Version 2.2015)
Date Released	2013	2014	2015
Guideline Developer	European Society for Medical Oncology (ESMO)	Cancer Council Australia	National Cancer Comprehensive Network (NCCN), United States
Description of Method of Guideline Validation	Recommendations developed from discussion at consensus conferences (CCs). Group decision-making that seeks the consensus of experts and the fulfilment of objectives.	Working party develops clinical questions, searches literature, formulates recommendations and writes guideline chapters. Content is uploaded to Guidelines Wiki and undergoes public consultation prior to update. Annual working party meeting to review changes made by authors.	Statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Validation method not specified.
Target Population	Endometrial cancer	Endometrial cancer	Endometrial cancer
1. What is the Role of Chemotherapy Following Surgery in Women Diagnosed with Endometrial Cancer?	Could be considered for: - Stage IA, grade III with high risk features or stage IB with high risk features (age >65 years, lymphovascular positive, high tumour volume, cervical glandular involvement) (2B)* - Stage II with high risk features (2B)* - Stage III, stage IV	Should be considered for: - Stage I-III, completely resected high risk disease, particularly if high risk disease, and to encourage participation in trial using chemotherapy (level B)* - Stage III with residual disease - Stage IV	Could be considered for: - Stage IB, grade III, with adverse risk factor (2B)* - Stage II, grade III (2B)* - Stage IIIA – with or without chemotherapy, radiation therapy or both (stage IIIA is heterogeneous disease) - Stage IIIB, IIIC, IV (Based on updated staging FIGO/AJCC 2010)
Member Votes	All	All	All
2. What are the Chemotherapeutic Options for Women with Advanced or Recurrent Endometrial Cancers?	Carboplatin/paclitaxel preferred as first-line cytotoxics Hormonal therapy (mainly progestin therapy; tamoxifen or aromatase inhibitors can be considered) for endometroid histologies only	Sequential adjuvant chemotherapy either before or after radiotherapy, or given as part of a sandwich regimen (C)* Acceptable chemotherapy regimens include cisplatin and doxorubicin, or carboplatin and paclitaxel	Chemotherapy can be used for all carcinoma histologies Multi-agent chemotherapy regimens preferred Platinum-based chemotherapy preferred Hormonal therapy can be considered for endometroid histologies only with low-grade or asymptomatic or ER/PR positive
Member Votes	All	All	All
3. What is the Role of Chemotherapy in Women with Uterine Papillary Serous Carcinoma or Clear Cell Carcinoma?	Platinum-based chemotherapy for: - Stage I, II (3B)* - Stage III and IV (1A)*	Counselled that there is only very low evidence that adjuvant chemotherapy may have any impact on survival (level D)*	Considered for: - Stage IA without myometrial invasion (observe or chemotherapy) - Stage IA with myometrial invasion - Stage IB-4 Multi-agent platinum-based chemotherapy, if tolerated
Member Votes	All	All	All

ER/PR: Estrogen receptor/progesterone receptor

*() denotes level of evidence and strength of recommendation as predetermined by the guidelines.

Singapore Cancer Network (SCAN) Guidelines for Adjuvant Chemotherapy in Resected Non-Small Cell Lung Cancer

The Singapore Cancer Network (SCAN) Lung Cancer Workgroup

Abstract

Introduction: The SCAN lung cancer workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for the use of adjuvant systemic therapy for non-small cell lung cancer in Singapore. **Materials and Methods:** The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. **Results:** Five international guidelines were evaluated—those developed by the National Comprehensive Cancer Network (2014), European Society of Medical Oncology (2014), National Institute of Clinical Excellence (2012), Scottish Intercollegiate Guidelines Network (2014), and the Cancer Care Council Australia (2012). Recommendations on the selection of patients, chemotherapy regimen, treatment for stage I disease, treatment for positive margins and treatment options for pN2 disease with negative margins were produced. **Conclusion:** These adapted guidelines form the SCAN Guidelines 2015 for adjuvant systemic therapy of non-small cell lung cancer.

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Key words: Decision-making, Postoperative therapy

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Abstract

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Key words: Decision-making, Postoperative therapy

Introduction

In Singapore and also worldwide, lung cancer is one of the most common cancers and is also a leading cause of cancer-related deaths. In Singapore, there were 6558 cases of newly diagnosed lung cancer and 5628 deaths from 2009 to 2013. Lung cancer is the leading cause of cancer mortality among males and second highest among females in Singapore.¹ Approximately 15% of patients with non-small cell lung cancer (NSCLC) present in the early stage (stage I-II) where surgery is the mainstay of curative treatment.² Long-term survival however remains poor with distant failure being a major cause of relapse.

The role of adjuvant chemotherapy has been examined in multiple randomised controlled studies and several meta-analyses. Based on studies showing an improvement in 5-year overall survival of 4% to 15%,³⁻⁶ international guidelines have recommended adjuvant chemotherapy as the standard of care in patients with resected stage II-III NSCLC. However there are no local guidelines on treatment recommendations for local patients with resected stage II-III NSCLC.

The development and updating of high quality clinical practice guidelines requires extensive resources. As pre-existing guidelines are available and to reduce duplication of effort, guideline adaption has been formulated as an alternative to guideline development.⁷

Our objective is to produce local guidelines for adjuvant chemotherapy in patients with resected NSCLC by adapting pre-existing international guidelines.

The SCAN Guidelines for Adjuvant Systemic Therapy of NSCLC

The SCAN Guidelines are clinical practice guidelines for adjuvant chemotherapy in patients with resected NSCLC.

These first edition guidelines are intended to serve as treatment recommendations by members of this working group reflecting their views on current existing international guidelines for the management of NSCLC. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

Address for Correspondence: Dr Ross Soo, Department of Haematology-Oncology, National University Cancer Institute, Singapore, 1E Kent Ridge Road, NUHS Tower Block, Level 7, Singapore 119228.
Email: ross_soo@nuhs.edu.sg

Target Users of the Guidelines

The guidelines will be of interest to oncologists, oncology nurse specialists, pharmacists, allied health workers and general practitioners involved in the management of patients with NSCLC.

Guideline Recommendations/Development

The SCAN Lung Cancer Workgroup comprises a panel of 12 oncologists and 1 pharmacist from Singapore with special interests in the management of lung cancer. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework 7 was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, high quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to answer the following questions pertaining to the use of adjuvant chemotherapy in patients with NSCLC (Table 1):

1. Which patients are suitable?
2. What regimen should be used?

3. What is the role of adjuvant chemotherapy in stage I?
4. What treatment options are available for positive margins?
5. What are the treatment options for pN2 disease with negative margins?

Five international guidelines were selected for review (Supplementary Table 1):

- “NCCN Clinical Practice Guidelines for Non-Small Cell Lung Cancer” (version 5.2015) by the National Cancer Comprehensive Network (NCCN, USA)⁸
- “Early and Locally Advanced Non-Small-Cell Lung Cancer (NSCLC): ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up” by the European Society for Medical Oncology (ESMO), 2013⁹
- “NICE Pathways—Treatment for Non-Small-Cell Lung Cancer” by the National Institute for Health and Care Excellence (NICE, 2014)¹⁰
- “Management of Lung Cancer” by the Scottish Intercollegiate Guidelines Network (SIGN), 2014¹¹
- “Cancer Council Australia Lung Cancer Guidelines Working Party (CCCALCGWP) Clinical Practice Guidelines for the Treatment of Lung Cancer” by the Cancer Council Australia Lung Cancer Guidelines Working Party, 2014¹²

For each recommendation, the grade of recommendation as defined by the original guideline is given. The definition of the levels of evidence and grades of recommendation for each guideline are provided in the supplementary material. The level of evidence or grades of strength of their recommendation were not stated in the NICE guidelines.

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of NSCLC, it will be reviewed earlier.

1. Which Patients are Suitable?

The majority of randomised adjuvant trials studied patients with resected stage II-III NSCLC.⁶ The role of adjuvant chemotherapy in resected stage I NSCLC will be addressed in a later section. In a recent meta-analysis of individual patient data from 34 trial comparisons and 8447 patients, an absolute survival benefit of 4% (from 60% to 64%) at 5 years was seen with the addition of adjuvant chemotherapy with a hazard ratio [HR] of 0.86 (95% CI, 0.81 to 0.92; $P < 0.0001$).⁶ There is no local data available on the benefits of adjuvant chemotherapy in patients with NSCLC.

In the recent meta-analysis, it appeared there was an increasing relative effect of adjuvant chemotherapy on the

Table 1. Singapore Cancer Network (SCAN) Guidelines for the Use of Adjuvant Systemic Therapy for Non-Small Cell Lung Cancer

Guideline Recommendations	
1. Which Patients are Suitable?	SIGN Guidelines: 1. The risks and benefits of postoperative systemic anticancer therapy should be discussed with each patient (GPP). 2. Patients with good performance status (PS 0-1) and completely resected pathological stage II-III NSCLC with negative margins should be offered platinum-based postoperative systemic anticancer therapy (A).
2. What Regimen Should be Used?	CCCALCGWP Guidelines: Patients with completely resected stage II NSCLC should be offered 3-4 cycles of adjuvant cisplatin-based chemotherapy (A). Patients who have a good performance status (WHO 1, 2) and completely resected stage III non-small cell lung cancer should be offered adjuvant cisplatin-based chemotherapy (A).
3. What is the Role of Adjuvant Chemotherapy in Stage I?	NCCN Guidelines: 1. Observation is recommended for patients with T1ab, N0 tumours with negative surgical margins (Category 2A). 2. Patients with T2ab, N0 tumours with negative surgical margins are usually observed (Category 2A). 3. Chemotherapy for high risk features (include poorly differentiated tumours, vascular invasion, wedge resection, >4 cm, visceral pleural involvement, and incomplete LN sampling) (Category 2A).
4. What Treatment Options are Available for Positive Margins?	NCCN Guidelines: 1. Stage IA with R1 or R2: (1) re-resection (Category 2A) or (2) RT (Category 2B). 2. T2abN0: (1) re-resection +/- chemotherapy, (2) RT +/- chemotherapy (Category 2A). 3. Stage II positive margins with R1: (1) re-resection and chemotherapy, (2) chemo-radiation (either sequential or concurrent), with R2: (1) re-resection and chemotherapy or (2) concurrent chemo-radiation (Category 2A). 4. T1-3, N2 or T3N1 with R1: Chemo-radiation (either sequential or concurrent), with R2: concurrent chemo-radiation (Category 2A).
5. What are the Treatment Options for pN2 Disease with Negative Margins?	CCCALCGWP Guidelines: 1. Patients who have a good performance status and completely resected stage III NSCLC should be offered adjuvant platinum-based chemotherapy (A). 2. PORT in patients with pN2 disease is not recommended for routine use because of the lack of prospective randomised clinical trial data demonstrating an improvement in survival. PORT could be considered in selected patients with pN2 disease (C).

CCCALCGWP: Cancer Care Council Australia Lung Cancer Guidelines Working Party; ESMO: European Society for Medical Oncology; GPP: Good practice point; LN: Lymph node; NCCN: National Cancer Comprehensive Network; NICE: National Institute for Health and Care Excellence; NSCLC: Non-small cell lung cancer; PORT: Postoperative radiotherapy; SIGN: Scottish Intercollegiate Guidelines Network; WHO: World Health Organisation

improvement of performance status but it was noted very few patients with a performance status of ≥ 2 were included in the studies.⁶ Although age itself was not a contra-indication for adjuvant chemotherapy,¹³ in a larger analysis, no other subgroups defined by age, gender or histology benefited from adjuvant chemotherapy.⁶

Recommendations on Patient Inclusion

Following discussion, the workgroup has unanimously expressed support for the adoption of SIGN guidelines.

Recommendations are as follows:

1. The risks and benefits of postoperative systemic anticancer therapy should be discussed with each patient (Grade of recommendation: Good practice point).
2. Patients with good performance status (PS 0-1) and completely resected pathological stage II-III NSCLC with negative margins should be offered platinum based postoperative systemic anticancer therapy (A).

2. What Regimen Should be Used?

Most studies used a platinum based 2-drug combination administered in 3 to 4 cycles.⁶ No trials have compared different adjuvant chemotherapy regimens but based on the meta-analysis, it appears there are no significant differences between regimens. The LungAdjuvant Cisplatin Evaluation (LACE) meta-analysis, which included only modern cisplatin-based regimens, confirmed the survival benefits of adjuvant cisplatin (HR = 0.89; 95% CI, 0.82 to 0.96; $P = 0.005$) with 5-year absolute benefit of 5.4% from chemotherapy.¹⁴ All 5 guidelines have addressed the issue on what adjuvant chemotherapy regimen should be used (Supplementary Table 1).

Recommendations on Adjuvant Chemotherapy Regimen

Following discussion and consensus, the workgroup is in favour of adopting the CCCALCGWP Guidelines (Table 1).

Recommendations are as follows:

1. Patients with completely resected stage II NSCLC should

be offered 3 to 4 cycles of adjuvant cisplatin based chemotherapy (A).

2. Patients who have a good performance status (WHO 1, 2) and completely resected stage III NSCLC should be offered adjuvant cisplatin-based chemotherapy (A).

3. What is the Role of Adjuvant Chemotherapy in Stage I?

Most guidelines have recommended observation for T1ab, N0 NSCLC with negative margins (Supplementary Table 1). There is no evidence of a clear survival benefit for postoperative adjuvant chemotherapy for stage IA disease. The role of adjuvant chemotherapy in stage IB NSCLC remains controversial. There appears to be no benefit in patients with stage IA disease but there may be benefit in those with tumours >4 cm.^{15,16} In a phase III study of patients with resected stage IB NSCLC randomised to carboplatin/paclitaxel or observation (CALGB 9633), survival was similar in both arms (HR = 0.83; 95% CI, 0.64 to 1.08; $P = 0.12$). Posthoc exploratory analysis demonstrated a significant survival difference in favour of adjuvant chemotherapy for patients who had tumours ≥ 4 cm in size (HR = 0.69; 95% CI, 0.48 to 0.99; $P = .043$). In a retrospective analysis of an adjuvant study JBR.10,⁴ patients with tumours 4 cm or larger benefited from adjuvant chemotherapy (HR = 0.66; 95% CI, 0.39 to 1.14; $P = 0.13$).¹⁶ However, these analyses are posthoc and caution should be exercised in interpreting their significance.

Recommendations on the Role of Adjuvant Chemotherapy in Stage I

After review of the guidelines and by consensus, the workgroup is in favour of adopting the NCCN guidelines.

Recommendations are as follows:

1. Observation is recommended for patients with T1ab, N0 tumours with negative surgical margins (Category 2A).
2. Patients with T2ab, N0 tumours with negative surgical margins are usually observed (Category 2A).
3. Chemotherapy is recommended for high risk features (include poorly differentiated tumours, vascular invasion, wedge resection, >4 cm, visceral pleural involvement, and incomplete LN sampling) (Category 2A).

4. What Treatment Options are Available for Positive Margins?

Several guidelines have reviewed treatment options for positive margins and are summarised in Supplementary Table 1.

Recommendations on the Treatment Options Available for Positive Margins

By consensus, the workgroup has agreed to adopt the NCCN guidelines.

Recommendations are as follows:

1. Stage IA with R1 or R2: 1) re-resection (Category 2A) or 2) RT (Category 2B).
2. T2abN0: 1) re-resection +/- chemotherapy, 2) RT +/- chemotherapy (Category 2A).
3. Stage II positive margins with R1: 1) re-resection and chemotherapy, 2) chemo-radiation (either sequential or concurrent), with R2: 1) re-resection and chemotherapy or 2) concurrent chemo-radiation (Category 2A).
4. T1-3, N2 or T3N1 with R1: Chemo-radiation (either sequential or concurrent), with R2: concurrent chemo-radiation (Category 2A).

5. What are the Treatment Options for pN2 Disease with Negative Margins?

Postoperative radiotherapy (PORT) has been reported in a meta-analysis to have an adverse effect in patients after complete resection of clinical early stage NSCLC with pathological N0 or N1 disease whereas for patients with stage III, N2 disease there was no clear evidence of an adverse effect.¹⁷ However the results were limited by the inclusion of small randomised studies using older radiotherapy techniques and dosing regimens. In a population base analysis within the Surveillance, Epidemiology, and End Results database, patients with N2 nodal disease (HR = 0.855; 95% CI, 0.762 to 0.959; $P = 0.0077$).¹⁸ The Adjuvant Navelbine International Trialist Association (ANITA) study also reported postoperative radiotherapy improved survival in patients with N2 disease following adjuvant chemotherapy.¹⁹ Guidelines on treatment options for pN2 disease with negative margins are summarised in Supplementary Table 1.

Recommendations on the Treatment Options for pN2 Disease with Negative Margins

By consensus, the workgroup has adopted the CCCALCGWP guidelines.

Recommendations are as follows:

1. Patients who have a good performance status and completely resected stage III NSCLC should be offered adjuvant platinum-based chemotherapy (A).
2. PORT in patients with pN2 disease is not recommended for routine use because of the lack of prospective randomised clinical trial data demonstrating an improvement in survival. PORT could be considered in selected patients with pN2 disease (C).

Cost-effectiveness

The cost-effectiveness of adjuvant chemotherapy has been addressed in one study of patients.²⁰ In this study, a cost-effectiveness analysis of adjuvant chemotherapy from the perspective of Canada's public healthcare system was performed based on the study population derived from the landmark National Cancer Institute of Canada Clinical Trials Group JBR.10 adjuvant cisplatin-vinorelbine study.⁴ Ng and colleagues found the mean costs of treatment per patient in the observation and adjuvant chemotherapy arms were USD \$19,149 and \$25,110, respectively, with an incremental cost effectiveness ratio of USD \$5754 per life-year gained. The authors concluded adjuvant cisplatin and vinorelbine was a highly cost-effective treatment that compared favourably with other standard healthcare interventions.²⁰ No cost-benefit/cost-effectiveness analyses have been published locally.

Conclusion

Guidelines have recommended adjuvant chemotherapy as the standard of care in patients with resected stage II-III NSCLC. Clinical questions related to adjuvant therapy for patients with resected NSCLC were identified. Local data on adjuvant therapy in patients with resected NSCLC is lacking. The development of local guidelines from international treatment recommendations using the ADAPTE methodology was feasible. Future work to implement, review and revise the guidelines is warranted.

Conflicts of Interest

Dr Chang reports receiving advisory board fees from Pfizer, Celgene and BMS and lecture fees from MSD, Pfizer and BMS; Dr Tan, receiving research funding from Novartis and advisory board fees from Novartis, Boehringer Ingelheim and Pfizer; Dr Yeo, serving on advisory boards of Roche and Bayer; Ms Chew, Dr Chin, Dr Goh, Dr Leong, Dr Lim, Dr Lim, Dr Soo, Dr Tan and Dr Toh have nothing to disclose.

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Workgroup Members

The Members of the SCAN Lung Cancer Workgroup are Section Lead: Ross Soo, MBBS, FRACP, FAMS, Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore; Workgroup Chairperson: Darren Lim, MBBS, MRCP (UK), Division of Medical Oncology, National Cancer Centre Singapore, Singapore; Workgroup Members (Voting): Alex Chang, MD, Oncology, John Hopkins Singapore, Singapore; Lita Chew, BSc (Pharm), MMedSc (Oncology) (UK), Department of Pharmacy, National Cancer Centre Singapore, Singapore; Tan Min Chin, MBBS, MRCP (UK,

Edin), Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore; Boon Cher Goh, MBBS (S'pore), FAMS, FRCP (Edin), Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore; Swan Swan Leong, MBBS (S'pore), MRCP (UK), FAMS, OncoCare Cancer Centre, Singapore; Elaine Lim, FAMS, PhD, MBBChir, Singapore Oncology Consultants, Singapore; Hong Liang Lim, MBBS (S'pore), MMed (Int Med), FAMS (Med Onc), Parkway Cancer Centre, Singapore; Daniel Tan, MBBS (London), MRCP (UK), FAMS, Division of Medical Oncology, National Cancer Centre Singapore, Singapore; Tira Tan, BSc, MBBS, MRCP (UK), Division of Medical Oncology, National Cancer Centre Singapore, Singapore; Chee Keong Toh, MBBS, MRCP (UK), Division of Medical Oncology, National Cancer Centre Singapore, Singapore; Wee Lee Yeo, MBBS, MRCP (UK), FAMS (Med Onc), Oncology, John Hopkins Singapore, Singapore.

Reviewers

Invited reviewers were Gilberto Lopes, MD, MBA, Oncoclinicas Group, Brazil; Fergus Macbeth, MA, DM, FRCP, Wales Cancer Trials Unit, Cardiff University, UK.

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Supplementary Table 1. International Guidelines for Adjuvant Systemic Therapy of NSCLC

Guideline Title	Evidence Summary (Level of Evidence)	Recommendation (Grade of Recommendation)	Member Votes
1. Which Patients are Suitable?			
NCCN	NA	Stage II-III with negative surgical margins (Category I)	
	Postoperative SACT in patients with completely resected stage II to IIIa NSCLC confers an overall survival advantage of around 4% at 5 years (HR = 0.86; 95% CI, 0.8 to 0.92). The benefit appears to diminish with longer follow-up, possibly due to an increase in non-cancer deaths in those treated with SACT (Level I+).	Patients with good performance status (PS 0-1) who have completely resected NSCLC (stage II to IIIa) (A).	
SIGN	- There appears to be a correlation between an effect from SACT and better performance status, but very few patients with PS ≥ 2 were included in the trials (Level I++). - No other subgroup defined by sex, age or histology benefits more or less from adjuvant SACT (Level I++).	The risks and benefits of postoperative systemic anticancer therapy should be discussed with each patient (GPP).	13 of 13 votes.
NICE	NA	- Offer postoperative chemotherapy to patients with good performance status (WHO 0 or 1) and T1-3 N1-2 M0 NSCLC. - Ensure eligible patients have the benefit of detailed discussion of the risks and benefits of adjuvant chemotherapy.	
ESMO	NA	Adjuvant chemotherapy should be offered to patients with resected stage II or III NSCLC (I,A).	
CCCALCGWP	NA	For stage III NSCLC, caution is advised in recommending adjuvant cisplatin-based chemotherapy to good performance status patients who are 70 years of age or older and/or who have clinically significant cardio-respiratory or renal comorbidities (PP).	
2. What Regimen Should be Used?			
NCCN	NA	Cisplatin combined with vinorelbine, etoposide, vinblastine, gemcitabine, docetaxel or pemetrexed (Category IIA). For patients with comorbidities or unable to tolerate cisplatin, carboplatin combined with paclitaxel (Category IIA).	
SIGN	- Different SACT regimens were used in the trials but most contained platinum. - No particular SACT regimen appears better than any other (Level II+).	Platinum-based postoperative systemic anticancer therapy (A).	
NICE	NA	Offer a cisplatin-based combination chemotherapy regimen for adjuvant chemotherapy.	
ESMO	NA	A 2-drug combination with cisplatin is preferable (I, A).	
CCCALCGWP	- In patients with operable stage II NSCLC, the evidence supports the use of 3 to 4 cycles of adjuvant cisplatin-based chemotherapy (I, II). - In patients with completely resected stage III NSCLC, adjuvant cisplatin-based chemotherapy increases survival compared with observation. Further research is required to identify which stage III patients have the most favourable risk-benefit profile for adjuvant chemotherapy (I).	- Patients with completely resected stage II NSCLC should be offered 3 to 4 cycles of adjuvant cisplatin based chemotherapy (A). - Patients who have a good performance status (WHO 1, 2) and completely resected stage III non-small cell lung cancer should be offered adjuvant cisplatin-based chemotherapy (A).	13 of 13 votes.

CCCALCGWP: Cancer Care Council Australia Lung Cancer Guidelines Working Party; ESMO: European Society for Medical Oncology; GPP: Good practice point; LN: Lymph node; NA: Not applicable; NCCN: National Cancer Comprehensive Network; NICE: National Institute for Health and Care Excellence; NSCLC: Non-small cell lung cancer; PORT: Postoperative radiotherapy; PS: Performance status; PP: Practice point; RCT: Randomised controlled trial; SACT: Systemic anticancer therapy; SIGN: Scottish Intercollegiate Guidelines Network; WHO: World Health Organisation

Supplementary Table 1. International Guidelines for Adjuvant Systemic Therapy of NSCLC (Con't)

Guideline Title	Evidence Summary (Level of Evidence)	Recommendation (Grade of Recommendation)	Member Votes
3. What is the Role of Adjuvant Chemotherapy in Stage I?			
NCCN	NA	• Observation is recommended for patients with T1ab, N0 tumours with negative surgical margins (Category 2A). • Patients with T2ab, N0 tumours with negative surgical margins are usually observed (Category 2A). • Chemotherapy for high risk features (include poorly differentiated tumours, vascular invasion, wedge resection, >4 cm, visceral pleural involvement, and incomplete LN sampling) (Category 2A).	13 of 13 votes.
SIGN	• The benefit of adjuvant SACT in patients with stage I disease is less certain. There appears to be no benefit in patients with stage Ia disease but there may be benefit in those with tumours >4 cm. Further trials are required in this group (Level 1+).	NA	
NICE	NA	• Consider postoperative chemotherapy in patients with good performance status (WHO 0 or 1) and T2-3 N0 M0 NSCLC with tumours greater than 4 cm in diameter.	
ESMO	NA	• Consider in patients with resected stage IB disease and a primary tumour >4 cm [II, B].	
CCCALCGWP	• In studies of adjuvant chemotherapy for stage I NSCLC, stage IA patients were either excluded or represent a small percentage of the total number of included patients. There is no evidence of a clear survival benefit for postoperative adjuvant chemotherapy for stage IA disease (II). • Platinum-based adjuvant chemotherapy for patients with stage IB NSCLC has not been consistently demonstrated to provide a survival benefit. Meta-analyses reveal a small absolute survival benefit, in the order of 2% to 3%. A subgroup analysis from one randomised trial suggested that there may be a benefit for tumours greater than 4 cm in maximal diameter (II).	• Postoperative adjuvant chemotherapy is not recommended for stage IA NSCLC (B). • Platinum-based adjuvant chemotherapy is not recommended for all patients with stage IB NSCLC (B). • Based on the 7th edition of TNM classification, tumour size of >5 cm would fall under stage IIA. These patients may be considered for adjuvant chemotherapy (PP).	
4. What Treatment Options are Available for Positive Margins?			
NCCN	NA	• Stage IA with R1 or R2: 1) re-resection or 2) RT. • T2abN0: 1) re-resection +/- chemotherapy, 2) RT +/- chemotherapy (Category2B). • Stage II positive margins with R1: 1) re-resection and chemotherapy, 2) chemo-radiation (either sequential or concurrent), with R2: 1) re-resection and chemotherapy or 2) concurrent chemo-radiation (Category 2A). • T1-3, N2 or T3N1 with R1: Chemo-radiation (either sequential or concurrent), with R2: concurrent chemo-radiation (Category 2A).	13 of 13 votes.
SIGN	• Postoperative radiotherapy (PORT) has been shown to reduce local recurrence in the radiotherapy arm. • The PORT meta-analysis suggests an adverse effect of radiotherapy on survival with a hazard ratio of 1.21 (95% CI, 1.08 to 1.34), favouring surgery; 2-year survival with adjuvant RT was 48% versus 50% in the surgery alone group. A subsequent RCT examined the effect of PORT in pathological stage I patients and demonstrated a significant survival advantage in favour of RT (5-year survival 67% vs 58%, <i>P</i> = 0.048). It is not clear whether the adverse effect of PORT on survival applies to PORT using modern planning techniques and treatment technology (Level I++).	• Patients with NSCLC who have had complete tumour resection should not receive postoperative radiotherapy, except as part of a randomised trial (Grade A).	

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Supplementary Table 1. International Guidelines for Adjuvant Systemic Therapy of NSCLC (Con't)

Guideline Title	Evidence Summary (Level of Evidence)		Recommendation (Grade of Recommendation)	Member Votes
NICE	NA	NA		
ESMO	NA		• Postoperative radiotherapy in completely resected early-stage NSCLC is not recommended [I, A].	
CCCALCGWP	• A meta-analysis demonstrates no clear evidence of an adverse or beneficial effect of PORT on survival in patients with pN2 disease. The applicability of this finding to current day practice is questionable (Level I). • Data from 3 more recent but non-randomised studies suggest a survival benefit for PORT in pN2 disease (Level II, III-C).		• Postoperative radiation therapy in patients with pN2 disease is not recommended for routine use because of the lack of prospective randomised clinical trial data demonstrating an improvement in survival. The use of PORT could be considered in selected patients with pN2 disease (C).	
5. What are the Treatment Options for pN2 Disease with Negative Margins?				
NCCN	NA		• Sequential chemotherapy and radiotherapy (Category 1).	
SIGN	• Postoperative radiotherapy (PORT) has been shown to reduce local recurrence in the radiotherapy arm. • The PORT meta-analysis suggests an adverse effect of radiotherapy on survival with a hazard ratio of 1.21 (95% CI, 1.08 to 1.34), favouring surgery; 2- year survival with adjuvant RT was 48% versus 50% in the surgery-alone group. A subsequent RCT examined the effect of PORT in pathological stage I patients and demonstrated a significant survival advantage in favour of RT (5-year survival 67% vs 58%, <i>P</i> = 0.048). It is not clear whether the adverse effect of PORT on survival applies to PORT using modern planning techniques and treatment technology (Level I++).		• Patients with NSCLC who have had complete tumour resection should not receive postoperative radiotherapy, except as part of a randomised trial (Grade A).	
NICE	NA	NA		
ESMO	NA		• Postoperative radiotherapy in completely resected early-stage NSCLC is not recommended [I, A].	
CCCALCGWP	• A meta-analysis demonstrates no clear evidence of an adverse or beneficial effect of PORT on survival in patients with pN2 disease. The applicability of this finding to current day practice is questionable (Level I). • Data from 3 more recent but non-randomised studies suggest a survival benefit for PORT in pN2 disease (Level II, III-C).		• Postoperative radiation therapy in patients with pN2 disease is not recommended for routine use because of the lack of prospective randomised clinical trial data demonstrating an improvement in survival. The use of PORT could be considered in selected patients with pN2 disease (C).	13 of 13 votes.

CCCALCGWP: Cancer Care Council Australia Lung Cancer Guidelines Working Party; ESMO: European Society for Medical Oncology; GPP: Good practice point; LN: Lymph node; NA: Not applicable; NCCN: National Cancer Comprehensive Network; NICE: National Institute for Health and Care Excellence; NSCLC: Non-small cell lung cancer; PORT: Postoperative radiotherapy; PS: Performance status; PP: Practice point; RCT: Randomised controlled trial; SACT: Systemic anticancer therapy; SIGN: Scottish Intercollegiate Guidelines Network; WHO: World Health Organisation

Singapore Cancer Network (SCAN) Guidelines for the Use of Systemic Therapy in Advanced Non-Small Cell Lung Cancer

The Singapore Cancer Network (SCAN) Lung Cancer Workgroup

Abstract

Introduction: The SCAN lung cancer workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for the use of systemic therapy in advanced non-small cell lung cancer (NSCLC) in Singapore. **Materials and Methods:** The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. **Results:** Five international guidelines were evaluated—those developed by the National Comprehensive Cancer Network (2014), the European Society of Medical Oncology (2014), the National Institute of Clinical Excellence (2012), the Scottish Intercollegiate Guidelines Network (2014) and Cancer Care Council Australia (2012). Recommendations on systemic treatment for advanced NSCLC were produced. **Conclusion:** These adapted guidelines form the SCAN guidelines 2015 for systemic therapy of advanced or metastatic NSCLC.

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Key words: ADAPTE process, Asian population, Chemotherapy, Targeted therapy

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Introduction: The SCAN lung cancer workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for the use of systemic therapy in advanced non-small cell lung cancer (NSCLC) in Singapore. **Materials and Methods:** The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. **Results:** Five international guidelines were evaluated—those developed by the National Comprehensive Cancer Network (2014), the European Society of Medical Oncology (2014), the National Institute of Clinical Excellence (2012), the Scottish Intercollegiate Guidelines Network (2014) and Cancer Care Council Australia (2012). Recommendations on systemic treatment for advanced NSCLC were produced. **Conclusion:** These adapted guidelines form the SCAN guidelines 2015 for systemic therapy of advanced or metastatic NSCLC.

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Introduction

Non-small cell lung cancer (NSCLC) ranks as one of the most frequent cancers in Singapore with a total of 6407 new cases diagnosed from 2008 to 2012.¹ It remains the most lethal of all cancers, being the top cause of cancer death in men and second most lethal cancer in women.¹ Majority of patients (74.5%) are in advanced stages (III/IV) at point of diagnosis.¹

Over the past 2 decades, comprehensive genomic studies have led to significant advances in our understanding of the pathogenesis of NSCLC where therapeutically tractable molecular subgroups are increasingly delineated. Thus, NSCLC is no longer thought of as a single disease entity, but as several unique molecular and histological subtypes, each with peculiar clinical implications and potentially different standards of care.

The SCAN Guidelines for the Use of Systemic Therapy in NSCLC

The SCAN Guidelines are clinical practice guidelines for

the use of systemic therapy in NSCLC. It excludes small cell lung cancer.

These first edition guidelines are intended to serve as treatment recommendations by members of this working group reflecting their views on current existing international guidelines for the management of NSCLC. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

Target Users of the Guidelines

The guidelines will be of interest to oncologists, oncology nurse specialists, pharmacists, allied health workers and general practitioners involved in the management of patients with NSCLC.

Guideline Recommendations/Development

The SCAN Lung Cancer Workgroup comprises a panel of 12 oncologists and 1 pharmacist from Singapore with special interests in the management of lung cancer. Membership of

Address for Correspondence: A/Prof Darren Lim, Division of Medical Oncology, National Cancer Centre Singapore, 11 Hospital Drive, Singapore 169610.
Email: dmolwt@nccs.com.sg

the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope for guideline development: adjuvant lung cancer treatment and advanced lung cancer treatment. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework² was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, high quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to answer the following 7 key areas of the management of advanced NSCLC to provide recommendations on best practice (Table 1):

1. Pathological reporting and molecular subtyping
2. First-line treatment options for epidermal growth factor receptor (*EGFR*) sensitising mutation-positive advanced NSCLC
3. First-line treatment options for advanced NSCLC harbouring anaplastic lymphoma kinase (*ALK*) gene rearrangement
4. First-line chemotherapeutic options for advanced NSCLC with no driver mutation
5. Role of maintenance chemotherapy
6. Second-line chemotherapeutic options
7. Subsequent lines of treatment options

Five international guidelines were selected for review (Supplementary Table 1):

- “NCCN Clinical Practice Guidelines in Oncology—Non-small Cell Lung Cancer Version 4.2014” by the National Cancer Comprehensive Network (NCCN, USA)³
- “Metastatic Non-Small Cell Lung Cancer (NSCLC): ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up” by the European Society for Medical Oncology (ESMO), 2012⁴
- “NICE Pathway—Treatment for Non-Small Cell Lung Cancer” by the National Institute for Health and Care Excellence (NICE, 2014)⁵
- “SIGN 137: Management of Lung Cancer” by the Scottish Intercollegiate Guidelines Network (SIGN), 2014⁶
- “Clinical Practice Guideline for the Treatment of Lung Cancer” by the Cancer Council Australia, 2012⁷

The strength of the evidence and grade of recommendation of the international guidelines are reported and summarised. These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of NSCLC, it will be reviewed earlier.

1. Pathological Reporting and Molecular Subtyping

In the past, all histological subgroups of NSCLC were treated uniformly. There was limited use in expanding additional efforts in pathological reporting of a biopsy sample. In recent years, we have seen a paradigm shift in lung cancer treatment to one that is individualised according to histological subtyping. For example, life-threatening toxicities such as haemoptysis are associated with the use of bevacizumab in the treatment of squamous cell carcinoma (SCC) of the lung⁸ and pemetrexed shows benefit over gemcitabine-based platinum 2-drug chemotherapy in non-squamous NSCLC.⁹ *EGFR* mutations and *ALK* gene rearrangements are almost exclusively seen in lung adenocarcinomas.¹⁰ These genetic alterations have been well validated as targets for a molecularly directed systemic therapy. First-line treatment should an *EGFR*-sensitising mutation or *ALK* gene rearrangement be identified would be an *EGFR* tyrosine kinase inhibitor (TKI),^{11–13} crizotinib¹⁴ or ceritinib¹⁵ respectively. Emerging local data supports *ALK* testing in parallel with *EGFR* testing. Crizotinib can also be considered in those who possess genetic alteration in the *Ros1* gene.¹⁶

Recommendations on Pathological Reporting and Molecular Subtyping

There is unanimous agreement among the workgroup

Table 1. Singapore Cancer Network (SCAN) Guidelines for Systemic Therapy of Advanced NSCLC

Pathological Reporting and Molecular Subtyping	
• Diagnosis made according to WHO classification.	Category IIA
• If non-squamous in histology (Category I), never or former light smokers squamous histology (Level IV, A), small biopsy specimen or mixed histology, testing for <i>EGFR</i> activating mutations and <i>ALK</i> testing are recommended.	Category I (non-squamous) Level IV, A (never or former light smokers squamous)
• The workgroup supports detection of <i>ALK</i> translocation by fluorescence in situ hybridisation (FISH) as standard, however immunohistochemistry (IHC) and RT-PCR-based methods can be used if validated and qualified.	Category IIA
• If possible, parallel testing for molecular aberration is preferable to avoid delay in treatment.	Workgroup consensus
• <i>ROS1</i> testing can be considered.	Category IIA
• The workgroup also supports NCCN endorsement of broader molecular profiling with the aims of identifying tractable mutations and informing patients on the availability of clinical trials.	Category IIA
• Rebiopsy at disease progression should be considered.	Category IIA
First-line <i>EGFR</i> Mutation Positive	
• Either of the <i>EGFR</i> -TKI—gefitinib, erlotinib or afatinib—should be considered in the treatment of advanced NSCLC harbouring <i>EGFR</i> sensitising mutations.	Category I
• Should the mutation be discovered in the midst of first-line treatment, the systemic therapy can be interrupted or first-line chemotherapy can be completed prior to starting <i>EGFR</i> -TKI.	Category IIA
First-line <i>ALK</i> Mutation Positive	
• Clinical trials.	Category IIA
• Consider crizotinib as first-line treatment for <i>ALK</i> gene rearranged advanced lung cancer. The workgroup recommends a discussion with patients on the cost implications of this option prior to mutational testing.	Category I
• May switch to ceritinib if intolerant to crizotinib.	Category IIA
First-line Chemotherapy, Driver Mutation Negative	
• In fit patients, platinum doublet chemotherapy is recommended in the first-line treatment of advanced NSCLC.	Category I
• In view of better outcomes with the use of pemetrexed in non-squamous histology and in considering cost effectiveness, the workgroup is of the opinion that pemetrexed/platinum chemotherapy is preferable in the first-line treatment of non-squamous advanced NSCLC.	Workgroup consensus
• Addition of bevacizumab to platinum doublet is an option in non-squamous histology.	Category IIA
• The use of bevacizumab as well as pemetrexed is limited to those non squamous in histology.	Category IIA
• There is insufficient evidence to support the use of cetuximab for which the workgroup unanimously does not recommended in this setting.	Workgroup consensus
Maintenance Chemotherapy	
• In patients with good performance status of 0 – 1, continuation of pemetrexed (is recommended in non-squamous NSCLC if stable disease or response is seen following induction chemotherapy).	Level I, B
• In patients with non-squamous histology and good PS 0 – 1, should first-line chemotherapy be non-pemetrexed based, then switch maintenance to pemetrexed can be considered (Level I, B).	Level I, B
• In patients with all histology, switch to erlotinib can be considered (Level I, B) however the workgroup recommends this only if a sensitising <i>EGFR</i> mutation is detected (workgroup consensus).	Level I, B Workgroup consensus
Second-line Chemotherapy	
• The workgroup committee recommends consideration of clinical trials.	Workgroup consensus
• Docetaxel or pemetrexed (restricted to non-squamous in histology) can be considered in fit patients as second-line treatment of advanced lung cancer.	Level I, B
Subsequent Lines of Chemotherapy	
• The workgroup recommends first the consideration of clinical trials.	Workgroup consensus
• Erlotinib can be considered in the treatment of advanced lung cancer beyond second-line chemotherapy in patients with unknown <i>EGFR</i> status or <i>EGFR</i> -WT who have not received <i>EGFR</i> -TKI.	Level II, B
• Given the burgeoning pipeline of novel therapeutics addressing either distinct genetic drivers or resistance mechanisms, molecular profiling for “actionable” alterations either from archival tissue, or a repeat biopsy is also a reasonable consideration.	Workgroup consensus

ALK: Anaplastic lymphoma kinase; EGFR: Epidermal growth factor receptor; NCCN: National Comprehensive Cancer Network; NSCLC: Non-small cell lung cancer; PS: Performance status; RT-PCR: Reverse transcription polymerase chain reaction; TKI: Tyrosine kinase inhibitors; WHO: World Health Organization; WT: Wild type

members in adopting both the ESMO and NCCN guidelines.

1. Pathological diagnosis should be made according to WHO classification (Category IIA). If non-squamous in histology (Category I), never or former light smokers squamous histology (Level IV, A), small biopsy specimen or mixed histology, testing for *EGFR*-activating mutations and *ALK* testing are recommended.
2. The workgroup supports detection of *ALK* translocation by fluorescence in situ hybridisation (FISH) as standard, however immunohistochemistry (IHC) and reverse transcription polymerase chain reaction (RT-PCR)-based methods can be used if validated and qualified.
3. If possible, parallel testing for molecular aberration is preferable to avoid delay in treatment.
4. *ROS1* testing can be considered and if positive treatment with crizotinib may be considered as per NCCN guidelines (Category IIA).
5. The workgroup also supports NCCN endorsement of broader molecular profiling with the aims of identifying tractable mutations and informing patients on availability of clinical trials (Category IIA).
6. Rebiopsy at disease progression should be considered.

2. First-line Treatment Options for *EGFR* Sensitising Mutation Positive Advanced NSCLC

A substantially higher proportion of mutations in the *EGFR* tyrosine kinase is observed in Asian populations. Tumours that possess mutations in *EGFR* are highly sensitive to TKIs. Randomised phase III studies on various TKIs—gefitinib,¹⁷⁻²¹ erlotinib^{22,23} and afatinib^{12, 24} versus chemotherapy exist. *EGFR*-TKI treatment resulted in significantly increased overall response rates (ORR) (HR = 2.08; 95% CI, 1.75 to 2.46; $P \leq 0.0001$)²⁵ and in a meta-analysis of data from trials examining the role of *EGFR*-TKI in all major clinical settings, *EGFR*-TKI treatment was associated with a lower risk of disease progression in the first-line (HR = 0.43; 95% CI, 0.38 to 0.49; $P \leq 0.001$) and subsequent line setting (HR = 0.34; 95% CI, 0.2 to 0.6; $P \leq 0.001$).²⁶ To date, no phase III trial has demonstrated overall survival (OS) benefit with *EGFR*-TKI use.²⁶ This is likely confounded by treatment postprogression in both comparator arms.

Cost-effectiveness

The cost-effectiveness of *EGFR*-targeted therapy has been addressed in several papers.²⁷⁻²⁹ Of particular note, in a local analysis of the cost-effectiveness of *EGFR* testing followed by first-line gefitinib and second-line chemotherapy in *EGFR* mutants versus the practice of no

EGFR testing (e.g. by clinical phenotype alone), first-line chemotherapy followed by second-line gefitinib, it was demonstrated that the major driver of cost savings was not providing gefitinib to patients who are not likely to benefit supporting the implementation of *EGFR* mutation testing prior to initiation of first-line systemic therapy.²⁸ The calculated incremental cost and quality-adjusted life year (QALY) were USD \$15,197 and 0.27 with an incremental cost effective ratio (ICER) of USD \$56,916 per QALY.²⁸

Recommendations on First-line Treatment Options for *EGFR* Sensitising Mutation Positive Advanced NSCLC

The workgroup committee unanimously recommends adopting NCCN guidelines.

1. Either of the *EGFR*-TKIs—gefitinib, erlotinib or afatinib should be considered in the treatment of advanced NSCLC harbouring *EGFR*-sensitising mutations (Category II).
2. Should the mutation be discovered in the midst of first-line treatment, the systemic therapy can be interrupted or first-line chemotherapy can be completed prior to starting *EGFR*-TKI (Category IIA).

3. First-line Treatment Options for Advanced NSCLC Harbouring *ALK* Gene Rearrangement

Around 5% of NSCLC tumours harbour a novel fusion oncogene echinoderm microtubule-associated protein-like 4 gene (*EML4*) fused with *ALK* gene. These tumours are highly sensitive to therapy with *ALK* inhibitors.

Crizotinib is a multikinase inhibitor of *ALK* tyrosine kinase, mesenchymal epithelial transition growth factor (c-MET) and *ROS1* receptor tyrosine kinase. When compared to second-line chemotherapy (pemetrexed or docetaxel) in a phase III randomised controlled trial, treatment with crizotinib was associated with a significantly higher response rate of 65% vs 20% ($P < 0.001$), progression-free survival (PFS) of 7.7 months versus 3 months (HR = 0.49; 95% CI, 0.37 to 0.64; $P \leq 0.001$) and improvement in global quality of life.³⁰

Ceritinib is a second-generation *ALK* inhibitor with clinical activity demonstrated in patients whom have received prior crizotinib and in those who had not received crizotinib.¹⁵

Cost-effectiveness

The cost-effectiveness of *EML4*-*ALK* fusion testing and first-line therapy with crizotinib was analysed from the perspective of the Canadian public healthcare system. Molecular testing and first-line therapy with crizotinib cost an additional USD \$208,708 per QALY gained compared

with standard of care with no testing and no crizotinib treatment.³¹ The authors concluded that *EML4-ALK* fusion molecular testing and targeted therapy with crizotinib in their setting of low prevalence of *EML4-ALK* fusion gene and the high cost of crizotinib is not cost-effective.³¹

Recommendations on First-line Treatment Options for Advanced NSCLC Harboring *ALK* Gene Rearrangement

1. The workgroup unanimously recommends consideration of enrolment into clinical trials or to adopt NCCN guidelines for the consideration of crizotinib as first-line treatment for *ALK* gene rearranged advanced lung cancer (Category I). The workgroup recommends a discussion with patients on the cost implications of the option of crizotinib.
2. Patients who are intolerant to crizotinib may be switched to ceritinib (Category IIA).

4. First-line Chemotherapeutic Options for Advanced NSCLC Negative for Driver Mutation

Systemic platinum-based doublet chemotherapy is the preferred initial treatment option for patients with advanced NSCLC, good performance status and without a driver mutation. Chemotherapy in fit patients has been conclusively shown in a meta-analysis to improve OS when compared to best supportive care (HR = 0.77; 95% CI, 0.71 to 0.83; $P \leq 0.01$).³² A randomised study comparing 4 platinum-based chemotherapy regimens showed no significant advantage of 1 regimen over the other.³³ More recently, evidence from a phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed showed similar efficacy, median OS (10.3 vs 10.3 months, HR = 0.94; 95% CI, 0.84 to 1.05) with better tolerability.⁹ Importantly, a prespecified analysis of OS by treatment arm demonstrated a significantly better survival in patients with adenocarcinoma and large cell carcinoma treated with pemetrexed/cisplatin as compared to gemcitabine/cisplatin (12.6 months vs 10.9 months, HR = 0.84; 95% CI, 0.71 to 0.99; $P = 0.03$).

Subsequent trials have shown additional survival benefit with the addition of biologic agents such as bevacizumab. The Eastern Cooperative Oncology Group (ECOG) conducted a randomised study which showed a significant survival benefit of adding bevacizumab to paclitaxel plus carboplatin in the treatment of select patients with non-squamous NSCLC.³⁴ A systematic review and meta-analysis of trials adding bevacizumab to platinum-based chemotherapy in first-line treatment further confirms this survival benefit.³⁵

The role of cetuximab, an *EGFR* monoclonal antibody in the first-line treatment for advanced NSCLC remains to be defined and has not been approved for use in this patient population.^{36,37}

Cost-effectiveness

In a systematic review and economic evaluation of the clinical effectiveness and cost-effectiveness of first-line chemotherapy for advanced NSCLC, the preferred drugs for patients with advanced NSCLC are paclitaxel followed by gemcitabine and subsequently docetaxel.³⁸ In patients with non-SCC disease, pemetrexed/cisplatin is cost-effective with USD \$53,238 per QALY gained.³⁸ In a cost-utility assessment of bevacizumab, the ICER of bevacizumab and chemotherapy when compared with chemotherapy alone was USD \$560,000 per QALY.³⁹ Bevacizumab thus does not appear to be cost-effective when added to chemotherapy. There is no local data with regard to the cost-effectiveness of chemotherapy and or bevacizumab.

Recommendations on First-line Chemotherapeutic Options for Advanced NSCLC Negative for Driver Mutation

1. In fit patients, platinum doublet chemotherapy is unanimously recommended in the first-line treatment of advanced NSCLC (Category I).
2. In view of better outcomes with the use of pemetrexed in non-squamous histology and in considering cost-effectiveness, the workgroup is of the opinion that pemetrexed/platinum chemotherapy is preferable in the first-line treatment of non-squamous advanced NSCLC (workgroup consensus).
3. Bevacizumab when added to chemotherapy is an option (Category IIA).
4. The use of bevacizumab as well as pemetrexed is limited to those non-squamous in histology.
5. There is insufficient evidence to support the use of cetuximab for which the workgroup unanimously does not recommend in this setting (workgroup consensus).

5. Role of Maintenance Chemotherapy

Maintenance therapy is started immediately after first-line therapy with aims of prolonging tumour response or stable disease.

Trials using bevacizumab in combination with first-line platinum-based chemotherapy have continued bevacizumab as maintenance therapy after completion of 4 to 6 cycles of chemotherapy. In the pivotal randomised phase III trial comparing paclitaxel and carboplatin chemotherapy alone versus paclitaxel carboplatin bevacizumab, addition of bevacizumab was shown to improve OS (12.3 months vs 10.3 months, HR = 0.79; 95% CI, 0.67 to 0.92; $P = 0.003$), PFS (6.2 months vs 4.5 months, HR = 0.66; 95% CI, 0.57 to 0.77; $P < 0.001$) and response rates (35% vs 15%, $P < 0.001$) in patients with advanced non-squamous NSCLC. Out of 407 patients, 215 (53%) continued with bevacizumab

monotherapy with 107 (50%) receiving more than 5 cycles of monotherapy.³⁴

Maintenance pemetrexed has been studied in 2 large trials.⁴⁰⁻⁴² “Switch maintenance” was examined in a randomised double-blinded international study where monotherapy pemetrexed versus placebo was commenced following 4 cycles of platinum-based chemotherapy. A switch to pemetrexed maintenance significantly improved PFS (4.3 months vs 2.6 months, HR = 0.5; 95% CI, 0.42 to 0.61; $P \leq 0.0001$) and OS (13.4 months vs 10.6 months, HR = 0.79; 95% CI, 0.65 to 0.95; $P = 0.012$).⁴¹ In the PARAMOUNT trial, 539 advanced non-squamous NSCLC patients who received 4 cycles of pemetrexed-cisplatin induction therapy with no disease progression were randomly assigned to receiving continuation maintenance with pemetrexed plus best supportive care or with placebo plus best supportive care. Final OS analysis showed a statistically significantly longer OS of 13.9 months versus 11 months (unadjusted HR = 0.78; 95% CI, 0.64 to 0.96; $P = 0.0195$). In this trial, maintenance pemetrexed was well tolerated with no new safety findings.⁴²

Cost-effectiveness

Cost-effectiveness of pemetrexed as first-line maintenance therapy was assessed by an American group as well as NICE. The American paper showed that in the subgroup of patients with non-squamous histology, the incremental cost per life year gained was USD \$122,371 when compared to observation.⁴³ The ICERs as estimated by the manufacturer’s model submitted to NICE were USD \$51,289 per QALY for the non-squamous population.⁴⁴

Recommendations on the Role of Maintenance Chemotherapy

1. In patients with good performance status of 0 – 1, continuation of pemetrexed is unanimously recommended in non-squamous NSCLC if stable disease or response is seen following induction chemotherapy (Level I, B).
2. In patients with non-squamous histology and good performance status of 0 – 1, should first-line chemotherapy be non-pemetrexed based, then switch of maintenance to pemetrexed can be considered (Level I, B).
3. In patients with all histologies, switch to erlotinib can be considered (Level I, B). However, the workgroup recommends this only if a sensitising *EGFR* mutation is detected (workgroup consensus).

6. Second-line Chemotherapeutic Options for Advanced NSCLC

Docetaxel dosed at 75 mg/m² has been shown to

offer clinically meaningful benefit to patients with advanced NSCLC who have failed platinum-containing chemotherapy.^{45, 46} A randomised phase II trial comparing docetaxel dosed at 100 mg/m² reduced to 75 mg/m² after a protocol amendment versus best supportive care in 103 patients showed a longer duration of survival for the chemotherapy arm (7 months, 95% CI, 5.5 to 9 months vs 4.6 months, 95% CI, 3.7 to 6 months; $P = 0.047$). When compared separately, patients who were treated with docetaxel at 75 mg/m² had significantly better survival than those treated with best supportive care (log-rank test; $P = 0.01$).⁴⁶ TAX 320 is a phase III randomised study of 373 patients comparing docetaxel dosed at 100 mg/m² or 75 mg/m² versus a control of vinorelbine or ifosfamide.⁴⁵ Patients treated with docetaxel dosed at 75 mg/m² every 3 weeks had significantly greater 1-year survival than those with control treatment (32% vs 19%; $P = 0.025$).

A subsequent randomised phase III trial comparing pemetrexed versus docetaxel as second-line treatment in patients with advanced NSCLC showed equivalent efficacy outcomes by way of OS (8.3 months vs 7.9 months; HR = 0.99; 95% CI, 0.82 to 1.2; $P = 0.226$), PFS and overall response rates (9.1% vs 8.8%).⁴⁷ The side effect profile of pemetrexed was favourable in comparison to docetaxel.⁴⁷ A secondary analysis further identified differing efficacy for pemetrexed over docetaxel in patients with non-squamous histology.⁴⁸

Cost-effectiveness

Cost-effectiveness of second-line chemotherapy has been assessed. Docetaxel was associated with significantly lower treatment period cost and was more favourable with regards to cost-utility ratio as compared to pemetrexed. When compared to best supportive care, the cost utility of docetaxel was USD \$35,668 per QALY whilst the cost utility per QALY for pemetrexed was USD \$44,770.⁴⁹

Recommendations on Second-line Chemotherapeutic Options for Advanced NSCLC

1. The workgroup committee unanimously recommends consideration of clinical trials.
2. Docetaxel or pemetrexed (restricted to non-squamous in histology) can be considered in fit patients as second-line treatment of advanced lung cancer (Level I, B).

7. Subsequent Lines of Chemotherapy for Advanced NSCLC

There is 1 randomised controlled trial that studied the role of erlotinib after failure of first- or second-line chemotherapy.⁵⁰ In this international, phase III randomised

double-blinded, placebo controlled trial, 731 patients who had received 1 or 2 prior lines of chemotherapy were randomly assigned in a 2:1 ratio to receive erlotinib or placebo. The primary endpoint of OS was met (6.7 months vs 4.7 months, HR = 0.7 95%; CI, 0.58 to 0.85; $P < 0.001$). There were significantly more overall responses in the erlotinib group (8.9% vs <1%; $P < 0.001$). The median PFS was significantly longer in the erlotinib group (2.2 months vs 1.8 months, HR = 0.61; 95% CI, 0.51 to 0.74; $P < 0.001$). We are however mindful that patients enrolled on this trial are unselected and therefore extrapolation of this data in the current era of molecular subtyping must be done so with care. Nevertheless, this trial did provide clinically meaningful prolongation of survival despite heavy pretreatment of 50% of the enrolled patients.

Recommendations on Subsequent Lines of Chemotherapy for Advanced NSCLC

1. The workgroup unanimously recommends to first consider clinical trials.
2. Erlotinib can be considered in the treatment of advanced lung cancer beyond second-line chemotherapy in patients with unknown *EGFR* status or *EGFR*-WT who have not received *EGFR* TKI (Level II, B).
3. Given the burgeoning pipeline of novel therapeutics addressing either distinct genetic drivers or resistance mechanisms, molecular profiling for “actionable” alterations either from archival tissue, or a repeat biopsy is also a reasonable consideration (workgroup consensus).

All recommendations are unanimous.

Conflicts of Interest

Dr A Chang reports receiving advisory board fees from Pfizer, Celgene and BMS and lecture fees from MSD, Pfizer and BMS; Dr DSW Tan, receiving research funding from Novartis and advisory board fees from Novartis, Boehringer Ingelheim and Pfizer; Dr WL Yeo, serving on advisory boards of Roche and Bayer; Ms L Chew, Dr TM Chin, Dr SS Leong, Dr HL Lim, Dr EH Lim, Dr RA Soo, Dr T Tan and Dr CK Toh have nothing to disclose.

Workgroup Members

The Members of the SCAN Lung Cancer Workgroup are Section Lead and Workgroup Chairperson: Darren Lim, MBBS, MRCP (UK), Division of Medical Oncology, National Cancer Centre Singapore, Singapore; Workgroup Members (Voting): Alex Chang, MD, Oncology, John Hopkins Singapore, Singapore; Lita Chew, BSc (Pharm), MMedSc (Oncology) (UK), Department of Pharmacy, National Cancer Centre Singapore, Singapore; Tan Min Chin, MBBS, MRCP (UK, Edin), Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore; Boon

Cher Goh, MBBS (S'pore), MMed (Int Med), FRCP (Edin), Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore; Swan Swan Leong, MBBS (S'pore), MRCP (UK), FAMS (Med Onc), OncoCare Cancer Centre, Singapore; Elaine Lim, PhD, MBChir, MRCP (UK), Division of Medical Oncology, National Cancer Centre Singapore, Singapore; Hong Liang Lim, MBBS (S'pore), MMed (Int Med), FAMS (Med Onc), Parkway Cancer Centre, Singapore; Ross Soo, MBBS, FRACP, FAMS, Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore; Daniel Tan, BSc (Hons), MBBS (London), MRCP (UK), Division of Medical Oncology, National Cancer Centre Singapore, Singapore; Tira Tan, BSc (Hons), MBBS, MRCP (UK), Division of Medical Oncology, National Cancer Centre Singapore, Singapore; Chee Keong Toh, MBBS, MRCP (UK), Division of Medical Oncology, National Cancer Centre Singapore, Singapore; Wee Lee Yeo, MBBS, MRCP (UK), FAMS (Med Onc), Oncology, John Hopkins Singapore, Singapore.

Reviewers

Invited reviewers were Gilberto Lopes, MD, MBA, Oncoclinicas Group, Brazil; Fergus Macbeth, MA, DM, FRCP, Wales Cancer Trials Unit, Cardiff University, UK.

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Supplementary Table 1. International Guidelines for the Systemic Therapy of Advanced NSCLC

Guideline Title	NICE Guidance			Clinical Practice Guidelines for the Treatment of Lung Cancer
	1. The Diagnosis and Treatment of Lung Cancer (Update of NICE Clinical Guideline 24) (CG 121)	2. Lung Cancer (Non-Small Cell) – Erlotinib (TA162)	3. Lung Cancer (Non-Small Cell, First-Line Treatment) – Pemetrexed (TA181)	
Guideline Title	Metastatic Non-Small Cell Lung Cancer: ESMO Clinical Practice Guidelines			Clinical Practice Guidelines for the Treatment of Lung Cancer
	4. Lung Cancer (Non-Small Cell) – Pemetrexed (Maintenance) (TA190)	5. Lung Cancer (Non-Small Cell, First-Line) – Gefitinib (TA192)	6. Lung Cancer (Non-Small Cell, EGFR-TK Mutation Positive) – Erlotinib (First-Line) (TA258)	
Guideline Title	NCCN Guidelines Version 2.2014 Non-Small Cell Lung Cancer			Clinical Practice Guidelines for the Treatment of Lung Cancer
	7. Lung Cancer (Non-Small Cell, Anaplastic Lymphoma Kinase Fusion Gene, Previously Treated) – Crizotinib: Guidance (TA296)			
Date Released	11 April 2013	October 2012	January 2014	
Guideline Developer	National Cancer Comprehensive Network (NCCN), United States	European Society for Medical Oncology (ESMO)	National Institute of Health and Clinical Excellence (NICE), United Kingdom	Clinical Guidelines Network Cancer Council Australia Commissioned by Australian Government
Description of Method of Guideline Validation	Statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Validation method not specified.	Recommendations developed from discussion at consensus conferences. Group decision-making that seeks the consensus of experts and the fulfillment of objectives. Guidelines are endorsed by the Japanese Society of Medical Oncology (JSMO).	Open and transparent consultation process which allows individuals, patient groups, charities and industry to comment on recommendations.	Working party develops clinical questions, searches literature, formulates recommendations and write guideline chapters. Content is uploaded to Guidelines Wiki and undergoes public consultation prior to update. Annual working party meeting to review changes made by authors.
Target Population	All adults with non-small cell lung cancer	All adults with non-small cell lung cancer	All adults with non-small cell lung cancer	All adults with non-small cell lung cancer
ALK: Anaplastic lymphoma kinase; BSC: Best supportive care; EGFR: Epidermal growth factor receptor; IASLC: International Association for the Study of Lung Cancer; IHC: Immunohistochemistry; NSCLC: Non-small cell lung cancer; PS: Performance status; SRE: Skeletal-related events; WHO: World Health Organization				
Note: The above summary is focused on systemic therapy for advanced NSCLC only.				

ALK: Anaplastic lymphoma kinase; BSC: Best supportive care; EGFR: Epidermal growth factor receptor; IASLC: International Association for the Study of Lung Cancer; IHC: Immunohistochemistry; NSCLC: Non-small cell lung cancer; PS: Performance status; SRE: Skeletal-related events; WHO: World Health Organization

Note: The above summary is focused on systemic therapy for advanced NSCLC only.

Supplementary Table 1. International Guidelines for the Systemic Therapy of Advanced NSCLC (Cont'd)

Guideline Title	NCCN Guidelines Version 2.2014 Non-Small Cell Lung Cancer	Metastatic Non-Small Cell Lung Cancer: ESMO Clinical Practice Guidelines	NICE Guidance	
			1. The Diagnosis and Treatment of Lung Cancer (Update of NICE Clinical Guideline 24) (CG 121)	2. Lung Cancer (Non-Small Cell) – Erlotinib (TA162)
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			5. Lung Cancer (Non-Small Cell, First-Line) – Gefitinib (TA192)	6. Lung Cancer (Non-Small Cell, <i>EGFR</i> -TK Mutation Positive) – Erlotinib (First-Line) (TA258)
			7. Lung Cancer (Non-Small Cell, Anaplastic Lymphoma Kinase Fusion Gene, Previously Treated) – Crizotinib: Guidance (TA296)	
Diagnosis	Pathological diagnosis: - Establish histologic subtype with adequate tissue for molecular testing (consider rebiopsy if appropriate). <i>EGFR</i> mutation and <i>ALK</i> testing as part of multiplex/next generation sequencing. - Mutation testing if non-squamous and in non-smoker squamous or small biopsy specimens or mixed histology.	Pathological diagnosis: - WHO and IASLC classification of adenocarcinoma. - Specific subtype necessary. - Obtain sufficient tissue. - Rebiopsy at disease progression. <i>EGFR</i> mutation status in non-squamous histology. <i>EGFR</i> testing not recommended in patients with confident squamous histology except never/former light smoker. - Discuss <i>EML4-ALK</i> testing in non-squamous histology if crizotinib available.	Ensure adequate samples taken without unacceptable risk to the patient to permit pathological diagnosis including tumour subtyping and measurement of predictive markers.	Due to therapeutic implications, important to classify histologic subtype of NSCLC as accurately as possible to enable distinction between adenocarcinoma and squamous cell carcinoma.
Systemic Therapy	First-line: - Doublet chemotherapy - Bevacizumab + chemotherapy* - Cetuximab/vinorelbine/cisplatin First-line (poor PS/elderly) If PS 2 - Gemcitabine - Vinorelbine - Taxanes - Platinum-based combination	First-line: - Platinum-based combination chemotherapy 4 – 6 cycles - Cisplatin is platinum of choice - Pemetrexed[‡] - Bevacizumab[§] - Cetuximab - Non-platinum-based combination chemotherapy only if platinum contraindicated.	First-line: - Third-generation platinum-based combination chemotherapy (with vinorelbine, paclitaxel, docetaxel, gemcitabine). - Cisplatin preferred to carboplatin for patients with high tumour burden and symptoms for purpose of inducing a response. However, this benefit may be offset by its greater risk of toxicity.	

ALK: Anaplastic lymphoma kinase; BSC: Best supportive care; EGFR: Epidermal growth factor receptor; IASLC: International Association for the Study of Lung Cancer; IHC: Immunohistochemistry; NSCLC: Non-small cell lung cancer; PS: Performance status; SRE: Skeletal-related events; WHO: World Health Organization

Note: The above summary is focused on systemic therapy for advanced NSCLC only.

Supplementary Table 1. International Guidelines for the Systemic Therapy of Advanced NSCLC (Cont't)

Guideline Title	NCCN Guidelines Version 2.2014 Non-Small Cell Lung Cancer	Metastatic Non-Small Cell Lung Cancer: ESMO Clinical Practice Guidelines	NICE Guidance 1. The Diagnosis and Treatment of Lung Cancer (Update of NICE Clinical Guideline 24) (CG 121) 2. Lung Cancer (Non-Small Cell) – Erlotinib (TA162) 3. Lung Cancer (Non-Small Cell, First-Line Treatment) – Pemetrexed (TA181) 4. Lung Cancer (Non-Small Cell) – Pemetrexed (Maintenance) (TA190) 5. Lung Cancer (Non-Small Cell, First-Line) – Gefitinib (TA192) 6. Lung Cancer (Non-Small Cell, EGFR-TK Mutation Positive) – Erlotinib (First-Line) (TA258) 7. Lung Cancer (Non-Small Cell, Anaplastic Lymphoma Kinase Fusion Gene, Previously Treated) – Crizotinib: Guidance (TA296)	Clinical Practice Guidelines for the Treatment of Lung Cancer
	If PS 3 – 4 - Erlotinib[†] - Afinib[†] First-line (activating <i>EGFR</i> mutations) - Erlotinib[†] - Afinib[†] First-line (<i>ALK</i> rearrangement) - Crizotinib[†]		First-line (poor PS): If PS 2 - Gemcitabine - Vinorelbine - Taxanes - Platinum-based combination If PS 3 – 4 and absent <i>EGFR</i> sensitising mutation - BSC First-line (elderly) - Platinum combination if PS 0 – 1 - Single agent in selected PS 2 First-line (activating <i>EGFR</i> mutations) - Erlotinib - Gefitinib First-line (<i>ALK</i> rearrangement) - Crizotinib	- Cisplatin/pemetrexed recommended in preference to cisplatin/gemcitabine in patients with non-squamous histology. - Cisplatin/gemcitabine preferred to cisplatin/pemetrexed in patients with squamous histology. - Non-platinum third-generation doublet (e.g. gemcitabine/paclitaxel) is an alternative for patients unsuitable for platinum-based therapy. - First-line combination chemotherapy should be stopped at disease progression or after 4 cycles. - Bevacizumab (15 mg/kg) + chemotherapy^j - Cetuximab + cisplatin/vinoreline^k First-line (unfit for combination chemotherapy): - Gemcitabine - Vinorelbine - Docetaxel - Paclitaxel

ALK: Anaplastic lymphoma kinase; BSC: Best supportive care; EGFR: Epidermal growth factor receptor; IASLC: International Association for the Study of Lung Cancer; IHC: Immunohistochemistry; NSCLC: Non-small cell lung cancer; PS: Performance status; SRE: Skeletal-related events; WHO: World Health Organization

Note: The above summary is focused on systemic therapy for advanced NSCLC only.

Supplementary Table 1. International Guidelines for the Systemic Therapy of Advanced NSCLC (Cont't)

Guideline Title	NCCN Guidelines Version 2.2014 Non-Small Cell Lung Cancer	Metastatic Non-Small Cell Lung Cancer: ESMO Clinical Practice Guidelines	NICE Guidance 1. The Diagnosis and Treatment of Lung Cancer (Update of NICE Clinical Guideline 24) (CG 121) 2. Lung Cancer (Non-Small Cell) – Erlotinib (TA162) 3. Lung Cancer (Non-Small Cell, First-Line Treatment) – Pemetrexed (TA181) 4. Lung Cancer (Non-Small Cell) – Pemetrexed (Maintenance) (TA190) 5. Lung Cancer (Non-Small Cell, First-Line) – Gefitinib (TA192) 6. Lung Cancer (Non-Small Cell, <i>EGFR</i> -TK Mutation Positive) – Erlotinib (First-Line) (TA258) 7. Lung Cancer (Non-Small Cell, Anaplastic Lymphoma Kinase Fusion Gene, Previously Treated) – Crizotinib: Guidance (TA296)	Clinical Practice Guidelines for the Treatment of Lung Cancer
	Maintenance: Continuation • Bevacizumab* • Cetuximab • Pemetrexed* • Bevacizumab + pemetrexed* • Gemcitabine Switch • Pemetrexed • Erlotinib • Docetaxel[#]		Maintenance: • Pemetrexed – recommended in non-predominantly squamous and non-progressive disease following platinum-based chemotherapy. Maintenance: • Pemetrexed^{##} • Docetaxel • Erlotinib	First-line (elderly) • Vinorelbine • Docetaxel • Gemcitabine • Weekly paclitaxel/carboplatin First-line (activating <i>EGFR</i> mutations) • <i>EGFR</i>-TKI
	Maintenance: Continuation • Bevacizumab* • Cetuximab • Pemetrexed* • Bevacizumab + pemetrexed* • Gemcitabine Switch • Pemetrexed • Erlotinib • Docetaxel[#]		Maintenance: • Pemetrexed – recommended in non-predominantly squamous and non-progressive disease following platinum-based chemotherapy. Maintenance: • Pemetrexed^{##} • Docetaxel • Erlotinib	First-line (elderly) • Vinorelbine • Docetaxel • Gemcitabine • Weekly paclitaxel/carboplatin First-line (activating <i>EGFR</i> mutations) • <i>EGFR</i>-TKI
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	Maintenance: Continuation • Bevacizumab* • Cetuximab • Pemetrexed* • Bevacizumab + pemetrexed* • Gemcitabine Switch • Pemetrexed • Erlotinib • Docetaxel[#]		Maintenance: • Pemetrexed – recommended in non-predominantly squamous and non-progressive disease following platinum-based chemotherapy. Maintenance: • Pemetrexed^{##} • Docetaxel • Erlotinib	First-line (elderly) • Vinorelbine • Docetaxel • Gemcitabine • Weekly paclitaxel/carboplatin First-line (activating <i>EGFR</i> mutations) • <i>EGFR</i>-TKI
	Maintenance: Continuation • Bevacizumab* • Cetuximab • Pemetrexed* • Bevacizumab + pemetrexed* • Gemcitabine Switch • Pemetrexed • Erlotinib • Docetaxel[#]		Maintenance: • Pemetrexed – recommended in non-predominantly squamous and non-progressive disease following platinum-based chemotherapy. Maintenance: • Pemetrexed^{##} • Docetaxel • Erlotinib	First-line (elderly) • Vinorelbine • Docetaxel • Gemcitabine • Weekly paclitaxel/carboplatin First-line (activating <i>EGFR</i> mutations) • <i>EGFR</i>-TKI
	Maintenance: Continuation • Bevacizumab* • Cetuximab • Pemetrexed* • Bevacizumab + pemetrexed* • Gemcitabine Switch • Pemetrexed • Erlotinib • Docetaxel[#]		Maintenance: • Pemetrexed – recommended in non-predominantly squamous and non-progressive disease following platinum-based chemotherapy. Maintenance: • Pemetrexed^{##} • Docetaxel • Erlotinib	First-line (elderly) • Vinorelbine • Docetaxel • Gemcitabine • Weekly paclitaxel/carboplatin First-line (activating <i>EGFR</i> mutations) • <i>EGFR</i>-TKI
	Maintenance: Continuation • Bevacizumab* • Cetuximab • Pemetrexed* • Bevacizumab + pemetrexed* • Gemcitabine Switch • Pemetrexed • Erlotinib • Docetaxel[#]		Maintenance: • Pemetrexed – recommended in non-predominantly squamous and non-progressive disease following platinum-based chemotherapy. Maintenance: • Pemetrexed^{##} • Docetaxel • Erlotinib	First-line (elderly) • Vinorelbine • Docetaxel • Gemcitab

ALK: Anaplastic lymphoma kinase; BSC: Best supportive care; EGFR: Epidermal growth factor receptor; IASLC: International Association for the Study of Lung Cancer; IHC: Immunohistochemistry; NSCLC: Non-small cell lung cancer; PS: Performance status; SRE: Skeletal-related events; WHO: World Health Organization

Note: The above summary is focused on systemic therapy for advanced NSCLC only.

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NCCN Guidelines Version 2.2014 Non-Small Cell Lung Cancer	Metastatic Non-Small Cell Lung Cancer: ESMO Clinical Practice Guidelines				Guidance (TA296)
	Subsequent-lines:	Subsequent-line:	Subsequent-line:	Subsequent-line:	
PS 3 – 4					
• BSC					
Subsequent-lines:					
• Docetaxel					
• Pemetrexed*					
• Erlotinib					
• Gemcitabine					
Bone Metastases	Not specified	To reduce SRE: • Zoledronic acid • Denosumab	Not specified	Not specified	Not specified
Palliative Care	Recommended	Recommend early palliative care intervention.	Recommend early palliative care intervention.	Recommend early palliative care intervention.	Not specified
Smoking Cessation	Recommended	Recommended	Recommended	Recommended	Not specified

ALK: Anaplastic lymphoma kinase; BSC: Best supportive care; EGFR: Epidermal growth factor receptor; IASLC: International Association for the Study of Lung Cancer; IHC: Immunohistochemistry; NSCLC: Non-small cell lung cancer; PS: Performance status; SRE: Skeletal-related events; WHO: World Health Organization
 Note: The above summary is focused on systemic therapy for advanced NSCLC only.

*Non-squamous only.

†Interrupt or complete first-line chemotherapy if mutation discovered during first-line chemotherapy. In case of *EGFR* mutation, erlotinib/afatinib may also be added to current chemotherapy.

‡Restrict to non-squamous tumours.

§Combined with paclitaxel-carboplatin regimen in non-squamous.

||In non-squamous histology and selected patients.

¶In tumours shown to express *EGFR* by IHC.

#Squamous only.

**Restrict to non-squamous tumours as switch or continuation maintenance.

††All histologies in particular patients with activating *EGFR* mutation tumours who have not received *EGFR*-TKI as first-line.

‡‡Non-squamous histology.

§§All histologies in particular patients with activating *EGFR* mutation tumours who have not previously received *EGFR*-TKI.

|||Crizotinib should be considered in presence of *ALK* rearrangement if not received as first-line.

¶¶Preferred in squamous histology.

##Preferred in non-squamous histology.

Singapore Cancer Network (SCAN) Guidelines for Systemic Therapy of High-Grade Glioma

The Singapore Cancer Network (SCAN) Neuro-Oncology Workgroup

Abstract

Introduction: The SCAN Neuro-Oncology workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for systemic therapy for high-grade glioma in Singapore. **Materials and Methods:** The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. **Results:** Six international guidelines were evaluated—those developed by the National Comprehensive Cancer Network (2013), the European Association for Neuro-Oncology (EANO) Task Force on Malignant Glioma (2014), the European Society of Medical Oncology (2014), the Canadian GBM Recommendations Committee (2007) and the Australian Cancer Network (2009). Recommendations on the systemic therapy of high-grade glioma were produced. **Conclusion:** These adapted guidelines form the SCAN Guidelines 2015 for systemic therapy of high-grade glioma.

Ann Acad Med Singapore 2015;44:463-73

Key words: Anaplastic glioma, Chemotherapy, Glioblastoma

Singapore Cancer Network (SCAN) Guidelines for Systemic Therapy of High-Grade Glioma

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Abstract

Introduction: The SCAN Neuro-Oncology workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for systemic therapy for high-grade glioma in Singapore. **Materials and Methods:** The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. **Results:** Six international guidelines were evaluated—those developed by the National Comprehensive Cancer Network (2013), the European Association for Neuro-Oncology (EANO) Task Force on Malignant Glioma (2014), the European Society of Medical Oncology (2014), the Canadian GBM Recommendations Committee (2007) and the Australian Cancer Network (2009). Recommendations on the systemic therapy of high-grade glioma were produced. **Conclusion:** These adapted guidelines form the SCAN Guidelines 2015 for systemic therapy of high-grade glioma.

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Key words: Anaplastic glioma, Chemotherapy, Glioblastoma

Introduction

Malignant gliomas are the most common primary malignant brain tumours, with an annual incidence of about 5 per 100,000.¹ It is associated with a dismal prognosis, poor quality of life and cognitive dysfunction.

Surgical resection and radiation therapy (RT) have been the mainstays of treatment. There is increasing evidence to support the addition of systemic therapies.^{2,3} In fact, for patients with glioblastoma, chemoradiation with temozolomide has become standard of care, and has raised average life expectancy from 12 to 14 months. Bevacizumab, an anti-angiogenic agent, is an emerging treatment alternative in the recurrent glioblastoma.⁴

Recently, attention is being drawn to molecular markers that may predict responsiveness to systemic therapies. Specifically, chromosomes 1p19q co-deletion in oligodendroglial tumours has been shown to be associated with improved outcome after treatment with procarbazine, lomustine and vincristine (PCV) and RT.⁵

Despite improvement in multi-modality treatment, malignant gliomas eventually recur or progress. These guidelines summarise current evidence in systemic therapy of high-grade glioma.

The SCAN Guidelines for the Systemic Therapy of High-Grade Glioma

The SCAN Guidelines are clinical practice guidelines for the systemic treatment of high-grade glioma. It includes adults with anaplastic astrocytomas, anaplastic oligodendroglioma and anaplastic mixed oligoastrocytoma (World Health Organization (WHO) grade III), and glioblastoma (WHO grade IV).

These first edition guidelines are intended to serve as treatment recommendations by members of this working group reflecting their views on current existing international guidelines for the management of high-grade glioma. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

Target Users of the Guidelines

The guidelines will be of interest to oncologists, neurologists, oncology nurse specialists, pharmacists, allied health workers and general practitioners involved in the management of patients with high-grade glioma.

Guideline Recommendations/Development

The SCAN neuro-oncology workgroup comprises a panel of 3 medical oncologists and 1 neurologist from Singapore with special interests in the management of brain tumours. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead with input from the workgroup members. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework⁶ was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, high quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to address the 3 main management issues which were selected for this topic (Table 1):

1. Front-line Systemic Therapy for Anaplastic Glioma
2. Front-line Systemic Therapy for Glioblastoma
3. Systemic Therapy for Recurrent High-Grade Glioma

Five international guidelines were selected for review (Supplementary Table 1):

- “NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Central Nervous System Cancers” (version 2.2013) by the National Cancer Comprehensive Network (NCCN, USA)⁷

- “EANO Guideline for the Diagnosis and Treatment of Anaplastic Gliomas and Glioblastoma” by the European Association for Neuro-Oncology (EANO) Task Force on Malignant Glioma – 2014⁸
- “High-Grade Malignant Glioma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up” by the European Society of Medical Oncology (ESMO) – 2014⁹
- “Canadian Recommendation for the Treatment of Glioblastoma Multiforme” by the Canadian GBM Recommendations Committee – 2007¹⁰
- “Clinical Practice Guidelines for the Management of Adult Gliomas: Astrocytomas and Oligodendrogliomas” by the Australian Cancer Network – 2009¹¹

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of high-grade glioma, it will be reviewed earlier.

1. Front-line Systemic Therapy for Anaplastic Glioma

There is emerging evidence to support use of systemic therapy in treatment of newly diagnosed anaplastic glioma. Specifically, fractionated external beam RT with adjuvant or neoadjuvant chemotherapy is now a standard of care for patients with 1p19q co-deleted anaplastic oligodendroglioma and oligoastrocytoma.

Procarbazine, Lomustine and Vincristine (PCV)

The largest trial conducted in patients with malignant glioma showed that adjuvant PCV given at 6-week intervals derived no benefit over RT alone.¹² A subsequent meta-analysis of 12 randomised controlled trials of 3004 patients demonstrated a significant increase in survival with use of chemotherapy (HR = 0.85; 95% CI, 0.78 to 0.91; $P < 0.0001$), with an absolute increase in 1-year survival of 6% from 40% to 46%.¹³ This finding was consistent with previous meta-analysis, which showed an increase in 1-year and 2-year survival for patients treated with adjuvant chemotherapy compared to RT alone.¹⁴

RTOG 9402, a phase III trial of adjuvant PCV in anaplastic oligodendroglioma or anaplastic mixed oligoastrocytoma patients with Karnofsky performance score (KPS) ≥ 60 , initially failed to demonstrate improved overall survival (OS) in patients receiving adjuvant PCV (PCV followed by RT) compared to RT alone at 3 years.¹⁵ In addition, 65% of patients in treatment arm experienced grade III or IV toxicity and 1 patient died. Subsequently, a long-term follow-up (median follow-up 11.3 years) reported there remained no difference in median survival by treatment for the entire patient cohort (4.6 years for PCV plus RT

Table 1. Singapore Cancer Network (SCAN) Guidelines for the Systemic Therapy of High-Grade Glioma

Guideline Recommendations	
Recommendations for Front-line Systemic Therapy for Anaplastic Glioma	NCCN Guidelines: - 1p/19q deletion should be tested on all anaplastic oligodendroglioma or oligoastrocytoma. - For patients with good PS, and anaplastic astrocytoma, anaplastic oligodendroglioma or oligoastrocytoma without 1p19q co-deletion, fractionated external beam radiation therapy (EBRT) remains the standard after surgical intervention. Temozolomide or PCV with deferred RT is a reasonable choice. Fractionated RT concurrent with temozolomide is another reasonable option but has not been shown to be beneficial in a small local retrospective study. - For patients with good PS, and anaplastic oligoastrocytoma or anaplastic oligodendroglioma harbouring 1p19q co-deletion, we recommend RT with adjuvant PCV after surgical intervention. Fractionated RT concurrent with temozolomide is a reasonable option after discussion with patients regarding current limited phase III clinical data. - For patients with poor PS, hypofractionated RT, temozolomide or best supportive care alone is reasonable.
	NCCN Guidelines: - Fractionated RT concurrent with temozolomide followed by adjuvant temozolomide is the standard of care for glioblastoma patients age ≤ 70 years with good PS, defined by WHO PS ≤ 2 (Category I). Dose-dense therapy is not recommended. - For glioblastoma patients age > 70 years with good PS, options of treatment include hypofractionated RT, temozolomide with deferred RT or RT with concurrent temozolomide followed by adjuvant temozolomide. We suggest checking MGMT promoter methylation status in this group, and recommend temozolomide therapy if positive.
	Recommendations for Front-line Systemic Therapy for Glioblastoma - The routine addition of bevacizumab as upfront therapy is not recommended. - The role of nimotuzumab as front-line therapy was debated. One of the workgroup members felt that the randomised phase II Cuban trial provided sufficient evidence to recommend nimotuzumab, in addition to RT, as front-line therapy in rare situations where myelosuppression of temozolomide cannot be tolerated. The rest of the workgroup members argued that the trial was conducted with small patient numbers with results not reproduced in other trials, had also not been supported by other national guidelines committees and that given its additional cost and lack of confirmatory trial data, nimotuzumab cannot be recommended as standard front-line therapy. - Given the lack of data on front-line therapy in patients with poor PS, combination therapy with PCV, temozolomide monotherapy, RT alone or best supportive care is reasonable.
Recommendations for Systemic Therapy for Recurrent Malignant Gliomas	NCCN and ESMO Guidelines: - For patients with good PS, reasonable chemotherapy options include temozolomide, lomustine, combination PCV, cyclophosphamide, platinum-based agents and irinotecan. - Bevacizumab, as monotherapy or in combination with other chemotherapy, may also be considered in recurrent glioblastoma. - For patients with poor PS, best supportive care is reasonable.

ESMO: European Society for Medical Oncology; MGMT: 0-6-methylguanine-DNA methyltransferase; NCCN: National Cancer Comprehensive Network; PCV: Procarbazine, lomustine and vincristine; PS: Performance status; RT: Radiation therapy; WHO: World Health Organization

vs 4.7 years for RT; HR = 0.79; 95% CI, 0.60 to 1.04; $P = 0.1$).¹⁶ Patients with 1p19q co-deleted tumours, however, survived longer than those with non-co-deleted tumours (PCV plus RT: 14.7 vs 2.6 years, HR = 0.36; 95% CI, 0.23 to 0.57; $P = 0.001$; RT: 7.3 vs 2.7 years, HR = 0.40; 95% CI, 0.27 to 0.60; $P = 0.01$). Also, the median survival of those with co-deleted tumours treated with adjuvant PCV was twice that of patients receiving RT (14.7 vs 7.3 years; HR = 0.59; 95% CI, 0.37 to 0.95; $P = 0.03$). For those with non-co-deleted tumours, there was no difference in median survival by treatment arm (2.6 vs 2.7 years; HR = 0.85; 95% CI, 0.58 to 1.23; $P = 0.39$).

In the same period, the European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumor Group conducted a prospective phase III study of adjuvant PCV (RT followed by PCV) in age ≤ 70 years and Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2 , and demonstrated significant improved 5-year progression free survival (PFS) (1.9 vs 1.1 years) but not OS when compared to RT alone.¹⁶ With 12 years follow-up, median OS was significantly prolonged in the adjuvant PCV arm when compared to RT arm (42.3 vs 30.6 months).⁵ Similar to findings from RTOG 9402, subgroup analysis of a cohort of 76 patients with 1p19q co-deletion from

EORTC 26951 trial, showed that treatment with adjuvant PCV resulted in significantly improved median OS compared to RT alone (not reached vs 112 months).⁵ In contrast, the patients without co-deletion showed no difference in survival. It is worth noting that 38% of patients in the chemoradiation arm discontinued adjuvant PCV due to toxicity.¹⁷

Temozolomide

Temozolomide is an alkylating agent. Newly diagnosed anaplastic oligodendroglioma has shown response to temozolomide monotherapy.^{18,19} In addition, benefits of combined chemoradiation with temozolomide in grade III glioma have been extrapolated from phase III trials conducted in glioblastoma patients.^{2,3} A local retrospective study of 62 patients however failed to show significant difference between patients who received chemoradiation with temozolomide and RT only (PFS: 14.8 vs 16.7 months; OS: 34.1 vs 27.4 months).²⁰ Results from 2 ongoing phase III trials, CODEL (ClinicalTrials.gov NCT00887146) and CATNON (NCT00626990) will answer the question of whether chemoradiation with temozolomide is beneficial in patients with newly diagnosed 1p19q-co-deleted and non-1p19q deleted anaplastic gliomas respectively.

Sequence of Chemoradiation

NOA-04 phase III trial randomised 318 patients with anaplastic glioma to receive RT (arm A), PCV (arm B1) or temozolomide (arm B2) at diagnosis.²¹ At unacceptable toxicity or disease progression, arm A was randomised to receive PCV or temozolomide, whereas arm B1 or B2 received RT. The study examined a total of 274 patients with anaplastic glioma (144 anaplastic astrocytoma, 91 anaplastic oligoastrocytoma, 39 anaplastic oligodendroglioma) using a modified intention-to-treat analysis, and demonstrated no significant difference in time-to-treatment failure (TTF), PFS and OS among the 3 treatment arms. Hence, PCV or temozolomide can be an upfront treatment option to defer RT treatment in a selected group of patients with anaplastic glioma.

Cost-effectiveness

To the best of our knowledge, there are no cost-effectiveness analyses available for systemic therapy in anaplastic glioma.

Recommendations for Front-line Systemic Therapy for Anaplastic Glioma

All members of the workgroup supported the adoption of NCCN guidelines. 1p/19q deletion should be tested on all anaplastic oligodendroglioma or oligoastrocytoma.

For patients with good PS, and anaplastic astrocytoma, anaplastic oligodendroglioma or oligoastrocytoma without 1p19q co-deletion, fractionated external beam radiation therapy (EBRT) remains the standard after surgical intervention. Temozolomide or PCV with deferred RT is a reasonable choice. Fractionated RT concurrent with temozolomide is another reasonable option but has not been shown to be beneficial in a small local retrospective study.

For patients with good PS, and anaplastic oligoastrocytoma or anaplastic oligodendroglioma harbouring 1p19q co-deletion, we recommend RT with adjuvant PCV after surgical intervention. Fractionated RT concurrent with temozolomide is a reasonable option after discussion with patients regarding current limited phase III clinical data.

For patients with poor PS, hypofractionated RT, temozolomide or best supportive care alone is reasonable.

2. Front-line Systemic Therapy for Glioblastoma

Combined chemoradiation is currently standard of care for glioblastoma patients age ≤ 70 years with good PS.

Temozolomide

Benefits of combined chemoradiation with temozolomide were demonstrated in a large phase III, randomised trial. Stupp et al assessed temozolomide in 573 glioblastoma patients age ≤ 70 years with a WHO PS ≤ 2 , and showed that RT with concurrent and adjuvant temozolomide improved median (14.6 vs 12.1 months), 2-year (26.5% vs 10.4%) and 5-year (10% vs 2%) survivals when compared with RT alone.^{2,3} Significant improvement in survival outcome did not adversely affect health-related quality of life (HRQOL).²²

Temozolomide is administered at 75 mg/m² daily concurrent with RT, followed by 150 to 200 mg/m² for 5 days every 28 days for 6 cycles post-RT.^{2,3} Alternate dose-dense regime showed no improvement in survival outcomes.²³

A local cohort study of 50 adult patients with glioblastoma treated with adjuvant temozolomide demonstrated similar median (13.6 months) and 2-year (24.4%) survival rates as the large European Multicentre Study.²⁴ It supports the use of temozolomide in our local population. Of note, there were no grade IV haematological or gastrointestinal toxicity in the patient cohort. Nevertheless, we recommend monitoring of blood count during chemoradiation therapy. Prophylaxis against *Pneumocystis jiroveci* pneumonia is advised when temozolomide is administered concurrent with RT due to risk of lymphopenia and subsequent opportunistic infection.

Special Population—Elderly Patients (Age >65 Years)

The first randomised trial examining the effectiveness of an abbreviated RT course (40 Gy in 15 fractions over 3

weeks) in older patients (age ≥ 60 years) with glioblastoma showed no significant difference in OS compared to those who received standard RT (60 Gy in 30 fractions over 6 weeks).²⁵ Patients in the abbreviated RT arm also had similar KPS and reduced increment in corticosteroid requirements.

The Nordic randomised phase III trial assessed treatment in 342 glioblastoma patients age >60 years with WHO PS ≤ 2 .²⁶ After 4 years of recruitment, in light of positive results from the EORTC 26981 trial, age cutoff was raised to >65 years. Better median survival was demonstrated in patients >70 years who received temozolomide (200 mg/m² on days 1 to 5 of every 28 days for up to 6 cycles) or hypofractionated RT (34.0 Gy administered in 3.4 Gy fractions over 2 weeks) than those who received standard RT (60.0 Gy administered in 2.0 Gy fractions over 6 weeks) (9.0 vs 7.0 vs 5.2 months). Survival did not differ between treatments for patients aged 60 to 70 years.

The NOA-08 randomised phase III trial assessed treatment in 373 high-grade glioma (malignant astrocytoma or glioblastoma) patients age >65 years with KPS ≥ 60 ,²⁷ and demonstrated that dose-dense temozolomide (100 mg/m² on days 1 to 7 of every 14 days) alone was non-inferior to RT (60.0 Gy administered in 1.8–2.0 Gy fractions over 6 to 7 weeks) (median OS 8.6 vs 9.6 months). There was no significant difference in HRQOL between the 2 treatment groups. Event-free survival (EFS) was longer in patients with MGMT promoter methylation (see below) who received temozolomide than in those who underwent RT (8.4 [95% CI, 5.5 to 11.7] vs 4.6 months [95% CI, 4.2 to 5.0]), whereas for patients with no methylation of the MGMT promoter, EFS was longer for those who received RT (3.3 [95% CI, 3.0 to 3.5] vs 4.6 months [95% CI, 3.7 to 6.3]).

A meta-analysis of 5 studies, including the Nordic and NOA-08 trials, showed a marginally significant reduction in mortality in elderly GBM patients receiving temozolomide monotherapy compared to RT.²⁸ This borderline significance was lost after sensitivity analysis. The role of early RT and temozolomide will be better defined with results from the ongoing EORTC and National Cancer Institute of Canada (NCIC) Clinical Trial Group elderly trial (NCT00482677).

O-6-methylguanine-DNA Methyltransferase (MGMT)

MGMT is a DNA repair enzyme that can adversely affect tumour response to DNA-alkylating agents. Methylation of MGMT gene promoter results in gene-silencing and has been shown to improve median OS in glioblastoma patients age ≤ 70 years with a WHO PS ≤ 2 (18.2 vs 12.2 months).²⁹ Among high-grade glioma patients age >65 years, those with MGMT promoter methylation also demonstrated longer median OS compared to those without methylation (11.9 vs 8.2 months; HR = 0.62; 95% CI, 0.42 to 0.91;

$P = 0.014$).²⁷ Its predictive role in treatment response to temozolomide alone was suggested in the NOA-08 trial as discussed above. Similarly, the Nordic trial demonstrated a non-significant improvement in median OS in glioblastoma patients with MGMT promoter methylation compared to those without methylation (9.7 vs 6.8 months; HR = 0.97; $P = 0.81$).²⁶ This improvement in survival was not seen in patients treated with RT only. Overall, MGMT methylation status remains at best a prognostic marker. Its predictive role in response to therapy requires validation in future prospective studies.

Bevacizumab

Bevacizumab was thought to be able to improve outcomes in patients with newly diagnosed glioblastoma by potentiating the therapeutic effects of both RT and chemotherapy. This was supported by 2 phase II studies that showed favourable OS and PFS compared to historical controls respectively.^{30,31} However, 2 subsequent randomised, placebo-controlled phase III trials of standard chemoradiation (concurrent temozolomide and RT followed by adjuvant temozolomide) with or without bevacizumab in newly diagnosed glioblastoma patients failed to demonstrate any survival benefits in patients treated with bevacizumab compared to placebo.^{32,33} Although both trials showed similar adverse effects of bevacizumab, AVAglio³² demonstrated maintenance of HRQOL, while RTOG 0825³³ reported increased symptom burden, worse HRQOL and decline in neurocognitive function.

Nimotuzumab

Nimotuzumab is a humanised monoclonal antibody that binds to epidermal growth factor receptor (EGFR) and alters cell division. A randomised, double-blind phase II trial conducted in patients with high-grade glioma and KPS ≥ 60 demonstrated improved median OS when treated with nimotuzumab and RT compared to RT alone (17.8 vs 12.6 months; HR = 0.64; $P = 0.032$).³⁴ Of note, majority of the patients in this trial have anaplastic astrocytoma (41 anaplastic astrocytoma and 29 glioblastoma multiforme), hence results from this study cannot be generalised to patients with glioblastoma. A German phase III trial also showed no significant PFS or OS difference in glioblastoma patients treated with standard chemoradiation (temozolomide and RT) with or without nimotuzumab; EGFR amplification status did not predict treatment response.³⁵ In both studies, there was a trend towards improved efficacy in MGMT non-methylated glioblastoma patients. This efficacy stratified by MGMT methylation status remains to be validated.

Cost-effectiveness

Alongside the landmark trial by Stupp et al,² economic data were collected prospectively for a subgroup of 219 (38%) patients, and analysed from the perspective of the public healthcare system in the Netherlands, Switzerland and Canada.³⁶ The incremental cost-effectiveness ratio (ICER) was estimated at USD \$40,716 per life-year gained, comparable to accepted first-line chemotherapy in cancer patients. In England, an economic evaluation of treatment with temozolomide in the adjuvant and concomitant phase revealed an additional cost of around USD \$11,971 for an additional 0.217 quality-adjusted life year (QALY) per patient, translating to a base-case ICER of USD \$55,254/QALY.³⁷ Similarly, in China, the addition of temozolomide increased the cost and QALY relative to RT alone by USD \$25,328 and 0.29 respectively, giving rise to an ICER of USD \$87,940/QALY.³⁸ Authors in both of these latter studies concluded that temozolomide is not a cost-effective option for glioblastoma patients but suggested an improved cost-effectiveness with selection and treatment of patients with more favourable prognostic factors. There is currently no local cost-effectiveness study available.

Recommendations for Front-line Systemic Therapy for Glioblastoma

All members of the workgroup supported the adoption of NCCN guidelines.

There is unanimous agreement that fractionated RT concurrent with temozolomide followed by adjuvant temozolomide is the standard of care for glioblastoma patients age ≤ 70 years with good PS, defined by WHO PS ≤ 2 (Category I). Similar efficacy to European Multicentre Phase III trial has been demonstrated in a local study.²⁴ Dose-dense therapy is not recommended.

For glioblastoma patients age > 70 years with good PS, options of treatment include hypofractionated RT, temozolomide with deferred RT or RT with concurrent temozolomide followed by adjuvant temozolomide. We suggest checking MGMT promoter methylation status in this group, and recommend temozolomide therapy, if positive.

The routine addition of bevacizumab as upfront therapy is not recommended.

The role of nimotuzumab as front-line therapy was debated. One of the workgroup members felt that the randomised phase II Cuban trial provided sufficient evidence to recommend nimotuzumab, in addition to RT, as front-line therapy in rare situations where myelosuppression of temozolomide cannot be tolerated. The rest of the workgroup members argued that the trial was conducted with small patient numbers with results not reproduced in other trials, had also not been supported by other national guidelines committees and that given its additional cost

and lack of confirmatory trial data, nimotuzumab cannot be recommended as standard front-line therapy.

Given the lack of data on front-line therapy in patients with poor PS, combination therapy with PCV, temozolomide monotherapy, RT alone or best supportive care is reasonable.

3. Systemic Therapy for Recurrent High-Grade Glioma

Current available chemotherapy is not curative and recurrence or progression of malignant glioma will eventually occur. There is currently no established standard systemic therapy for patients who have experienced treatment failure.

Chemotherapy

Continuous temozolomide (50 mg/m²) is a treatment option in patients with recurrent or progressive malignant glioma. The RESCUE study, a phase II study, demonstrated good 6-month PFS rates of 23.9% and 35.7% in glioblastoma and anaplastic astrocytoma patients respectively.³⁹ Other possible regimes include temozolomide at 200 mg/m²/day for 5 days in 28-day cycles for chemotherapy-naïve patients and 150 to 200 mg/m²/day for 5 days in 28-day cycles for patients previously treated with chemotherapy.⁴⁰⁻⁴²

The role of PCV in recurrent oligodendroglioma was examined retrospectively in a cohort of patients treated with first-line temozolomide within the EORTC study 26971, and demonstrated a modest response rate of 17% and 6-month PFS of 50%.⁴³ Brada et al conducted the first randomised trial of temozolomide versus PCV in chemotherapy-naïve patients with recurrent high-grade glioma, and demonstrated no clear significant survival benefits of temozolomide over PCV.⁴⁰ This study also compared 2 temozolomide treatment schedules and showed that the 5-day schedule (200 mg/m²/day for 5 days in 28-day cycle) improved overall PFS, OS and global quality of life when compared to the 21-day schedule (100 mg/m²/day for 21 days in 28-day cycle).

Lomustine, another treatment option, was used as a comparator in the first phase III trial conducted in patients with recurrent glioblastoma.⁴⁴ The trial was terminated early as study drug, enzasturin, failed to demonstrate superior PFS to lomustine (6-month PFS 11.1% vs 19.0%; $P = 0.13$). A subsequent phase III trial also failed to demonstrate significant PFS improvement with cediranib, an oral pan-vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor, as monotherapy (HR = 1.05; 95% CI, 0.74 to 1.50; $P = 0.90$) or in combination with lomustine (HR = 0.76; 95% CI, 0.53 to 1.08; $P = 0.16$), versus lomustine alone in patients with recurrent glioblastoma.⁴⁵

Two phase II studies of cyclophosphamide conducted in patients with recurrent, temozolomide-refractory glioblastoma and anaplastic astrocytoma showed 6-month

PFS of 20% and 30% respectively.^{46,47}

For recurrent or progressive oligodendroglioma patients treated with surgery, RT, PCV and temozolomide, carboplatin and teniposide are also treatment options. Use of carboplatin and teniposide as third-line chemotherapy is supported by a phase II study demonstrating a 6-months PFS of 34.8%.⁴⁸

Other treatment options include etoposide (VP16) in patients with recurrent supratentorial malignant glioma previously treated with RT and nitrosurea,⁴⁹ and CPT-11 (irinotecan) in patients with recurrent temozolomide-refractory anaplastic astrocytoma⁵⁰ and anaplastic oligodendroglioma.⁵¹ In a pooled analysis of 596 patients enrolled in The North American Brain Tumor Consortium (NABTC) phase II studies conducted from 1998 to 2002, 6-month PFS was 28% and 16%, and median OS was 39 weeks and 30 weeks, for patients with recurrent grade III and grade IV tumours respectively.⁵² The data serves as historical controls.

Bevacizumab

Bevacizumab is a humanised monoclonal antibody against VEGF and inhibits angiogenesis. Its role in recurrent glioblastoma has been defined by 2 phase II studies. Friedman et al evaluated the efficacy of bevacizumab, alone and in combination with irinotecan, in patients with recurrent glioblastoma, and demonstrated MRI-defined objective response rates (ORR) of 28.2% and 37.8% as well as 6-month PFS rates of 42.6% and 50.3% respectively.⁴ The PFS demonstrated was similar to a previous trial.⁵³ In the other pivotal phase II study by Kreisl et al, bevacizumab monotherapy yielded ORR of 71% and 35% based on Levin and MacDonald criteria respectively, 6-month PFS of 29% (95% CI, 18% to 48%), and median OS of 31 weeks (95% CI, 21 to 54 weeks).⁵⁴ Treatment with bevacizumab was associated with a reduction of corticosteroids requirement in both trials.

In patients with recurrent anaplastic gliomas, treatment with single-agent bevacizumab demonstrated median OS of 12 months (95% CI, 6.08 to 22.8), median PFS of 2.93 months (2.01 to 4.93) and 6-month PFS of 20.9% (10.3 to 42.5).⁵⁵ A pooled analysis of 96 patients with recurrent grade III malignant glioma enrolled in 3 consecutive phase II bevacizumab salvage trials demonstrated 6-month PFS and median OS of 39.1% and 9.2 months respectively among patients who continued bevacizumab therapy after study progression, compared to 23.1% and 10.3 months in patients who initiated non-bevacizumab containing therapy, suggesting that salvage therapies following bevacizumab failure have modest activity independent of further use of bevacizumab.⁵⁶ Reported serious adverse events associated

with bevacizumab include hypertension, spontaneous colon perforation, poor wound healing and thromboembolic events.⁵⁷

Combination therapies with bevacizumab have also been studied in prospective trials. In a phase II trial, treatment with bevacizumab and irinotecan in patients with recurrent grade III glioma demonstrated 6-month PFS of 55% and 6-month OS of 79%.⁵⁸ In a more recent open-label, multicentre phase II study of lomustine, bevacizumab or combination treatment with lomustine and bevacizumab in patients with first recurrence of glioblastoma, only the combination therapy arm met prespecified criteria for further assessment in phase III studies (9-month OS: lomustine 43% (95% CI, 29 to 57); bevacizumab 38% (25 to 52); lomustine 90 mg/m² + bevacizumab 59% (43 to 73)).⁵⁹

Cost-effectiveness

Due to the lack of statistically significant extension of median survival time and quality of life data, estimation of cost per QALY is difficult. For glioblastoma, the incremental cost per progression-free week for temozolomide was estimated at USD \$1534 when compared to procarbazine, and USD \$613 when compared to placebo (assuming placebo would give no cost and no effect).⁶⁰ For anaplastic astrocytoma, cost per progression-free week for temozolomide against placebo was USD \$629. There is no local study on cost-effectiveness.

Recommendations for Systemic Therapy for Recurrent Malignant Gliomas

All members of the workgroup support the adoption of NCCN and ESMO guidelines.

There is currently no established systemic therapy for recurrent malignant glioma. For patients with good PS, reasonable chemotherapy options include temozolomide, lomustine, combination PCV, cyclophosphamide, platinum-based agents and irinotecan.

Bevacizumab, as monotherapy or in combination with other chemotherapy, may also be considered in recurrent glioblastoma. For patients with poor PS, best supportive care is reasonable. The SCAN workgroup acknowledges that there is no local data on systemic therapy in recurrent high-grade glioma.

Conflicts of Interest

Dr Chan reports receiving honoraria from Eli Lilly, MSD and Bayer; Dr Tham, receiving honoraria from Merck Sonoro; Dr Lin and Dr Ong have nothing to disclose.

Workgroup Members

The Members of the SCAN Neuro-Oncology Workgroup are Section Lead and Workgroup Chairperson: Chee Kian Tham, MBBS, MMed (Int Med), MRCP (UK), Division of Medical Oncology, National Cancer Centre Singapore, Singapore; Workgroup Members (Voting): Xuling Lin, MBBS, MMed (Int Med), MRCP (UK), Department of Neurology, National Neuroscience Institute Singapore, Singapore; Sin Jen Ong, MBBS (London), MMed (Int Med), MRCP (UK), Division of Medical Oncology, National Cancer Centre Singapore, Singapore; Daniel BY Chan, MBBS (Hons), MRCP (UK), FAMS (Med Onc), SOC@KWGE Oncology Centre, Gleneagles Medical Centre Singapore, Singapore.

Reviewers

Invited reviewers were Thomas Kaley, MD, Department of Neurology, Memorial Sloan Kettering Cancer Center, USA; Sith Sathornsumetee, MD, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Thailand.

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Supplementary Table 1. International Guidelines for the Systemic Therapy of High-Grade Glioma

Guideline Title	NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), Central Nervous System Cancers v.2.2013	EANO Guidelines for the Diagnosis and Treatment of Anaplastic Gliomas and Glioblastomas	High-Grade Malignant Glioma: ESMO Clinical Practice Guidelines	Canadian Recommendations for the Treatment of Glioblastoma Multiforme	Clinical Practice Guidelines for the Management of Adult Gliomas: Astrocytomas and Oligodendrogliomas
Year Released	2013	2014	2014	2007	2009
Guideline Developer	National Comprehensive Cancer Network (NCCN)	European Association for Neuro-Oncology (EANO)	European Society for Medical Oncology (ESMO)	Canadian GBM Recommendations Committee	Australian Cancer Network
Frontline Systemic Therapy for Anaplastic Glioma					
AO/ AOA	Fractionated external beam RT + PCV [cat I] or Fractionated external beam RT + TMZ or PCV or TMZ [cat IIB] KPS ≥ 70 ; 1p19q co-deleted KPS ≥ 70 ; 1p19q uni- or non-deleted	CT with alkylating agent with or without RT [II, B]	RT + PCV [I, B]; stated no difference in efficacy was apparent between PCV and TMZ [III, B]	Not applicable	No specific recommendations
AA	Fractionated external beam RT [cat I] or Fractionated external beam RT + TMZ or PCV or TMZ	Involved-field RT [I, A] or TMZ [II, B] or PCV [II, B]		Not applicable	Adjuvant CT and RT [II]
AG	Fractionated external beam RT or PCV or TMZ or BSC	Not specified		Not applicable	No specific recommendations
Member Votes	4 of 4 votes				
Frontline Systemic Therapy for Glioblastoma					
GBM	Age ≤ 70 : Fractionated external beam RT + concurrent and adjuvant TMZ [cat I]; Age > 70 : Fractionated external beam RT [cat I] + concurrent and adjuvant TMZ or Fractionated external beam RT (hypofractionated) [cat I] or TMZ (if MGMT positive) Good PFS (KPS ≥ 70 or ECOG ≤ 2) Poor PFS (KPS < 70 or ECOG > 2)	Age $< 65 - 70$ yr: Involved-field RT + concomitant and adjuvant (six cycles) TMZ [I, A] Age $\geq 65 - 70$ yr: RT + TMZ or hypofractionated RT [I, A] or TMZ [I, A] based on MGMT promoter methylation status	No recommendations	Concomitant (75 mg/m ² x typically 42 days) + adjuvant (5/28-day schedule; start 150 mg/m ² then increase to 200 mg/m ² at cycle 2) TMZ	Age ≤ 70 : concomitant and adjuvant TMZ; age > 70 : consider adjuvant TMZ only [III]
Member Votes	4 of 4 votes		Concomitant and adjuvant (5 days every 4 weeks x 6 cycles) TMZ [I, A]	No recommendations	No recommendations

AG: Anaplastic glioma; AO: Anaplastic oligodendroglioma; AOA: Anaplastic oligoastrocytoma; BSC: Best supportive care; cat: Category; CT: Chemotherapy; ECOG: Eastern Cooperative Oncology Group; GBM: Glioblastoma multiforme; KPS: Karnofsky performance score; MGMT: O-6-methylguanine-DNA methyltransferase; PCV: Procarbazine, lomustine and vincristine; PFS: Performance status; RMG: Recurrent malignant glioma; RT: Radiation therapy; TMZ: Temozolomide; yr: Year(s); []: Recommendation

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Systemic Therapy for Recurrent Malignant Gliomas					
RMG	BSC (if performance status) or systemic CT or surgery for symptomatic, large lesion or alternating electric field tx [GBM - cat IIB]	AG: TMZ GBM: nitrosurea regimens or TMZ rechallenge or bevacizumab or recruitment into clinical trials [II,B]	No established CT regimen; single agent nitrosurea in some patients; Erlotinib/irinotecan failed to show antitumour efficacy [II,C]; Bevacizumab +/- irinotecan effect on life expectancy unknown [III,C]; re-operation [IV,C]; CT-impregnated polymers with repeat radical op show marginal survival benefits [II,B]	Consider repeat resection; no established optimal CT strategy	CT has modest activity in recurrent high-grade astrocytoma
	Local resectable				
	Local unresectable				
Member Votes	4 of 4 votes		4 of 4 votes		

AG: Anaplastic glioma; AO: Anaplastic oligodendroglioma; AOA: Anaplastic oligoastrocytoma; BSC: Best supportive care; cat: Category; CT: Chemotherapy; ECOG: Eastern Cooperative Oncology Group; GBM: Glioblastoma multiforme; KPS: Karnofsky performance score; MGMT: O-6-methylguanine-DNA methyltransferase; PCV: Procarbazine, lomustine and vincristine; PFS: Performance status; RMG: Recurrent malignant glioma; RT: Radiation therapy; TMZ: Temozolomide; yr: Year(s); []: Recommendation

Singapore Cancer Network (SCAN) Guidelines for the Initial Evaluation, Diagnosis, and Management of Extremity Soft Tissue Sarcoma and Osteosarcoma

The Singapore Cancer Network (SCAN) Sarcoma Workgroup

Abstract

Introduction: The SCAN sarcoma workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for the initial evaluation, diagnosis, and management of extremity soft tissue sarcoma and osteosarcoma. **Materials and Methods:** The workgroup utilised a consensus approach to create high quality evidence-based clinical practice guidelines suited for our local setting. **Results:** Various international guidelines from the fields of radiology, pathology, orthopaedic surgery, medical, radiation and paediatric oncology were reviewed, including those developed by von Mehren M et al (J Natl Compr Canc Netw 2014), the National Collaborating Centre for Cancer (2006), the European Sarcoma Network Working Group (2012) and Grimer RJ et al (Sarcoma 2008). Our clinical practice guidelines contextualised to the local patient will streamline care and improve clinical outcomes for patients with extremity soft tissue and osteosarcoma. **Conclusion:** These guidelines form the SCAN Guidelines 2015 for the initial evaluation, diagnosis, and management of extremity soft tissue sarcoma and osteosarcoma.

Ann Acad Med Singapore 2015;44:474-83

Key words: Asian patients, Limb, STS, Treatment

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Introduction

Sarcoma is an uncommon and heterogeneous family of cancers, with more than 50 clinico-pathologically distinct subtypes representing 1% of all malignancies.¹ Although ubiquitous in presentation, a significant proportion arises from the extremities. Data from our large sarcoma database which comprise 1029 unique patients demonstrates that 35% of all sarcomas arise from the extremities with soft tissue sarcomas (STS) accounting for 87% of these cases. The 3 most common STS histotypes include liposarcoma, unclassified pleomorphic sarcoma (UPS) formerly termed malignant fibrous histiocytoma (MFH), and myxofibrosarcoma. In the remaining 13% of extremity bone sarcomas, osteosarcomas account for half of the cases.

While several international guidelines exist for the treatment of extremity sarcomas, due to unique geographical differences, patient population, presentation, healthcare resources, and reimbursement issues, direct application of these international guidelines to our local patients may not always be possible. In addition, unique differences in our patient population as well as acceptance and tolerance of various treatment modalities exist. Therefore, there is a need

to develop a set of local clinical practice guidelines which would address our own patient population and sarcoma practice within our healthcare context.

In this article, we aim to provide an evidence-based consensus approach to the initial evaluation, diagnosis, and management of an extremity sarcoma, described in close parallel to a patient's journey. Because patients with limb sarcomas, be it from a soft tissue or bone primary, may present similarly with a painless enlarging mass and physical examination alone may not adequately distinguish them, the initial evaluation of an extremity mass follows the same initial diagnostic paradigm but quickly dichotomises once a bony tumour is differentiated from a soft tissue mass. This article first describes the radiological, diagnostic, and pathological management of an extremity mass and once diagnosis is confirmed, separately discusses the specific management guidelines of limb STS and osteosarcoma.

The SCAN Guidelines for the Initial Evaluation, Diagnosis, and Management of Extremity STS and Osteo-sarcoma

The SCAN Guidelines are clinical practice guidelines

Address for Correspondence: Dr Richard Quek, Division of Medical Oncology, National Cancer Centre Singapore, 11, Hospital Drive, Singapore 169610.
Email: dmqrh@nccs.com.sg

for the initial evaluation, diagnosis, and management of extremity STS and osteosarcoma.

These first edition guidelines are intended to serve as treatment recommendations by members of this working group reflecting their views on the management of extremity STS and osteosarcoma. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

Target Users of the Guidelines

The guidelines will be of interest to oncologists, oncology nurse specialists, pharmacists, allied health workers and general practitioners involved in the management of extremity STS and osteosarcoma.

Guideline Recommendations/Development

The SCAN Sarcoma Working Group comprises a panel of 14 members with special interests in the management of sarcoma. Members come from diverse specialities including orthopaedic surgery, pathology, diagnostic radiology and medical, radiation, surgical, paediatric and musculoskeletal oncology. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICJME) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the cancer network team. The group met once in person, and completed guideline development through email communication.

A consensus approach was used to develop guidelines streamlined to the Singapore context. First, available resources were considered. High quality guidelines²⁻⁵ were selected for review and structured approaches developed for guideline evaluation. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. The SCAN guidelines were then written with consensus from workgroup members for each recommendation. Calibration of guidelines to the local context based on available Singapore data was encouraged. The final phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to address the 4 main management issues which were selected for this topic:

1. Radiological Imaging
2. Pathologic Assessment
3. Treatment of Osteosarcoma
4. Treatment of STS

The following international guidelines were selected for review:

- “Soft Tissue Sarcoma” (version 2.2014) by von Mehren M et al (J Natl Compr Canc Netw, 2014)²
- “Improving Outcomes for People with Sarcoma” by the National Collaborating Centre for Cancer (National Institute for Health and Clinical Excellence, London 2006)³
- “Soft Tissue and Visceral Sarcomas: EMSO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up” by the European Sarcoma Network Working Group (2012)⁴
- “UK Guidelines for the Management of Bone Sarcomas” by Grimer RJ et al (Sarcoma, 2008)⁵

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of sarcoma, it will be reviewed earlier.

1. Radiological Imaging

The initial investigation for anyone presenting with a mass in the extremity is a plain radiograph done in 2 planes.⁵⁻⁷ This helps to differentiate between STS and bone tumours. Additional oblique radiographs of the bone tumours may help evaluate cortical continuity and joint involvement.

Magnetic resonance imaging (MRI) is used for local staging.^{2,4-8} An MRI allows for the evaluation of tumour size, the extent (including involvement of contiguous structures), and involvement of the neurovascular bundle. For bone tumours, an additional sequence of the entire long bone is done to look for skipped intramedullary lesions. If the tumour is close to a joint, the joint should be included in the images to check for contiguous involvement. The use of gadolinium contrast is optional for initial staging scans (but is required for follow-up scans post-therapy) and is generally administered unless there is a contraindication. An MRI provides details of the anatomical structures adjacent to the tumour and detects any distortion or involvement. A computed tomography (CT) scan of the local area is generally used for problem solving—to visualise calcification, periosteal bone formation, and subtle cortical erosion.^{6,7} If the MRI is contraindicated, a CT scan (with iodinated contrast) or CT angiogram can be performed.⁸

If sarcoma is confirmed, staging of the disease is accomplished with a helical CT scan of the chest.^{2,4,8} CT scan of the abdomen and pelvis may be considered after biopsy has been performed and metastatic disease is diagnosed. For bone sarcomas, an isotope bone scan is performed to look for metastatic disease of the bone.⁵⁻⁷ An MRI of the whole body is a sensitive imaging technique for the detection of skeletal metastases in patients with small cell neoplasms, Ewing's sarcoma, and osteosarcoma.⁷

Additional staging investigations may be needed for selected STS, depending on the histology results. A staging CT scan of the abdomen/pelvis may be considered for myxoid liposarcoma, angiosarcoma or epithelioid sarcoma.^{2,4,8} Of these, myxoid liposarcoma metastasises more frequently to the mediastinal and retroperitoneal spaces than the rest. In addition, myxoid liposarcomas have a higher risk of metastasis to the spine compared to other STS and an MRI of the whole spine should be considered.² In STS with a propensity for nodal spread (such as synovial sarcoma, epithelioid sarcoma, clear cell sarcoma^{4,8} and alveolar soft part sarcoma),⁸ an assessment of the regional lymph nodes should be done. For alveolar soft part sarcoma and angiosarcoma, an assessment of the central nervous system should be considered as part of staging.^{2,4}

The utility of a whole body MRI and a positron emission tomography (PET)-CT is still being evaluated for staging and treatment response for bone sarcomas. However, it is not routinely recommended.⁵ Reports have demonstrated the utility of PET scans in the evaluation of response to chemotherapy in patients with osteosarcoma, Ewing's sarcoma, and advanced chordoma.⁷ Research is ongoing.

Although a PET-CT is not recommended for routine staging,⁸ it may be useful for prognostication, grading, and determining a patient's response to chemotherapy for firm, deep lesions larger than 3 cm in high-grade extremity STS.² Tumour SUVmax has been shown to correlate with tumour grade and prognostication and was an independent predictor of survival and disease progression.⁹ Pretreatment SUVmax and change in SUVmax after preoperative chemotherapy independently identified patients at high risk of recurrence.¹⁰ Patients with a change of SUVmax of 40% or more in response to chemotherapy were at a significantly lower risk of recurrence and death after complete resection and postoperative radiotherapy.¹⁰ PET was useful in the early assessment response to preoperative chemotherapy and was also significantly more accurate than RECIST¹¹ in the assessment of histopathologic response to preoperative chemotherapy.²

2. Pathologic Assessment

Principles of Biopsy

A biopsy for histological diagnosis is pivotal in the investigation and subsequent management of bone and STS.¹² This biopsy should be performed by the same surgeon who will be performing the surgical resection.¹³

A biopsy should be kept as minimally invasive as possible, while still yielding sufficient tissue to obtain a diagnosis, as more immunohistochemistry and genomic tests are being done to classify sarcoma than previously. Fine needle aspiration cytology is, however, not appropriate as the pathologist needs sufficient tissue for analysis. A percutaneous trucut core needle biopsy, under ultrasound or computed tomogram guidance if necessary, is preferred.^{14,15} Open biopsy may still be indicated if the anatomy precludes percutaneous core needle biopsy or if percutaneous core needle biopsy is unsuccessful.

A biopsy should be performed only after detailed imaging of the lesion has been completed.¹⁶ This allows for careful planning of the biopsy tract.¹⁶ A poorly performed biopsy can compromise treatment outcomes, especially those of possible limb salvage surgery.¹⁵

The biopsy skin incision should be kept to the minimum required for access.¹¹ Planning ahead for possible future surgical resection, the biopsy skin incision should be orientated longitudinally, allowing for an extensile surgical approach to the limb.^{15,17}

In general the most direct route is taken to the lesion, avoiding neurovascular structures and traversing of joints. The biopsy should ideally be kept to a single compartment and should minimise the opening of fascial planes. Meticulous haemostasis throughout the biopsy is critical.¹⁸ A muscle splitting approach whenever traversing muscle planes is advised.

If a bone window is required to be made for access, attention should be paid to its size and shape. The bone window should only be made as large as necessary for access and sharp edges are to be avoided as they act as stress risers.

Sampling of the lesion should be directed by the prebiopsy imaging which would identify the part of the lesion with the greatest suspicion for sarcomatous tissue. Intraoperative frozen section analysis to confirm lesional tissue is advised.¹⁹ It is important to take adequate amounts of representative tissue for the pathologist.¹⁴ These samples should ideally be sent to a pathologist with an interest in musculoskeletal oncology.¹⁹ A detailed clinical and radiological patient history in the accompanying histology request form would be helpful to the pathologist and should be included.^{15,16} Samples should also be taken for cultures by the microbiologist to exclude infection, such as tuberculosis and fungal cultures.

Principles of Pathologic Assessment

The diagnostic approach of limb sarcomas is highly complex and labour intensive due to the sheer volume of differential diagnoses to consider covering bone, STS, and sometimes carcinomas and melanomas, and therefore requires a multidisciplinary approach. This is especially relevant for bone tumours where input by the clinicians and radiologists are critical to avoid well known diagnostic pitfalls.

Before interpreting the biopsy, pathologists need to be furnished with relevant clinicoradiological information and radiological images. This information should include at least:

- a) site of the tumour (for instance, bone versus soft tissue-centred, anatomical region of the bone),
- b) characteristics of the tumour (for instance, benign versus aggressive, homogenous versus heterogeneous, bone or cartilage forming) and
- c) tumour relationship with other structures such as nerves, bone, muscle, vessels, etc.

Besides influencing the diagnosis, this information may help the pathologist decide whether the biopsies are likely to be diagnostic or representative.

Assessment of Biopsy Specimen

A preliminary investigation of limb sarcomas usually involves obtaining multiple core biopsies (at least 4 to 5 cores) or incisional biopsies from the patient. Excision biopsies may be considered for STS that are small, superficial, and easily resectable. However, fine needle aspiration is not recommended as a primary diagnostic modality, except for confirming disease recurrence or obtaining material for ancillary tests. For bone tumours or specimens, it is likely that the tissue will undergo decalcification, potentially affecting immunohistochemical results or genomic analyses. The frozen-section technique for immediate diagnosis should be avoided in bone tumours due to suboptimal histological interpretation, sampling issues, and lack of immediate ancillary support.

Assessment of Resection Specimen

Histological evaluation of limb sarcomas usually involves a description of the tumour in the resected specimens which should at least include its site, size, gross characteristics and relationships with surrounding structures and margins. A detailed description of the margins (such as intralesional, marginal, or wide) with close communication between the clinician and pathologist is important since the margin status often determines the tumour recurrence rate.

For post-treated osteosarcoma specimens, there is an

additional requirement of detailed tumour mapping and estimation of the amount of tumour necrosis by percentage. Detailed discussions on the gross handling and tumour reporting datasets for resected limb sarcoma specimens are covered comprehensively in the websites of various pathology organisations and colleges.²⁰⁻²²

Histological Diagnosis

Histological diagnosis of limb sarcomas should be made according to the latest (2013) World Health Organisation (WHO) classification for bone and STS.¹ For STS, grading should be provided following the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system, which is based on tumour differentiation, mitotic count, and necrosis. Malignancy grading may be underestimated in small biopsies particularly in heterogeneous tumours.

The histological assessment of both STS and osteosarcoma requires a combination of careful morphological examination complemented by ancillary investigations especially immunohistochemistry and molecular diagnostic tests to determine the subtype. Morphological examination involves a systematic pattern-based approach taking into consideration the architecture, cytomorphological features and matrix of tumours. The diagnosis of osteosarcoma requires the identification of osteoid forming cells or matrix for both low- and high-grade osteosarcoma variants.¹ However, diagnostic difficulties may arise where the presence of osteoid cannot be confirmed (for instance, sampling problem related to small biopsies, osteoid-poor osteosarcoma variants) or in low-grade tumours.

Ancillary Investigations

A panel of immunohistochemistry stains is often required for the diagnosis of most STS and more rarely in bone sarcoma. Comprehensive discussions of the appropriate immunohistochemistry panels with the corresponding differential diagnoses can be found in most specialised pathology textbooks.

Molecular diagnostic tests play a critical role in determining the final diagnosis of many sarcomas particularly in those with recurrent chromosomal translocations (for instance, Ewing sarcoma, synovial sarcoma, alveolar rhabdomyosarcoma, etc.). Recent studies have also shown that these tests can be utilised to diagnose certain types of low-grade osteosarcoma²³ and benign bone tumours (for instance, aneurysmal bone cyst).²⁴ Molecular tests are often employed in problematic tumours that demonstrate unusual clinical presentation, atypical morphology, encompass numerous differential diagnoses (for instance, small round cell tumours) and overlapping immune-phenotype.

In summary, the diagnostic algorithm of limb sarcoma is a highly specialised and complex process that often requires a sarcoma pathologist with clinical and morphological expertise and a deep familiarity with modern ancillary techniques.

3. Treatment of Osteosarcoma

Once the diagnosis of sarcoma is made and staging completed, treatment of osteosarcoma and STS follows a divergent paradigm. In the following sections we outline the optimal management strategies of limb osteosarcoma and STS.

Surgery in Osteosarcoma

The decision for surgery, including whether the osteosarcoma is resectable, the timing, and type of surgery, should be made by the multidisciplinary oncology team caring for the patient.

Patients with high-grade osteosarcoma of the limbs will typically receive several rounds of preoperative, neo-adjuvant chemotherapy before surgical resection. Postoperative, adjuvant chemotherapy often follows resection. Details on optimal chemotherapy in osteosarcoma will be discussed in the following section.

Low-grade osteosarcoma, such as low-grade central and parosteal osteosarcoma, can however sometimes be treated by wide surgical resection alone. Updated imaging of the osteosarcoma should be carefully reviewed by the multidisciplinary oncology team to determine the optimal surgical procedure for each individual patient, i.e. whether limb salvage or amputation surgery is indicated.

Any surgery performed should be by the same surgeon who performed the initial biopsy procedure. This surgeon should ideally be an orthopaedic oncologist who is familiar with both sarcoma resection, as well as the subsequent reconstructive surgery.

The primary aim of surgery is en-bloc resection of the osteosarcoma (including the biopsy tract, if any) with adequately clear surgical margins. Intraoperative frozen section is helpful in evaluating operative margins. Close surgical margins should be marked with MRI compatible titanium surgical clips for postoperative surveillance and the possible need for adjuvant radiotherapy.

If limb salvage surgery is to be performed, wide resection has to be thoughtfully executed, with surgeons mindful of the need to preserve as much limb function as possible. Reconstruction can involve the use of autografts, allografts, endoprosthesis, or combinations of the above. A multidisciplinary team of surgeons may need to be involved in the reconstructive phase of the surgery, for example,

plastic surgeons to assist with skin and soft tissue coverage and vascular surgeons for vessel reconstruction.

Primary solitary or oligometastatic osteosarcoma, especially in cases with completely resectable lung metastases only, strongly merits consideration for curative treatment intent along the principles of localised osteosarcomas. Of note, there are subsets of patients who may have a very similar prognosis to that of localised disease provided surgical removal of all known metastatic disease is achieved.

In the management of recurrent osteosarcoma, one needs to consider the timing of the recurrence, as well as the number and site of any metastases. If surgery is to be performed, complete removal of all recurrent and metastatic tissue must be attempted otherwise the prognosis is very poor.^{25,26}

Radiotherapy in Osteosarcoma

In general, there is no indication for the role of radiotherapy in the adjuvant management of osteosarcoma. However, in clinical and anatomical situations where complete surgical excision is not possible, e.g. spine or skull base, radiotherapy may be an option to delay disease recurrence and extend progression-free survival.⁶

Systemic Chemotherapy in Osteosarcoma

High-grade osteosarcoma, which accounts for the majority of osteosarcoma in children and adolescents, is predominantly treated by chemotherapy and surgery.^{27,28} The advantages of preoperative chemotherapy include:

1. providing symptom relief,
2. reducing size of primary tumour and therefore improving resectability and chance of limb salvage,
3. treating metastatic disease as well as micrometastases, and
4. allowing the assessment of response to chemotherapy.

The histological response to preoperative chemotherapy predicts survival outcome. Tumours with over 90% necrosis following preoperative chemotherapy are associated with a more favourable outcome.²⁹ Metastatic disease is also strongly prognostic. However, the optimal chemotherapy regimen and schedules are yet to be determined. High-dose methotrexate, adriamycin (doxorubicin), and cisplatin (MAP) form the backbone in most chemotherapeutic regimes for high-grade osteosarcoma, especially in children and young adults.^{6,7} In older adults, doxorubicin and cisplatin alone without methotrexate is a reasonable option in view of poor tolerance to high-dose methotrexate in this patient population.^{6,7,30} The addition of ifosfamide to the traditional MAP backbone for osteosarcoma did not improve survival,

and thus is not employed in the adjuvant setting.³¹ At this moment, it remains unclear if switching or adding other drugs to the postoperative chemotherapy for patients with poor response to preoperative chemotherapy will improve survival outcome.

The European and American Osteosarcoma Study Group (EURAMOS)-1 randomised poor responders (defined as patients with >10% viable tumour after preoperative chemotherapy) to continue with the same chemotherapy (MAP), or to receive additional drugs (ifosfamide and etoposide, MAPIE). The results of this large study are eagerly awaited. Patients with metastatic disease (mainly to the lungs) have a significantly poorer outcome than those with non-metastatic disease. Thoracotomies with removal of all lung metastases should be considered. Options for salvage chemotherapies include high-dose ifosfamide with etoposide (IE), and gemcitabine with docetaxel. The role of interferon or muramyl tripeptide, either upfront or in salvage setting, remains unclear.^{31,32} Although the addition of muramyl tripeptide to standard chemotherapy in patients with completely resected osteosarcoma significantly improved overall survival in a large phase III randomised study, this finding was not associated with a significant corresponding improvement in the event free survival.³¹ Muramyl tripeptide is not available in Singapore.

4. Treatment of STS

Surgery in STS

Surgical resection, with appropriate negative margins, is the mainstay of treatment for STS. There is no universally agreed margin, but generally 1 cm of soft tissue, or an appropriate anatomic layer like fascia, is accepted.³³ Closer margins can be accepted in order to preserve uninvolved critical neurovascular structures.

Preoperative radiotherapy and/or chemotherapy can be considered to downstage large high-grade tumours to enable effective surgical resection. However, there is a risk of tumour progression on treatment and higher wound infection rates with preoperative radiotherapy. Postoperative radiotherapy should be considered following resections with close margins, or microscopically positive margins on bone, critical nerves, and vessels (see following section on Radiotherapy in STS).

The biopsy tract should be excised en bloc together with the main tumour during the definitive resection. Dissection should be done through grossly normal tissue that is not contaminated by tumour. Critical vessels and nerves can be preserved if they are not grossly involved by the tumour, by dissecting through the adventitia or epineurium. Radical resection of the entire anatomic compartments is not routinely required. In some situations, amputations may be

required in order to achieve adequate local control. These are situations where complete resection of the tumour will result in a non-functional limb.

If positive microscopic or gross margins are suspected, surgical clips should be used to mark the site to facilitate subsequent radiotherapy planning or surgical resection. If surgical drains are used, they should be placed close to, preferably in line with, the surgical incision, to facilitate subsequent radiotherapy or repeat surgical resection.

The margins should be marked by the surgeon and reviewed with the pathologist. Should there be a positive gross margin, repeat resection to negative margins should be strongly considered. Microscopic positive margins may be acceptable in situations where wide excisions would result in severe morbidity (e.g. when sacrifice of major vessels or nerves is required) in which case, postoperative radiation treatment should be discussed.

Radiotherapy in STS

Good limb conservation surgery combined with postoperative radiotherapy is standard treatment for limb STS and achieves a high rate of local control while maintaining optimal function. Radiotherapy may be avoided in patients with low-grade tumours that have been completely resected or those with small and superficial high-grade tumours resected with adequate wide margins.

Postoperative radiotherapy is considered to be the standard of care for intermediate and high-grade STS as well as deep and large lesions. This allows preservation of function with similar local control rates and survival to radical resection.³⁴ The majority of patients with low-grade tumours will not require radiotherapy, however it should be considered for those with large, deep tumours that are incompletely resected, especially if adjacent to vital structures that could limit further surgery in the future.^{35,36} Patients who have undergone a compartmental resection or amputation do not require adjuvant irradiation assuming that the margins are clear.

The recommended postoperative radiation dose is 60-66 Gy in 1.8-2 Gy fractions. A 2-phase technique using a shrinking field is commonly used; 50 Gy to the initial larger volume followed by 10-16 Gy to a smaller volume.^{35,36} This dose may need to be reduced if the field includes critical structures (for instance, the brachial plexus). Dose to the skeletal bone should be avoided if possible, to prevent risks of fractures in future, and the volume should take into consideration natural tissue plane/compartments and fascia.

There is a VORTEX randomised clinical trial for extremity STS in the United Kingdom. It compares the standard 2-phase conventional radiotherapy technique with a single phase to a smaller tissue volume, in an attempt to

spare normal tissue and hence improve subsequent limb function without compromising local control. The study has completed accrual and results are pending.

Comparing pre versus postoperative radiation in limb sarcoma, preoperative radiation has been shown to be associated with increased postoperative wound complications compared to the standard postoperative treatment but less late toxicity and better limb function.³⁷ The standard regimen for preoperative radiotherapy is 50 Gy, in 1.8-2 Gy fractions, followed by surgery approximately 6 weeks following completion of radiotherapy. Further radiotherapy (10-16 Gy) may be given postoperatively if tumour margins are positive. Preoperative radiation dose is lower compared to postoperative radiation and the treatment volumes are also smaller. Preoperative radiotherapy is not used routinely, but may be preferred in certain situations where the size of the radiation field required for postoperative treatment is likely to be associated with significant late morbidity, or when the tumour is of borderline operability and preoperative radiotherapy is judged to be capable of rendering the tumour operable. In such situations, more radiosensitive histological types like myxoid liposarcoma may benefit from this approach.

Systemic Chemotherapy in STS

The value of adjuvant chemotherapy in STS, as with any malignancy, is predicated upon 2 fundamental issues—the rates and patterns of recurrence and the efficacy of any therapy in modifying them. Factors like age, size, depth, histology, and anatomical site have been incorporated into validated nomograms to yield recurrence estimations for sarcomas based upon the cumulative datasets of several specialised sarcoma centres.^{38,39} Despite the greater accuracy in predicting recurrences using these tools, data directly addressing the benefit of adjuvant chemotherapy is patchy and inconsistent.

A European study involving 468 patients between 1977 and 1988 revealed no significant benefit of multi-agent combination adjuvant chemotherapy.⁴⁰ However, a subsequent meta-analysis evaluating 18 trials revealed absolute risk reductions in recurrence and death of 12% and 11%, respectively, with the use of adjuvant doxorubicin in combination with ifosfamide.⁴¹ Despite this, the most recently reported large randomised trial using a modern day sarcoma combination chemotherapy regimen of doxorubicin and ifosfamide in 351 patients, two-thirds of whom had extremity sarcoma, revealed no benefit in recurrence free and overall survival.⁴² Concerns have been raised regarding certain aspects of this trial, including the relatively low dose intensity of ifosfamide used, the inclusion of a substantial number of patients with clinicopathological lower risk disease, and the heterogeneity of diagnoses

studied. Nonetheless, it remains the largest randomised clinical trial of adjuvant doxorubicin-based chemotherapy in recent years.

Beyond the uncertainty surrounding absolute efficacy, there is also little data to guide the choice and duration of the regimen to be used in adjuvant therapy. A European randomised trial revealed no differences in outcomes between 3 and 5 cycles of neoadjuvant epirubicin in combination with ifosfamide for STS with high-risk clinicopathological features, suggesting that, if and when adjuvant chemotherapy is used, more dose intense regimens may not always be superior.⁴³ A large criticism of most studies in STS is the inappropriateness of treating disparate histologies, with unquestionably differing biologies and chemosensitivities, in an identical manner. An ongoing randomised trial is thus evaluating a histologically adapted approach (using agents with known preferential activity in particular histologies) in comparison with 3 cycles of epirubicin and ifosfamide.⁴⁴ At the time of this writing, the role of adjuvant chemotherapy in completely resected STS remains controversial, and must be discussed on a case-by-case basis. In addition, we do not recommend the routine use of adjuvant chemotherapy as standard of care in resected extremity STS.

Extremity sarcomas are predisposed to both local and distant recurrence, with disease-associated mortality predominantly contributed by the latter. Doxorubicin has been used in the systemic treatment of advanced sarcomas for the last 40 years and remains the most broadly active agent. Ifosfamide is another commonly used drug in first-line therapy, with a more pronounced disparity in activity across different histologic subtypes.

A landmark randomised controlled trial compared single-agent doxorubicin against the combination of doxorubicin and ifosfamide in advanced STS with more than 200 patients evaluated from 2003 to 2010. While combination therapy doubled objective response rates (26% versus 14%) and improved progression-free survival (7.4 versus 4.6 months), overall survival was no different in the 2 arms.⁴⁵ In second-line therapy, there are several active agents, either as single agents or in combination. The combination of gemcitabine with either docetaxel or dacarbazine has demonstrated salutary improvements in overall survival in pretreated advanced STS in 2 large randomised phase II studies.^{46,47} Single agent gemcitabine is also reported to be effective in leiomyosarcoma.⁴⁸

Pazopanib, a multi-targeted tyrosine kinase inhibitor directed against the receptors of vascular endothelial growth factor, platelet derived growth factor, fibroblast growth factor and KIT, is approved for the treatment of advanced pretreated non-adipocytic STS, following demonstration of a significant progression-free survival benefit when compared

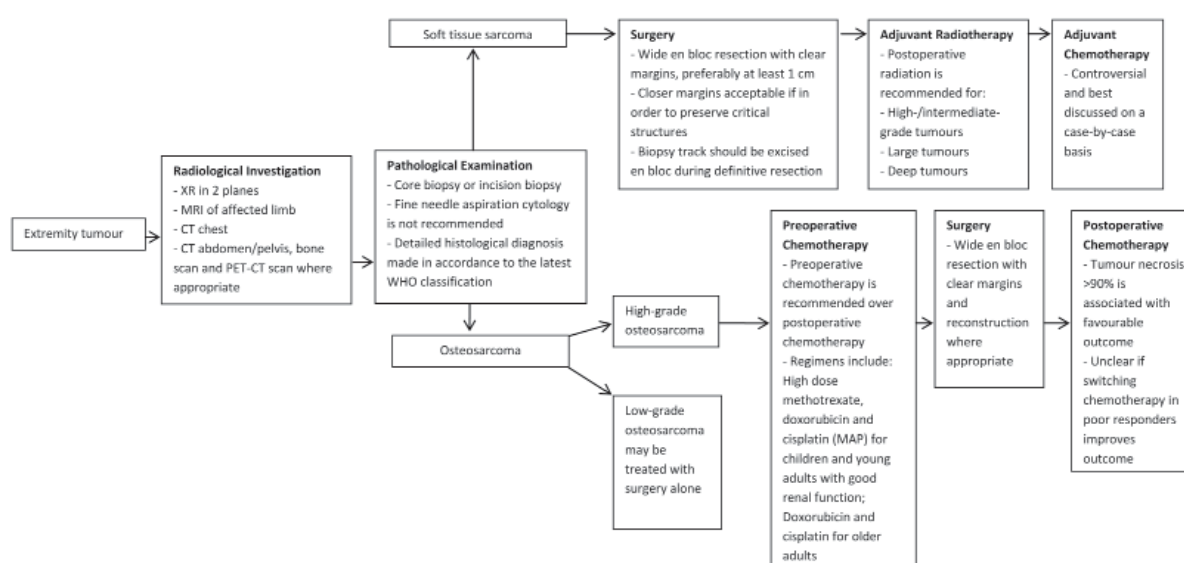


Fig. 1. Treatment flow diagram of a typical patient presenting with an extremity sarcoma.

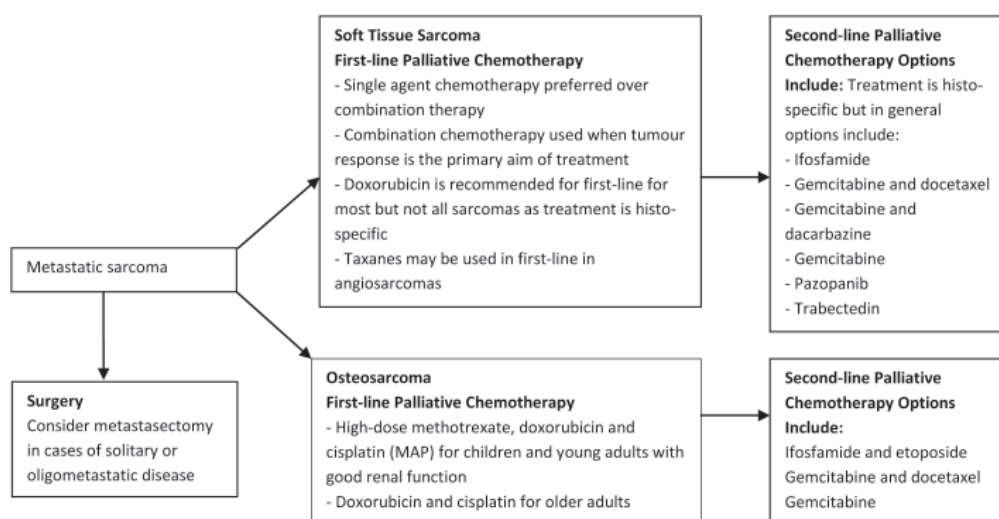


Fig. 2. Treatment flow diagram of a typical patient with metastatic extremity sarcoma.

against a placebo in a large randomised phase III trial.⁴⁹ Several histological subtypes are often treated based upon observed preferential sensitivity to specific agents, such as trabectedin in myxoid liposarcoma⁵⁰ and weekly paclitaxel in angiosarcoma,⁵¹ emphasising again the crucial need for appreciating the clinicobiological diversity of sarcomas in order to select appropriate therapy.

Conclusion

In conclusion, extremity sarcoma is a complex and

heterogeneous group of diseases best managed in a high volume sarcoma centre experienced in the management of these diseases. The initial efforts are aimed at securing an accurate diagnosis leading to a disease-stratified approach in terms of surgery and adjunctive therapies comprising chemotherapy and radiotherapy as appropriate (Figs. 1 and 2). Clinical practice guidelines contextualised to the local patient and unique healthcare setup in Singapore will hopefully streamline care and improve clinical outcomes for our sarcoma patients.

Conflicts of Interest

All the authors have nothing to disclose.

Workgroup Members

The Members of the SCAN Sarcoma Workgroup are Section Lead and Workgroup Chairperson: Richard Quek, MBBS, MRCP (UK), Division of Medical Oncology, National Cancer Centre Singapore, Singapore; Workgroup Members (Voting): Mohamad Farid, MBBS, MRCP (UK), Division of Medical Oncology, National Cancer Centre Singapore, Singapore; Lai Peng Chan, MBBS, FRCR, FAMS, Department of Diagnostic Radiology, Singapore General Hospital, Singapore; Francis CC Kuok, MBBS, MSc (Rad Biol), FRCR (Clinical Oncology) (UK), Division of Radiation Oncology, National Cancer Centre Singapore, Singapore; Leon SS Foo, MBBS (S'pore), MMed (Ortho Surg), FRCSEd (Ortho), Island Orthopaedic Consultants, Mount Elizabeth Medical Centre, Singapore; Victor KM Lee, MBBS, FRCPA, Department of Pathology, National University Health System, Singapore; Mark Edward Puhaindran, MBBS (S'pore), MRCS (Edin), MMed (Surgery), Division of Musculoskeletal Oncology, National University Health System, Singapore; Shui Yen Soh, MBBS, MRCPCH (UK), Department of Paediatric Subspecialties Haematology/Oncology Service, KK Women's and Children's Hospital, Singapore; Khee Chee Soo, MBBS, MD, FRACS, Division of Surgical Oncology, National Cancer Centre Singapore, Singapore; Mann Hong Tan, MBBS, FRCS (Edin & Glasg), FAMS, Department of Orthopaedic Surgery, Singapore General Hospital, Singapore; Jonathan YH Teh, MBBS, FRCR (Clinical Oncology) (UK), Division of Radiation Oncology, National Cancer Centre Singapore, Singapore; Melissa CC Teo, MBBS, FRCS, MPH, Division of Surgical Oncology, National Cancer Centre Singapore, Singapore; Steven BS Wong, MBChB (UK), MMED (NUS), FAMS, Department of Diagnostic Radiology, Singapore General Hospital, Singapore; Workgroup Member (Non-Voting): Ai Ling Shamrez Dandawala, BSc (Hons), Group Education, SingHealth Academy, SingHealth, Singapore.

Reviewers

Invited reviewers were Ian Judson, MA, MD, FRCP, Sarcoma Unit, Royal Marsden Hospital, UK; Sun Young Rha, MD, PhD, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, South Korea; Charlotte Benson, MBChB MRCP, Sarcoma Unit, Royal Marsden Hospital, UK; Robert Maki, MD, PhD, FACP, Tisch Cancer Institute, Mt Sinai Medical Centre (New York), USA.

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Singapore Cancer Network (SCAN) Guidelines for the Initial Evaluation, Diagnosis and Management of Retroperitoneal Soft Tissue Sarcoma

The Singapore Cancer Network (SCAN) Sarcoma Workgroup

Abstract

Introduction: The SCAN sarcoma workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for the initial evaluation, diagnosis and management of patients with retroperitoneal soft tissue sarcoma. **Materials and Methods:** The workgroup utilised a consensus approach to create high quality evidence-based clinical practice guidelines suited for our local setting. **Results:** Various international guidelines from the fields of radiology, pathology, surgical, medical and radiation oncology were reviewed. Recommendations on the role of radiological imaging, pathology, surgery, radiotherapy and systemic therapy in the management of retroperitoneal soft tissue sarcoma were developed. **Conclusion:** These guidelines form the SCAN Guidelines 2015 for the diagnosis, staging and optimal management of patients with retroperitoneal soft tissue sarcoma.

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Key words: Asian patients, Retroperitonuem, Sarcoma, STS, Treatment

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Introduction

Soft tissue sarcoma (STS) is a rare and heterogeneous group of cancers representing <1% of all newly diagnosed malignancies.¹ As an entity, it is made up of more than 50 pathologically and molecularly distinct subtypes of sarcomas. Originating at any site in the body, approximately 15% of STS originate from the retroperitoneal region.² Based on the National Cancer Centre Singapore's (NCCS) sarcoma database, the 3 most common STS histotypes include well differentiated/dedifferentiated liposarcoma, leiomyosarcoma and undifferentiated pleomorphic sarcoma (UPS) (formerly termed malignant fibrous histiocytoma).

While several international guidelines for treatment of retroperitoneal STS exist, due to unique differences in patient population, healthcare structure and reimbursement issues, direct application of these international guidelines to the local context is oftentimes not possible. Hence, there exists a need to develop a set of local Singaporean guidelines to address this unique patient population and sarcoma practice within our healthcare context.

In this consensus statement, we aim to provide an evidence-

based approach to the initial diagnosis, investigation and subsequent management of retroperitoneal STS.

The SCAN Guidelines for the Initial Evaluation, Diagnosis and Management of Patients with Retroperitoneal STS

The SCAN Guidelines are clinical practice guidelines for the initial evaluation, diagnosis and management of patients with retroperitoneal STS.

These first edition guidelines are intended to serve as treatment recommendations by members of this working group reflecting their views on the management of retroperitoneal STS. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

Target Users of the Guidelines

The guidelines will be of interest to oncologists, oncology nurse specialists, pharmacists, allied health workers and general practitioners involved in the management of patients

Address for Correspondence: Dr Richard Quek, Division of Medical Oncology, National Cancer Centre Singapore, 11 Hospital Drive, Singapore 169610.
Email: dmoreqh@nccs.com.sg

with retroperitoneal STS.

Guideline Recommendations/Development

The SCAN Sarcoma Workgroup comprises a panel of 14 members with special interests in the management of sarcoma. Members come from diverse specialities including orthopaedic surgery, pathology, diagnostic radiology and medical, radiation, surgical, paediatric and musculoskeletal oncology. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead with input from the workgroup members. The group met once in person, and completed guideline development through email communication.

A consensus approach was used to develop guidelines streamlined to the Singapore context. First, available resources were considered. High quality guidelines³⁻⁶ were selected for review and structured approaches developed for guideline evaluation. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. The SCAN guidelines were then written with consensus from workgroup members for each recommendation. Calibration of guidelines to the local context based on available Singapore data was encouraged. The final phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to address the 4 main management issues which were selected for this topic:

1. Radiological imaging
2. Pathology
3. Histological diagnosis
4. Surgery
5. Radiotherapy
6. Systemic therapy

The following international guidelines were selected for review:

- “Soft Tissue Sarcoma” (version 2.2014) by von Mehren M et al³

- “Improving Outcomes for People with Sarcoma” by the National Collaborating Centre for Cancer⁴
- “Soft Tissue and Visceral Sarcomas: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up” by the European Sarcoma Network Working Group, 2012⁵
- “Guidelines for the Management of Bone Sarcomas” by Grimer RJ et al⁶

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of sarcoma, it will be reviewed earlier.

1. Radiological Imaging

Regardless of presentation and clinical history, cross-sectional imaging, in the form of computed tomography (CT) and/or magnetic resonance imaging (MRI) is essential in any approach to sarcoma.⁷

CT is recommended as the first-line investigation. High resolution, thin slices CT scan with coronal and sagittal multiplanar reconstruction (MPR) capability is desired, with both intravenous and oral contrast medium administration.⁹ Intravenous contrast-enhanced helical CT scan of the abdomen and pelvis is the minimum investigation to be performed. This allows for characterisation of the mass, local staging, delineation of the margins and differentiation from adjacent organs and vascular structures. Differentiation between retroperitoneal, intraperitoneal, and visceral origin is essential.^{4,5,7,8}

A CT scan of the thorax to assess for any lung metastatic disease and other intrathoracic pathology can also be performed at the same time.^{3-5,7,9} In lieu of a CT thorax scan, a plain erect frontal chest radiograph may be obtained for screening.

MRI scans should be reserved to answer specific problems. With its superior tissue contrast resolution, MRI can be used to assess vascular and neural invasion and to characterise the solid, cystic and necrotic areas of the mass.^{3-5,7,8} Scans with and without intravenous MRI contrast medium administration is recommended when this modality is employed.

Preoperative core needle biopsy, if required, should be under CT guidance, with the track and targeted region determined after discussion with the surgical team. The National Comprehensive Cancer Network (NCCN) guidelines state that pre-resection biopsy is necessary in patients receiving preoperative radiation therapy (RT) or chemotherapy; fine needle aspiration is generally insufficient to obtain material sufficient to make a diagnosis, given multiple sarcoma subtypes and a variety of histological and fluorescence in situ hybridisation markers that can be brought

to bear on diagnosis (see below on biopsy guidelines).³

The utility of whole body MRI and positron emission tomography (PET) CT imaging is still being evaluated for both staging and post-treatment follow-up, with research still ongoing.

2. Pathology

The differential diagnoses of a retroperitoneal sarcoma (RPS) are diverse. Before considering a diagnosis of sarcoma, meticulous clinico-pathological effort should be made to exclude the possibility of sarcomatoid carcinoma or mesothelioma, metastasis and benign pseudo-sarcomatous entities. Careful correlation with the clinician and radiologist may yield critical information about the tumour (e.g. history of familial syndromes, necrosis, relationship with adjacent organs) that will greatly aid in narrowing the differential diagnoses.

In adults, the most common groups of RPS are often high-grade, which includes liposarcomas, leiomyosarcomas and undifferentiated pleomorphic sarcoma.¹⁰ Liposarcomas can be broadly divided into 3 unique classes: well differentiated/dedifferentiated, myxoid/round cell, and pleomorphic subtypes. RPS in paediatric patients are uncommon and more likely to be rhabdomyosarcomas, extraosseous primitive neuroectodermal tumour (PNET), neuroblastomas, and Wilms tumours.^{11,12}

Biopsy Specimen

If biopsy specimens are required, preliminary investigation generally involves obtaining multiple core biopsies (at least 5 cores) using needles of at least 16 gauge to subtype the tumour and assess tissue viability for further ancillary testing. Malignancy grading may be underestimated in small biopsies; therefore, a final diagnosis can only be reliably obtained after definitive tumour resection. Frozen-section technique for immediate diagnosis should be avoided due to suboptimal histological interpretation and lack of immediate ancillary support.

Resection Specimen

As with sarcoma elsewhere, tumour site, size, depth, vascular invasion and margin status should be recorded. Detailed discussions of the tumour datasets and gross handling are comprehensively covered in various pathology colleges and organisations guidelines.¹³⁻¹⁵ For RPS where tumours are often large and voluminous, a few practical suggestions could be made. Firstly, coordination between the surgeon and pathologist is important to ensure that fresh tissue is available for molecular studies and tumour banking. Secondly, “intelligent” sampling of critical sites

Table 1. Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) Histological Grading Criteria

Tumour Differentiation	Necrosis	Mitotic Count*
(1) Well	(0) No necrosis	(1) 0 – 9
(2) Moderate	(1) <50% tumour necrosis	(2) 10 – 19
(3) Poor	(2) ≥50% tumour necrosis	(3) >19

*Established on the basis of per 10 HPF; 1 HPF measures 0.1734 mm². Note: The individual score for each parameter (i.e. tumour differentiation, necrosis, and mitotic count) is in parenthesis. The sum of the scores of the 3 parameters determines the grade of malignancy. Grade 1: total score 2,3; Grade 2: 4,5; Grade 3: 6-8.

(e.g. interface region in a dedifferentiated tumour) rather than blind extensive sampling is more cost-effective in obtaining the correct diagnosis. Thirdly, tumours with heterogeneous appearance should be generously sampled to investigate heterologous or dedifferentiated elements.

3. Histological Diagnosis

Histological diagnosis should be made according to the latest (2013) World Health Organization (WHO) classification.¹⁶ Except in a few situations (e.g. preoperative chemotherapy, rarely metastasising tumours or newer entities not categorised in the current grading system), grading of the sarcoma should be provided following the Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system (Table 1), which is based on tumour differentiation, mitotic count and necrosis. Histological assessment of these tumours involves careful morphological examination complemented by ancillary investigations. Morphological examination involves a systematic pattern-based approach analysing parameters that generally include: a) architecture, b) cytomorphological features, and c) stromal characteristics. Identifying specific types of cells (e.g. lipoblasts, rhabdomyoblasts) can be extremely helpful in subtyping the tumour. For pleomorphic sarcomas it is critically important to subtype these tumours accurately wherever possible because each sarcoma is biologically and prognostically distinct. For example, a pleomorphic liposarcoma has a considerably worse prognosis than a dedifferentiated liposarcoma. Furthermore, what is seen to be UPS under the microscope may actually be 1 aspect of a well differentiated/dedifferentiated liposarcoma.

Ancillary Investigations

A panel of immunohistochemical stains is routinely ordered primarily to determine the tumour lineage. Some of the common stains used in approaching RPS would

include: a) *MDM2* and *CDK4* for well differentiated or dedifferentiated liposarcoma; b) H-caldesmon and desmin for smooth muscle differentiation, c) membranous *CD99* expression for PNET, d) S-100 for neural differentiation, which in some cases of dedifferentiated liposarcoma can be positive, and d) broad spectrum cytokeratin to exclude sarcomatoid carcinomas or mesotheliomas or more rarely other cytokeratin positive sarcoma (e.g. synovial sarcoma).

Molecular tests play a critical role in the diagnostic algorithm of problematic cases. These tests are often regarded as the “gold standard” in confirming diagnosis, especially in sarcomas with recurrent chromosomal translocations. In the context of RPS, molecular tests could be used to detect *HDM2* and *CDK4* amplification for well differentiated and dedifferentiated liposarcoma, translocation t(12;16)(q13;p11) for myxoid liposarcoma and *EWS* gene rearrangement for Ewing’s/PNET and desmoplastic small round cell tumour. As with other ancillary investigations, molecular tests are complementary but not a substitute for histological diagnosis.

In summary, due to its complexity, diagnosing RPS requires meticulous pathological examination with careful clinical and radiological correlation. With the availability of new ancillary diagnostic tools, every effort should be made to accurately subtype a high-grade sarcoma before signing it out as a “high-grade undifferentiated pleomorphic sarcoma”.

4. Surgery

Surgery is the mainstay of treatment for STS and the principles of management of RPS do not differ significantly from those of extremity sarcomas. All RPS are considered deep tumours (thus making the differentiation between superficial and deep tumours, a recognised prognostic factor for sarcoma outcomes, useless), located beneath the fascial plane, and their location often also results in a late diagnosis, with an average size of well over 10 cm at presentation. As such, the prognosis is considerably worse in view of these factors. A preoperative biopsy is usually not required if the radiological images are consistent with a retroperitoneal liposarcoma. However, it is useful for the exclusion of other non-sarcomatous tumours, and when preoperative treatment with radiation or chemotherapy is being considered. In a resectable lesion, surgery can be planned for and must achieve adequate margins.¹⁷ The emphasis is on obtaining wide or radical margin remains, though these margins are much harder to define. In the extremity, where a wide margin is attained by removing a rim of 1 cm to 2 cm of normal tissue and radical resection typically necessitates a compartmental resection, the retroperitoneum is less compartmentalised and structures

within it are often in close proximity, if not adjacent to the sarcoma.¹⁸ A contrast-enhanced CT scan is critical to define the potentially involved organs, with the absence of a distinct fat plane in such cases. It is also noted that with the diagnosis of dedifferentiated liposarcoma, the normal appearing fat surrounding will oftentimes represent well differentiated liposarcoma and should be removed en bloc intraoperatively. Resection with a curative intent must take into account the need for functionality after the surgery. Multivisceral resections are not uncommon, and may encompass an en bloc resection of surrounding structures such as the large or small intestine, kidney, stomach, spleen and, occasionally, the vascular structures. Resection of an involved inferior vena cava can be performed safely, and often does not require a reconstruction, especially in the face of long-standing compression by the enlarging retroperitoneal tumour, with the formation of adequately draining collateral vessels. Resection of a portion of the aorta will require reconstruction, most often with a prosthetic graft. In recurrent tumours, the planes for dissection become less distinct, and clear margins may necessitate the removal of adherent organs, as true invasion may be difficult to ascertain. It has been shown that patients with RPS are more likely to receive a complete resection of their tumour and have improved survival if they were treated at a specialist tertiary centre, and at a hospital with a high volume of sarcoma work.

Preoperative radiation therapy is administered by some centres in an attempt to “sterilise the margins”, with its proponents citing the need for a lower dosage of required radiation to the well vascularised field and the still-present tumour obviating a need for a spacer to prevent radiation to other uninvolved organs. However, preoperative radiation would necessitate a preoperative core biopsy, and the issues of contamination and subsequent excision of the biopsy pathway should be considered. Postoperative radiation, in the absence of preoperative radiation therapy, is offered to those with an involved margin and in selected patients with high-grade and large tumours (extrapolated from data from extremity sarcomas), but definitive evidence has yet to be established for pre or postoperative radiation of RPS, in particular since radiation postoperatively will by definition lead to a greater degree of radiation to normal tissue, which is pushed out of the way in preoperative radiation treatment of a retroperitoneal STS (see below). In the event of an unresectable RPS, downstaging can be considered with chemotherapy or radiation.

In summary, surgery is the mainstay of treatment for RPS. Clear margins, including an intact pseudocapsule are necessary to decrease the local recurrence rates. This may necessitate en bloc multivisceral resection of organs that are adherent to the RPS.

5. Radiotherapy

Local relapse rates remain around 50% even with macroscopic complete resection, hence the interest in adjuvant therapies such as radiotherapy to improve local control. As with limb sarcomas, radiotherapy can be delivered either preoperatively or postoperatively. There are potential advantages to the preoperative approach:

- a) the primary tumour in situ represents a well defined target volume;
- b) the tumour itself acts a spacer, displacing the small bowel from high dose treatment volume, thus reducing acute and late toxicity;
- c) radiotherapy may be more effective in the preoperative setting because of better oxygenation;
- d) preoperative radiotherapy may thicken the pseudocapsule of the tumour, thus aiding surgical resection and reducing intraperitoneal spillage;
- e) it may render an unresectable tumour resectable.

Two prospective trials¹⁹ of preoperative radiotherapy have shown favourable local control rates of 60% following macroscopically complete resection. The dose for preoperative radiotherapy is 50 Gy. The use of advanced radiotherapy delivery techniques such as intensity modulated radiation therapy (IMRT) or tomotherapy allows selective dose escalation beyond 55 Gy to the margin at risk and may be considered.²⁰ A randomised trial to compare surgery alone versus preoperative radiotherapy and surgery was attempted in North America, but closed due to poor accrual. A similar trial in Europe has been ongoing since 2012, but results are not expected until some years later.²¹ Intraoperative radiotherapy has been shown in retrospective series to improve local control rates and should be considered where available, usually in combination with pre- or postoperative external beam radiotherapy.²²

A non-randomised retrospective series²³ has documented improved local control without overall survival benefit with postoperative radiotherapy. However, the presence of radiation dose-limiting structures in the postoperative target volume presents a significant challenge and often limits the dose to 50 Gy to 55 Gy to well defined areas at risk.⁶ If it is to be considered, the use of omentum or other tissue spacers to displace bowel from the tumour bed is recommended to reduce the risk of radiation induced bowel toxicity.³

In summary, while a number of retrospective studies showing favourable local control with both pre- and postoperative radiotherapy exist, there is a distinct lack of level 1 randomised trial evidence for radiotherapy in RPS. Therefore, while the general indications for radiating any soft tissue sarcomas are still valid (large, intermediate-high grade, incompletely resected),³ the unique difficulties posed

by the proximity of radiosensitive organs at risk mandate multidisciplinary discussion to determine feasibility and sequencing of radiation therapy.

6. Systemic Therapy

Knowledge of the histologic spectrum of RPS, in addition to appreciation of their significantly disparate biologies, is critical to optimal management. Well differentiated liposarcomas have the most favourable prognosis, and are disposed almost exclusively to local recurrence, with negligible incidence of distant metastasis. They are also of low histological grade with no known responses to cytotoxic chemotherapy. These factors thus suggest no rationale for adjuvant systemic therapy with cytotoxic agents in primary or recurrent well differentiated liposarcoma. Both dedifferentiated liposarcoma and leiomyosarcoma are high-grade tumours with equally poor prognosis relative to well differentiated liposarcoma. Crucially, this similar eventual survival is mediated by diametrically disparate patterns of recurrence—while dedifferentiated liposarcoma, akin to well differentiated liposarcoma, is chiefly prone to local recurrence, leiomyosarcoma manifests primarily distant relapses.²⁴ This disparity in the pattern of treatment failure necessitates a tailored, histology-specific approach in thinking about primary and adjuvant therapy. For instance, of these diagnoses, it may be argued that leiomyosarcomas could benefit most from effective adjuvant systemic therapy.

Perhaps because of the predominance of well differentiated/dedifferentiated liposarcoma in the retroperitoneum and its relative chemotherapy resistance, scant prospective data are available regarding the use of adjuvant chemotherapy specifically in resected localised primary RPS. Fewer than 10% of major adjuvant chemotherapy trials in sarcoma conducted thus far comprised patients with retroperitoneal disease.^{25,26} A retrospective analysis of neoadjuvant therapy in high-grade RPS revealed no improvement in survival relative to that predicted by the appropriate nomogram, although histopathologic response to neoadjuvant therapy predicted for improved outcomes compared with non-responders.²⁷ There is no prospective data assessing the value of perioperative systemic therapy in the setting of locally recurrent disease. At this time, we do not recommend adjuvant chemotherapy as a routine standard of care in resected retroperitoneal STS except in rare chemotherapy sensitive subtypes more common in children, e.g. Ewing sarcoma.

While the objective of chemotherapy in the setting of unresectable or metastatic disease is palliative, a consideration especially relevant to RPS is the significant morbidity of bulky abdomino-peritoneal disease, thus amplifying the value of achieving substantive

clinicoradiologic responses with systemic therapy. A large French study evaluating almost 600 patients with locally advanced or metastatic RPS demonstrated an objective response rate of 16% and a progression-free survival of nearly 6 months with palliative chemotherapy.²⁸ Although histological subtype did not feature as a significant prognostic factor for chemotherapy response or overall outcome in this particular study, it remains the most important factor in choosing systemic agents for treatment. Well differentiated and dedifferentiated liposarcomas respond poorly to cytotoxic chemotherapy, associated with objective response rates of 10% to 12% with anthracycline-based treatment.^{29,30} A defining molecular pathway—amplification of the anti-apoptotic proteins *HDM2*, which inhibits the tumour suppressor *p53*, and *CDK4*, which suppresses the tumour suppressor retinoblastoma protein—is present in over 90% of well and dedifferentiated liposarcomas.³¹ These aberrations have become molecular signatures used for definitive diagnosis of liposarcoma, and present unique therapeutic opportunities through pharmacological antagonism of *HDM2* and *CDK4* in tumours with functional *p53* and Rb protein, respectively. Early phase clinical studies of both *HDM2* and *CDK4* inhibitors have revealed modest activity so far.^{32,33} In the case of leiomyosarcomas, there is moderate sensitivity, above and beyond anthracycline-based chemotherapy, to one of several agents given either singly or in combination, including gemcitabine in combination with docetaxel,³⁴ single agent trabectedin (approved outside of US),³⁵ dacarbazine or temozolomide, and gemcitabine in combination with dacarbazine.³⁶ Other histologies that make up a small proportion of retroperitoneal disease include undifferentiated pleomorphic sarcoma, malignant peripheral nerve sheath tumours and solitary fibrous tumour. While the former 2 diagnoses are high-grade tumours often treated with anthracycline-based combination chemotherapy, solitary fibrous tumour has a more varied biology, and a less predictable response to cytotoxic agents. It has, however, been shown to derive benefit from therapy directed against vascular endothelial growth factor, either singly or in combination with chemotherapy.^{37,38} Pazopanib, a multitargeted tyrosine kinase inhibitor directed against vascular endothelial growth factor, platelet-derived growth factor, fibroblast growth factor receptor and KIT, remains an option for any non-liposarcoma soft tissue sarcoma failing other chemotherapy in the recurrent or metastatic setting, having demonstrated significant benefit in progression-free survival in a landmark randomised phase 3 trial.³⁹

Conclusion

Due to its complexity, heterogeneity and rarity, retroperitoneal STS is a challenging disease to diagnose and treat and best managed in a high volume centre

experienced in the management of these diseases. Guidelines contextualised to the local patient and unique healthcare setup in Singapore will hopefully streamline care and improve clinical outcomes for our sarcoma patients.

Conflicts of Interest

The workgroup members have nothing to disclose.

Workgroup Members

The Members of the SCAN Sarcoma Workgroup are Section Lead and Workgroup Chairperson: Richard Quek, MBBS, MRCP (UK), Division of Medical Oncology, National Cancer Centre Singapore, Singapore; Workgroup Members (Voting): Mohamad Farid, MBBS, M Med (Int Med), MRCP (UK), Division of Medical Oncology, National Cancer Centre Singapore, Singapore; Lai Peng Chan, MBBS, FRCP, FAMS, Department of Diagnostic Radiology, Singapore General Hospital, Singapore; Francis KC Chin, MBBS, MSc (Rad Biol), FRCP (Clinical Oncology) (UK), Division of Radiation Oncology, National Cancer Centre Singapore, Singapore; Leon Foo, MBBS (S'pore), MMed (Ortho Surg), FRCSEd (Edin) (Ortho), Island Orthopaedic Consultants, Mount Elizabeth Medical Centre, Singapore; Victor KM Lee, MBBS, FRCPA, Department of Pathology, National University Health System, Singapore; Mark E Puhaindran, MBBS (S'pore), MRCS (Edin), MMed (Surgery), Division of Musculoskeletal Oncology, National University Health System, Singapore; Shui Yen Soh, MBBS, MRCPCH (UK), Department of Paediatric Subspecialties Haematology/Oncology Service, KK Women's and Children's Hospital, Singapore; Khee Chee Soo, MBBS, MD, FRACS, Division of Surgical Oncology, National Cancer Centre Singapore, Singapore; Mann Hong Tan, MBBS, MD, FRCS (Edin & Glasg), Department of Orthopaedic Surgery, Singapore General Hospital, Singapore; Jonathan YH Teh, MBBS, FRCP (Clinical Oncology) (UK), Division of Radiation Oncology, National Cancer Centre Singapore, Singapore; Melissa CC Teo, MBBS, FRCS, MPH, Division of Surgical Oncology, National Cancer Centre Singapore, Singapore; Steven BS Wong, MB ChB (UK), MMED (NUS), FAMS, Department of Diagnostic Radiology, Singapore General Hospital, Singapore; Workgroup Member (Non-Voting): Serene AK Ong, MSc, Group Education, SingHealth Academy, SingHealth, Singapore.

Reviewers

Invited reviewers were Sun Young Rha, MD, PhD, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, South Korea; Charlotte Benson, MBChB, MRCP, Sarcoma Unit, Royal Marsden Hospital, UK; Robert Maki, MD, PhD, FACP, Tisch Cancer Institute, Mt Sinai Medical Centre (New York), USA.

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Singapore Cancer Network (SCAN) Guidelines for Referral for Genetic Evaluation of Common Hereditary Cancer Syndromes

The Singapore Cancer Network (SCAN) Cancer Genetics Workgroup

Abstract

Introduction: The SCAN cancer genetics workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for referral for genetic evaluation of common hereditary cancer syndromes. **Materials and Methods:** The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. **Results:** To formulate referral guidelines for the 3 most commonly encountered hereditary cancer syndromes to guide healthcare providers in Singapore who care for cancer patients and/or their family members, 7, 5, and 3 sets of international guidelines respectively for hereditary breast and ovarian cancer (HBOC) syndrome, Lynch syndrome (LS), and familial adenomatous polyposis (FAP) were evaluated. For each syndrome, the most applicable one was selected, with modifications made such that they would be appropriate to the local context. **Conclusion:** These adapted guidelines form the SCAN Guidelines 2015 for referral for genetic evaluation of common hereditary cancer syndromes.

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Key words: Familial breast cancer, Hereditary cancer syndromes, Referral guidelines

Introduction

Mutations in high penetrance genes account for approximately 3% to 5% of all cancers. In the last 2 decades, there has been better characterisation of an ever growing list of hereditary cancer syndromes, largely due to the identification of causative genes. Formal management guidelines, including testing, screening and preventive options, have been established for many of these syndromes.^{1,2} Identification of these patients and families who are at extremely high risk of developing cancer for specialised management is crucial to reduce cancer occurrence and mortality. Formal cancer genetics programmes have been established in Singapore in both tertiary cancer centres in Singapore (National University Cancer Institute [NCIS], National Cancer Centre [NCCS]) since 2001.³ However, there are no formal local guidelines providing guidance to general practitioners, physicians or surgeons on who should be referred for cancer genetic assessment.

The SCAN Guidelines for Referral for Genetic Evaluation of Common Hereditary Cancer Syndromes

The SCAN Guidelines are clinical practice guidelines for referral for genetic evaluation of common hereditary cancer syndromes.

These first edition guidelines are intended to serve as recommendations by members of this working group reflecting their views on current existing international guidelines for the referral for genetic evaluation of common hereditary cancer syndromes. While it hopes to harmonise the management of such syndromes, it is not intended to serve as a standard or to replace good judgment and individualisation.

Target Users of the Guidelines

The guidelines will be of interest to healthcare providers in Singapore who care for cancer patients and/or their family members.

Address for Correspondence: A/Prof Lee Soo Chin, Department of Haematology-Oncology, National University Cancer Institute, Singapore, 1E Lower Kent Ridge Road, Level 7, NUHS Tower Block, Singapore 119228.
Email: csilsc@nus.edu.sg

Guideline Recommendations/Development

The SCAN Cancer Genetics Workgroup comprises a panel of 4 medical oncologists and 1 colorectal surgeon from Singapore with special interests in the management of hereditary cancer syndromes. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead with input from the workgroup members. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, high quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available.

The workgroup members shared a common view that referral guidelines represented a key issue that is both pressing and relevant to the medical community at large. In contrast, testing and management guidelines are less relevant as pre- and post-test genetic counselling, surveillance and preventive recommendations, test result interpretations, and the social and ethical implications of genetic testing would be most appropriately delivered by trained specialists, preferably in the setting of a specialised cancer genetics clinic in a tertiary cancer centre. Currently, only 2 such clinics exist in the 2 tertiary cancer centres in restructured hospitals in Singapore: NCIS and NCCS, to serve the entire

Singapore population of ~5.5 million. Both clinics are led by medical oncologists trained in cancer genetics, assisted by a cancer genetics counsellor. In addition, there are a few specialists in private medical centres who are trained to provide cancer genetics evaluation and counselling.

The workgroup decided to focus on the following 3 hereditary cancer syndromes most commonly encountered in practice:

1. Hereditary Breast and Ovarian Cancer (HBOC) Syndrome,
2. Lynch Syndrome (LS), and
3. Familial Adenomatous Polyposis (FAP).

Considering that at-risk patients may be referred from a diverse group of healthcare providers with different levels of knowledge on hereditary cancer syndromes, ranging from family physicians to specialists from different disciplines who may manage cancer patients or their families, it was decided that risk criteria chosen as referral guidelines should be clinical criteria that can be readily understood and assessed in the clinic. In addition, it was noted that while genetic evaluation and counselling is a health service that can be subsidised by the government, genetic tests are specialised tests that are self-paid by patients in Singapore and typically cost ~USD \$1500 to \$2000. High test cost has been cited as a barrier to genetic testing in Singapore.⁴ Recognising this and the fact that medical resources are limited in Singapore with only 2 specialised cancer genetics clinics in the restructured hospitals serving the entire nation, it was decided to set the referral threshold at a sensitivity level equivalent to an a priori probability of diagnosing hereditary cancer syndrome of $\geq 10\%$ to 20% , so as not to overwhelm the healthcare system.

Table 1 lists the guidelines that were reviewed, the details of which are summarised in Supplementary Tables 1-3. Guidelines were selected from various representative international professional bodies, excluding those that were published more than 10 years ago. Seven, 5, and 3 sets of international guidelines were reviewed for HBOC,⁵⁻⁸ LS,⁹⁻¹² and FAP^{10,12} respectively. The workgroup reviewed the guidelines and selected the most applicable one for each syndrome with modifications made for them to be appropriate to the local context (Table 2).

1. Hereditary Breast and Ovarian Cancer (HBOC)

International guidelines for HBOC typically divided the recommendations into 2 categories: for women with and without a personal history of cancer. All members elected to streamline the guidelines into a single category using the family as a unit and modify the wordings to include salient aspects of both personal and family histories. Most of the guidelines (NICE, Canadian Saskatchewan, USPSTF, ASCO,

Table 1. International Guidelines Reviewed for Common Hereditary Cancer Syndromes by the SCAN Cancer Genetics Workgroup

Hereditary Cancer Syndrome	International Guidelines Reviewed
Hereditary Breast and Ovarian Cancer Syndrome	National Comprehensive Cancer Network (NCCN, United States), 2014 United States Preventive Services Task Force (USPSTF), 2013 ⁵ National Institute for Health and Care Excellence (United Kingdom), 2013 American Society of Clinical Oncology (ASCO), 2012 ⁶ Saskatchewan Cancer Agency (Canada), 2012 European Society for Medical Oncology (ESMO) Guidelines Working Group, 2011 ⁷ The American College of Obstetricians and Gynaecologists (ACOG), 2011 ⁸
Lynch Syndrome	National Comprehensive Cancer Network (NCCN, United States), 2014 European revised guidelines for the management of Lynch syndrome, 2013 ⁹ American College of Medical Genetics (ACMG), 2013 ¹⁰ The Evaluation of Genomic Applications in Practice and Prevention working Group (EGAPP) Working Group, 2009 ¹¹ American College of Gastroenterologists, 2008 ¹²
Familial Adenomatous Polyposis	National Comprehensive Cancer Network (NCCN, United States), 2014 American College of Medical Genetics (ACMG), 2013 ¹⁰ American College of Gastroenterologists, 2009 ¹²

ESMO) were similar in recommending that women with young breast cancer, multiple family members with breast cancers, bilateral breast cancers, breast and ovarian cancers, male breast cancers, and multiple other related cancers (pancreatic, prostate, etc.) be included. In concordance with these recommendations, one local study showed that the highest risk group is families with breast and ovarian cancer.¹³

After reviewing the 7 sets of international guidelines, the committee decided to adopt the guidelines by the European Society for Medical Oncology (ESMO) Guidelines Working Group (2011) as the backbone guidelines,⁷ as they were most encompassing, recommending 4 broad categories of patients to be referred: family history of breast or ovarian cancer, young onset cancer, male breast cancer, and multiple tumours. The workgroup built upon these general guidelines and added specific information to make the guidelines easy for referring physicians to follow. Of note, the age threshold for 'young onset cancer' was specified to be less than 40, while 'family history of breast or ovarian cancer' was further divided into 'family history of breast and ovarian cancer' and 'family history of 2 or more breast cancers, with at least one diagnosed below age 50' (adopted from the 2014 NCCN guidelines). In addition, members added a special note for clinicians to ask for a family history of young onset pancreatic and prostate cancer (diagnosed below age 50) in patients and/or families with breast cancer, and to consider referring these patients/families to a cancer genetics clinic for further evaluation (adopted from the 2014 NCCN guidelines). Recognising that patients with certain histological subtypes of breast and ovarian cancer have up to 10% to 20% chance of carrying a *BRCA1/2* mutation, patients with triple negative breast cancer diagnosed below age 50 (adopted from the 2014 NCCN guidelines with age

threshold added to increase the specificity for referral)¹⁴ and patients with epithelial ovarian cancer diagnosed at any age (adopted from the 2012 ASCO guidelines), in particular those with high-grade serous ovarian cancer,¹⁵ were included in the referral criteria for HBOC.

The concept of population-based screening for *BRCA1/2* has been proposed recently.¹⁶ However, given the high test cost that has to be borne by the patients as well as our currently limited medical resources to handle pre- and post-test genetic counselling and test interpretations required from large scale genetic testing, all members of the workgroup agreed not to include universal screening for HBOC syndrome in the guidelines, recognising that genetic testing administered without appropriate counselling may result in misinterpretation and harm.¹⁷

2. Lynch Syndrome (LS) or Hereditary Non-Polyposis Colorectal Cancer

Colorectal cancer (CRC) is a major public health problem, being the third most common cancer in men and women.¹⁸ It is the second and third commonest cause of cancer-related deaths in men and women respectively and is largely preventable with recommended population screening.^{18,19} It is estimated that approximately 3% of CRCs are attributable to LS.²⁰⁻²² This autosomal dominant genetic disorder is associated with greatly increased risks of developing colorectal, endometrial, gastric and other cancers.²⁰⁻²³ Despite the increased risk of cancers seen in LS patients, long-term follow-up studies show that compliance with current surveillance recommendations is highly successful. LS patients show no increase in cancer-related mortality when compared to mutation-negative family members on long-term follow-up.²⁴ Unfortunately, unless

Table 2. Singapore Cancer Network (SCAN) Guidelines for the Referral for Genetic Evaluation of Common Hereditary Cancer Syndromes

Suspected Hereditary Cancer Syndrome	Patients Who Should be Referred for Cancer Genetic Risk Assessment	Guidelines Adapted From
Hereditary Breast and Ovarian Cancer Syndrome	• Personal or family history of breast cancer diagnosed <40 years of age; • Personal or family history of male breast cancer, any age; • Personal or family history of epithelial ovarian cancer, any age; • Personal or family history of triple negative breast cancer diagnosed <50 years of age • Family with 2 or more breast cancers, at least one aged <50 years of age; • Family with both breast and epithelial ovarian cancers; • Two or more tumours in the same patient (bilateral breast cancer; multiple breast cancers; breast and ovarian cancer); • Known <i>BRCA1/2</i> mutation in family. An a priori $\geq 10\%$ probability of finding a mutation based on predictive models such as BRCAPRO, BOADICEA or Manchester Score* (Special note: <i>BRCA1/2</i> mutation carriers are also at risk for pancreatic and prostate cancer and clinicians should additionally ask for these cancers in taking the family history. Physicians should consider referring families with breast cancer and young onset pancreatic or prostate cancer diagnosed before age 50.)	European Society for Medical Oncology (ESMO) Guidelines Working Group (2011)
Lynch Syndrome (LS)	Tumour microsatellite instability (MSI) and/or immunohistochemical (IHC) staining for mismatch repair (MMR) proteins should be considered in:† 1. Patient with CRC diagnosed <50; 2. Patient with synchronous or metachronous CRC or other LS-related tumours,‡ regardless of age; 3. Patient with CRC diagnosed <60 years of age with the MSI-H histology (presence of tumour infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet ring differentiation, or medullary growth pattern); 4. Patient with CRC diagnosed at any age, and who has at least 1 first-degree relative diagnosed with CRC or LS-related tumour diagnosed <50 years; 5. Patient with CRC at any age, and who has 2 or more first- or second-degree relatives with CRC or LS-related tumour at any age. (Special note: If an MSI unstable tumour harbours the BRAF gene <i>p.V600E</i> mutation, it is most likely sporadic and germ line testing for mismatch repair genes is not necessary.) When referral for clinical germline testing for mismatch repair genes should be considered: 1. Meets Amsterdam criteria§ or any of the above 5 listed criteria for tumour MSI or IHC testing for MMR proteins; 2. Endometrial cancer <50 years; 3. Known LS mutation in family; (Special note: Consider testing individuals with $\geq 10\%$ risk of LS on any mutation model³⁹⁻⁴² (e.g., MMRpro, PREMM, MMRpredict)*	National Comprehensive Cancer Network Guidelines - Genetic/Familial High Risk Assessment Colorectal (2014)
Familial Adenomatous Polyposis (FAP)	1. Patients with classic FAP (>100 adenomas) should be advised to pursue genetic counselling and genetic testing, particularly if they have siblings or children who could potentially benefit from predictive testing. 2. Patients with classic FAP, in whom APC genetic testing is negative, should undergo genetic testing for bi-allelic MYH mutations. 3. Patients with 10 – 100 adenomas can be considered for genetic testing for attenuated FAP and if negative, for MYH-associated polyposis. (Special note: It should be highlighted that the number of adenomas is the cumulative number of adenomas seen in a patient's lifetime.)	American College of Gastroenterology - Medical Specialty Society 2009

APC: Adenomatous polyposis coli; CRC: Colorectal cancer; MSI-H: Microsatellite instability (high)

*This assessment should be made by a trained cancer genetics specialist.

†Alternatively, patients fulfilling these criteria may be referred to a cancer genetics clinic for genetic evaluation and workup.

‡LS-related cancers include cancers of the endometrium, stomach, pancreas, small intestine, ovary, kidney, brain, ureters, or bile duct.

§Amsterdam criteria: At least 3 family members affected with cancer, spanning 2 generations, with at least 1 affected family member diagnosed below age 50 years; the 3 affected family members have to be first-degree relatives of each other. In the Amsterdam I criteria, all 3 affected family members must have colorectal cancer; in Amsterdam II criteria, the affected family members may have colorectal, uterine, small bowel, ureteric or renal pelvis cancer.

there is strong clinical suspicion, many cases of LS are missed.²³ Furthermore, standard population CRC screening guidelines fail to provide early detection or prevention for most LS colon cancers as they tend to occur at young ages.²⁰⁻²³ There is hence a clear need for better ways to detect patients at risk of LS.

The challenge in diagnosing LS, in contrast to FAP, is that it does not have pathognomonic clinical features of polyposis that distinguish it from a sporadic cancer. Guidelines for LS testing comprise one for screening of resected tumour specimens and another that targets germline genetic testing (usually blood) of at-risk individuals. Germline genetic testing by sequencing with or without multiplex ligation-dependent probe amplification is cost-effective in individuals who are of sufficient risk.²⁵

Unfortunately, a high proportion of patients are missed when clinicians rely only on high risk clinical and/or pathological features.^{21,26} Indeed, the revised Bethesda guidelines are now known to be inadequate for LS screening when family cancer history is not available. A universal screening paradigm greatly increased the rate of LS detection,²⁷ and the approach of universal screening for mismatch repair defect (MMR), the hallmark feature in LS,^{20,26} in all colorectal cancer specimens, with either tumour microsatellite instability (MSI) testing with or without BRAF testing, or immunohistochemistry (IHC) staining of MMR proteins, has been proposed.²⁸ For screening, IHC is thought to be almost equally sensitive as MSI but more readily available.²⁶ Either MSI and/or MMR IHC as a screening tool to identify candidate LS cases for further workup are available in both tertiary cancer centres (NCIS and NCCS). However, while universal screening has been shown to be cost-effective,²⁹⁻³² infrastructure comprising trained medical staff, pathologists and workflows is required for effective implementation.³³⁻³⁵ As such, there is disagreement within the workgroup with regard to universal screening, with 4 of 5 members voting not to include it in the current SCAN guidelines, given the lack of clear data and untested assumption in cost-effectiveness analysis studies that multiple family members will be tested following the identification of gene mutation in the proband in the local context.

The guidelines for LS were divided into criteria for tumour screening for MSI or IHC for MMR proteins, and criteria for referral for germline genetic testing. The 2013 American College of Medical Genetics (ACMG) guidelines¹⁰ and the 2014 NCCN guidelines were adopted as the backbone guidelines for tumour screening and germline genetic testing respectively. Tumour screening guidelines were largely based on the revised Bethesda criteria,³⁶ and were included as there are specialists who have access to tumour screening and sufficient expertise to interpret results in at-

risk individuals. However, the workgroup acknowledged that not all physicians are willing or able to order tumour screening tests, and added a special note that physicians may refer patients who fulfill criteria for tumour screening to a cancer genetics clinic for further workup, rather than arrange tumour testing themselves.

3. Familial Adenomatous Polyposis (FAP)

Classic FAP with its carpeting of adenomatous polyps throughout the colon and rectum is an easily recognisable phenotype and should prompt clinicians to initiate confirmatory genetic testing. More challenging would be the recognition of attenuated FAP or MYH-associated polyposis which has a less florid polyposis phenotype. The workgroup felt that an addendum to existing guidelines should be made to highlight that the number of adenomas (10-100) that would trigger consideration for attenuated FAP or MYH-associated polyposis refers to the cumulative incidence of adenomas over a patient's lifetime.

Pre-test Genetic Counselling and Test Interpretation by Trained Specialists

All members in the committee agreed that genetic counselling and informed consent is required before genetic testing.³⁷ In our local setting, this is provided by trained specialists with the recognition that erroneous interpretation of genetic tests results can cause harm.¹⁷ Moreover, many primary care physicians may be unprepared or unable to interpret genetic tests information.³⁸

Conclusion

The systematic development of guidelines will be helpful in the development of cancer genetics in Singapore. Inevitably, the increasing availability of genetic testing will allow greater opportunities for detecting patients with inherited disorders, while also increasing risks from indiscriminate utilisation. These adapted guidelines constitute best practice recommendations on the evaluation of at-risk individuals based on consensus and experience of trained clinical cancer geneticists familiar with the Singapore setting and its unique healthcare system. These guidelines also allow for dissemination of experience and education in Singapore for improving referral and interpretation of genetic tests results.

Of note, the workgroup eventually selected recommendations from multiple source guidelines developed by a variety of organisations, with additional calibration based on local data and experience. This bears testimony to the unique practice setting in Singapore, while also indicating that no single international organisation's

guidelines may be transplanted here as ideal practice. There was general consensus in the selection of relevant recommendations, with only one dissenting opinion in the development of LS guidelines, suggesting that there is a common view of how cancer genetics may be best developed in Singapore.

In conclusion, we have developed best practice recommendations surrounding referral for patients at risk of common hereditary cancer syndromes in Singapore. These recommendations are aimed at improving the identification and evaluation of such patients, and would be relevant to all physicians involved in caring for patients who may have or are at risk for cancer.

Conflicts of Interest

Dr Ang reports receiving lecture fees from Myriad Genetics; Dr Tan reports receiving grant support from Pfizer, and holding the following pending patents: "A Multigene Assay for Prognosis and Drug Response Prediction in Clear-Cell Renal Cell Carcinoma Patients that Identifies Distinct Biological Subtypes", "Method for Predicting Clinical Toxicities and Outcomes in Patients Receiving Sunitinib Using Gene Polymorphisms", "Self-Assembled Micellar Nanocomplexes Comprising Polyethylene Glycol-Epigallocatechin-3-Gallate Conjugates and Anticancer Drugs", "Antibody Specific for Parafibromin, a New Marker of Parathyroid Carcinoma", licensed to Santa Cruz Biotechnology, and "Method for Determining Mutation Status in Colorectal Cancer Patients Using Allele-Specific PCR", licensed to AIT Biotech; Dr Ngeow, Dr Koh and Dr Lee have nothing to disclose.

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Workgroup Members

The Members of the SCAN Cancer Genetics Workgroup are Section Lead and Workgroup Chairperson: Soo Chin Lee, MBBS, MRCP (UK), M Med (Int Med), Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore; Workgroup Members (Voting): Peter Ang, MBBS (S'pore), MMed (S'pore), MRCP (UK), Oncocare Cancer Centre, Singapore; Poh Koon Koh, MBBS (Spore), MMed (Surg), FRCS (Gen), Colorectal Surgical Oncology & Cancer Genetics Service, Fortis Surgical Hospital, Singapore; Joanne YY Ngeow, MBBS (Melbourne), MMed (Int Med), MRCP (UK), Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Min-Han Tan, MBBS, FRCP, PhD, Department of Medical Oncology, National Cancer Centre Singapore, Singapore.

Reviewers

Invited reviewers were Shirley Hodgson, BSc, BMBCh, FRCP, Department of Clinical Genetics, St Georges Hospital, UK; Ignacio Blanco, MD, PhD, Genetic Counseling and Clinical Genetics Program, Hospital Universitari Germans Trias i Pujol, Germany. An additional invited reviewer chose to be anonymous.

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Supplementary Table 1. International Guidelines Reviewed for Hereditary Breast and Ovarian Cancer Syndrome

Familial Breast Cancer: Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer							
Guideline Title	Genetic/Familial High Risk Assessment: Breast and Ovarian	June 2013	March 2012	January 2011	December 2013	November 2012	August 2011
Guideline Developer	NCCN: National Comprehensive Cancer Network (US)	NICE: National Institute for Health and Care Excellence (UK)	Saskatchewan Cancer Agency (Canada)	European Society for Medical Oncology (ESMO) Guidelines Working Group	US Preventive Services Task Force (USPSTF)	American Society of Clinical Oncology (ASCO)	The American College of Obstetricians and Gynecologists (ACOG)
Reference	NCCN: National Comprehensive Cancer Network (US) Guidelines. Genetic/Familial High-Risk Assessment: Breast and Ovarian. 2015 Version 1. Page 8.	NICE: National Institute for Health and Care Excellence (UK) Guideline 164. June 2013. Pages 24 – 28.	Saskatchewan Cancer Agency (Canada). Breast Cancer Treatment Guidelines. Page 2.	Annals of Oncology 22 (Supplement 6): vi31-vi34, 2011.	Ann Intern Med 2014; 160 (4):271-281.	Journal of Clinical Oncology 31.7 (2013):961-965.	Obstetrics and Gynecology (2011) Vol 118: Issue 2 – Part 1. Pages 372 – 382.
Who to Refer: Breast Cancer BRCA Screening for Women Without Personal History of Breast or Ovarian Cancer	• A known mutation in a breast cancer susceptibility gene within the family • ≥2 breast primaries in a single individual • ≥2 individuals with breast primaries on the same side of the family • ≥1 ovarian cancer primary from the same side of the family • First- or second-degree relative with breast cancer ≤45 years	People who should be offered a referral to a specialist genetic clinic: • At least the following female breast cancers only in the family: - Two first- or second-degree relatives diagnosed with breast cancer at younger than an average age of 50 years (at least 1 must be a first-degree relative) or - Three first- or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years (at least 1 must be a first-degree relative) or	• Age greater than 60 • A history of lobular carcinoma in situ (LCIS), ductal carcinoma in situ (DCIS), or atypical proliferative lesion of the breast (atypical ductal or lobular hyperplasia) • Women between 35 and 59 years of age with an estimated risk of breast cancer of 1.66% or higher over 5 years from the Gail model • Individuals with <i>BRCA 1</i> and <i>BRCA2</i> mutations	• Family history of breast or ovarian cancer • Young age at onset • Male breast cancer • Multiple tumours (bilateral breast cancer or breast and ovarian cancer in the same patient)	Family history factors associated with increased likelihood of potentially harmful <i>BRCA</i> mutations include • Breast cancer diagnosis <50 years • Bilateral breast cancer, family history of breast and ovarian cancer • Presence of breast cancer in ≥1 male family member • Multiple cases of breast cancer in the family	Women at high risk for familial breast cancer syndromes should be referred for genetic counselling in accordance with clinical guidelines recommended by the US Preventive Services Task Force. Criteria to recommend referral include the following: • Ashkenazi Jewish heritage • History of ovarian cancer at any age in the patient or any first- or second-degree relatives • Any first-degree relative with a history of breast cancer diagnosed before the age of 50	Relative risk >4.0 • Female • Age (65+ vs <65 years, although risk increases across all ages until age 80) • Certain inherited genetic mutations for breast cancer (<i>BRCA1</i> and/or <i>BRCA2</i>) • Two or more first-degree relatives with breast cancer diagnosed at an early age

GI: Gastrointestinal; MRI: Magnetic resonance imaging

Supplementary Table 1. International Guidelines Reviewed for Hereditary Breast and Ovarian Cancer Syndrome (Con't)

Guideline Title	Genetic/Familial High Risk Assessment: Breast and Ovarian	Familial Breast Cancer: Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer	Breast Cancer Treatment Guidelines	BRCA in Breast Cancer: ESMO Clinical Recommendations	Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility	Breast Cancer Follow-up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update	Breast Cancer Screening
	• ≥ 1 family member on the same side of the family with a combination of breast cancer and ≥ 1 of the following (especially if early onset): - Pancreatic cancer - Prostate cancer (Gleason score ≥ 7) - Sarcoma - Adrenocortical carcinoma - Brain tumours - Endometrial cancer - Leukaemia/lymphoma - Thyroid cancer - Dermatologic manifestations and/or macrocephaly - Hamartomatous polyps of GI tract - Diffuse gastric cancer • Male breast cancer	- Four relatives diagnosed with breast cancer at any age (at least 1 must be a first-degree relative) or • Families containing 1 relative with ovarian cancer at any age and, on the same side of the family: - One first-degree relative (including the relative with ovarian cancer) or second-degree relative diagnosed with breast cancer at younger than age 50 years or - Two first- or second-degree relatives diagnosed with breast cancer younger than an average age of 60 years or - Another ovarian cancer at any age or • Families affected by bilateral cancer - One first-degree relative with cancer diagnosed with cancer in both breasts at younger than an average age 50 years or - One first- or second-degree relative diagnosed with bilateral cancer and one first- or			• ≥ 1 or more family member with 2 primary types of BRCA-related cancer • Ashkenazi Jewish ethnicity • Several familial risk stratification tools are available to determine the need for in-depth genetic counselling, such as the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, and FHS-7 - Referral Screening Tool and FHS-7 are the simplest and quickest to administer	• Two or more first- or second-degree relatives diagnosed with breast cancer at any age • Relative with diagnosis of bilateral breast cancer • History of breast cancer in a male relative	• High breast tissue density • Biopsy-confirmed atypical hyperplasia 2.1 – 4.0 • One first-degree relative with breast cancer • High-dose radiation to chest • High bone density (postmenopausal) 1.1 – 2.0 Factors That Affect Circulating Hormones • Late age at first full-term pregnancy (>30 years) • Early menarche (<12 years) • Late menopause (>55 years) • No full-term pregnancies • Never breastfed a child • Recent oral contraceptive use

GI: Gastrointestinal; MRI: Magnetic resonance imaging

Supplementary Table 1. International Guidelines Reviewed for Hereditary Breast and Ovarian Cancer Syndrome (Con't)

Guideline Title	Genetic/Familial High Risk Assessment: Breast and Ovarian	Familial Breast Cancer: Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer	Breast Cancer Treatment Guidelines	BRCA in Breast Cancer: ESMO Clinical Recommendations	Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility	Breast Cancer Follow-up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update	Breast Cancer Screening
		second-degree relative diagnosed with bilateral cancer and one first- or second-degree relative diagnosed with breast cancer at younger than an average age of 60 years or • Families containing male breast cancer at any age and, on the same side of the family, at least: - One first- or second-degree relative diagnosed with breast cancer at younger than 50 years or - Two first- or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years. • If their combined <i>BRCA1</i> and <i>BRCA2</i> mutation carrier probability is 10% or more and an affected relative is unavailable for testing • A formal risk assessment has given risk estimates of:					• Recent and long-term use of estrogen and progestin • Obesity (postmenopausal) Other Factors • Personal history of endometrial or ovarian cancer • Alcohol consumption • Height (tall) • High socioeconomic status • Ashkenazi Jewish heritage <u>Others</u> • Women with a personal history of high risk breast biopsy results, including atypical hyperplasia and lobular carcinoma in situ

GI: Gastrointestinal; MRI: Magnetic resonance imaging

Supplementary Table 1. International Guidelines Reviewed for Hereditary Breast and Ovarian Cancer Syndrome (Con't)

Guideline Title	Familial Breast Cancer: Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer				Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility	Breast Cancer Follow-up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update	Breast Cancer Screening
	Genetic/Familial High Risk Assessment: Breast and Ovarian	Familial Breast Cancer	Breast Cancer Treatment Guidelines	BRCA in Breast Cancer: ESMO Clinical Recommendations			
		- A 10% or greater chance of a gene mutation being harboured in the family or - A greater than 8% risk of developing breast cancer in the next 10 years or - A 30% or greater lifetime risk of developing breast cancer					<u>MRI Screening</u> - American Cancer Society recommends MRI screening for women with a 20% or greater lifetime risk of developing breast cancer, including women with the following: - Known <i>BRCA1/2</i> mutation - Have a first-degree relative with <i>BRCA1/2</i> mutation and have not had any testing themselves - Lifetime risk of breast cancer of 20% or higher, according to risk assessment tools based mainly on family history - History of radiation therapy to the chest between age 10 – 30 years - Other genetic syndromes including Li-Fraumeni syndrome, Cowden syndrome, or Bannayan-Riley-Ruvalcaba syndrome or one of these in a first-degree relative

GI: Gastrointestinal; MRI: Magnetic resonance imaging

Supplementary Table 1. International Guidelines Reviewed for Hereditary Breast and Ovarian Cancer Syndrome (Con't)

Familial Breast Cancer: Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer					
Guideline Title	Genetic/Familial High Risk Assessment: Breast and Ovarian	Breast Cancer Treatment Guidelines	BRCA in Breast Cancer: ESMO Clinical Recommendations	Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility	Breast Cancer Follow-up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update Breast Cancer Screening
Who to Refer: Breast Cancer BRCA Screening for Women With Personal History of Breast or Ovarian Cancer	• A known mutation in a breast cancer susceptibility gene within the family • Early age onset breast cancer • Triple negative (ER-, PR-, HER2-) breast cancer • Two breast primaries in a single individual				
	• Breast cancer at any age, and - ≥1 close blood relative with breast cancer ≤50 years, or - ≥1 close blood relative with epithelial ovarian cancer at any age, or - ≥2 close blood relatives with breast cancer and/or pancreatic cancer at any age - From a population with increased risk (requirements for inclusion may be modified, e.g. of Ashkenazi Jew descent with breast/ovarian/pancreatic cancer at any age)				• Patient with diagnosis of bilateral breast cancer

GI: Gastrointestinal; MRI: Magnetic resonance imaging

Supplementary Table 1. International Guidelines Reviewed for Hereditary Breast and Ovarian Cancer Syndrome (Con't)

Familial Breast Cancer: Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer				
Guideline Title	Genetic/Familial High Risk Assessment: Breast and Ovarian	Breast Cancer Treatment Guidelines	BRCA in Breast Cancer: ESMO Clinical Recommendations	Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility
	• ≥ 1 family member on the same side of the family with a combination of breast cancer and ≥ 1 of the following (especially if early onset): - Pancreatic cancer - Prostate cancer (Gleason score ≥ 7) - Sarcoma - Adrenocortical carcinoma - Brain tumours - Endometrial cancer - Leukaemia/lymphoma - Thyroid cancer - Dermatologic manifestations and/or macrocephaly - Hamartomatous polyps of GI tract - Diffuse gastric cancer • Ovarian cancer • Male breast cancer			
Mutation Detection	• Individual from a family with a known deleterious <i>BRCA1/BRCA2</i> mutation • Personal history of breast cancer and 1 of more of the following: - Diagnosed ≤ 45 years - Diagnosed ≤ 50 years with:	• Tests aimed at mutation finding should first be carried out on an affected family member where possible • If possible, the development of a genetic test for a family should usually start with the testing of an affected individual	• Three or more breast and/or ovarian cancer family cases - With at least one <50 years - Two breast cancer cases <40 years - Male breast cancer and ovarian cancer or early onset female breast cancer	• Testing for BRCA mutations should only be done when: - An individual has personal or family history that suggests an inherited cancer susceptibility - An individual has access to a health professional who is trained to provide
				Family history to be considered: • Breast cancer cases, ovarian cancer cases, prostate cancer cases, and other types of cancer cases in first-, second- and third-degree relatives, including the age of onset for the family members with cancer

GI: Gastrointestinal; MRI: Magnetic resonance imaging

Supplementary Table 1. International Guidelines Reviewed for Hereditary Breast and Ovarian Cancer Syndrome (Con't)

Guideline Title	Genetic/Familial High Risk Assessment: Breast and Ovarian	Familial Breast Cancer: Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer	Breast Cancer Treatment Guidelines	BRCA in Breast Cancer: ESMO Clinical Recommendations	Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility	Breast Cancer Follow-up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update	Breast Cancer Screening
	- An additional primary - ≥ 1 close blood relative with breast cancer at any age - An unknown or limited family history - Diagnosed ≥ 60 years with: - ≥ 1 close blood relative with breast cancer diagnosed ≤ 50 years - ≥ 2 close blood relatives with breast cancer diagnosed at any age - ≥ 1 close blood relative with epithelial ovarian cancer - ≥ 2 close blood relatives with pancreatic cancer and/or prostate cancer (Gleason score ≥ 7) at any age - A close male blood relative with breast cancer - For an individual with ethnicity associated with higher mutation frequency (e.g. Ashkenazi Jewish), no additional family history may be required - Personal history of epithelial ovarian cancer	(mutation searching/screening) to try to identify a mutation in the appropriate gene (such as <i>BRCA1</i>, <i>BRCA2</i> or <i>TP53</i>) • Genetic testing for a person with no personal history of breast cancer but with an available affected relative - Offer genetic testing in specialist genetic clinics to a relative with a personal history of breast and/or ovarian cancer if that relative has a combined <i>BRCA1</i> and <i>BRCA2</i> mutation carrier probability of 10% or more • Genetic testing for a person with no personal history of breast cancer - Offer genetic testing in specialist genetic clinics to a person with no personal history of breast or ovarian cancer if their combined <i>BRCA1</i> and <i>BRCA2</i> mutation carrier probability is 10% or more and an affected relative is unavailable for testing	• Three or more breast and/or ovarian cancer family cases - With at least one <50 years - Two breast cancer cases <40 years - Male breast cancer and ovarian cancer or early onset female breast cancer • Ashkenazi Jew with breast cancer <60 years • Young onset bilateral breast cancer; and breast and ovarian cancer in the same person • Presence of medullary carcinoma and triple negative phenotype (estrogen receptor, progesterone receptor and no over expression of <i>HER2neu</i>) in women younger than 50 years • Three or more breast and/or ovarian cancer family cases - With at least one <50 years - Two breast cancer cases <40 years	• Three or more breast and/or ovarian cancer family cases - With at least one <50 years - Two breast cancer cases <40 years - Male breast cancer and ovarian cancer or early onset female breast cancer • Ashkenazi Jew with breast cancer <60 years • Young onset bilateral breast cancer; and breast and ovarian cancer in the same person • In some countries, the criterion for testing is based on an a priori 10-20% probability of finding a mutation based on predictive models such as BRCAPRO, BOADICEA or Manchester Score, while less specific criteria include a potential benefit in the medical or surgical management of the individual or his/her relatives	• Testing for BRCA mutations should only be done when: - An individual has personal or family history that suggests an inherited cancer susceptibility - An individual has access to a health professional who is trained to provide genetic counselling and interpret test results - Test results will aid in decision-making • Initial testing of a family member with breast or ovarian cancer is the preferred strategy in most cases, but it is reasonable to test if no affected relative is available • Type of mutation analysis required depends on family history. Individuals from families with known mutations or from ethnic groups in which certain mutations are more common (e.g. Ashkenazi Jewish women) can be tested for these specific mutations		

GI: Gastrointestinal; MRI: Magnetic resonance imaging

Supplementary Table 1. International Guidelines Reviewed for Hereditary Breast and Ovarian Cancer Syndrome (Con't)

Guideline Title	Genetic/Familial High Risk Assessment: Breast and Ovarian	Familial Breast Cancer: Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer	Breast Cancer Treatment Guidelines	BRCA in Breast Cancer: ESMO Clinical Recommendations	Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility	Breast Cancer Follow-up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update	Breast Cancer Screening
	• Personal history of male breast cancer • Personal history of pancreatic cancer or prostate cancer (Gleason score ≥ 7) at any age with ≥ 2 close blood relatives with breast and/or ovarian and/or pancreatic cancer (Gleason score ≥ 7) at any age - For pancreatic cancer, if Ashkenazi Jewish ancestry, only one additional affected relative is needed • Family history only (significant limitations of interpreting test results for an unaffected individual should be discussed): - First- or second-degree blood relative meeting any of the above criteria - Third-degree blood relative with breast cancer and/or ovarian cancer with ≥ 2 close blood relatives with breast cancer (at least one with breast cancer ≤ 50 years) and/or ovarian cancer	• Genetic testing for a person with breast or ovarian cancer - Offer genetic testing in specialist genetic clinics to a person with breast or ovarian cancer if their combined <i>BRCA1</i> and <i>BRCA2</i> mutation carrier probability is 10% or more	- male breast cancer and ovarian cancer or early onset female breast cancer • Ashkenazi Jew with breast cancer <60 years • Young onset bilateral breast cancer; and breast and ovarian cancer in the same person • Presence of medullary carcinoma and triple negative phenotype (estrogen receptor, progesterone receptor and no over expression of <i>HER2neu</i>) in women younger than 50 years. • Three or more breast and/or ovarian cancer family cases - With at least one <50 years - Two breast cancer cases <40 years - Male breast cancer and ovarian cancer or early onset female breast cancer • Ashkenazi Jew with breast cancer <60 years	• The addition of pathological features of breast cancer such as medullary carcinoma and triple negative phenotype (estrogen receptor, progesterone receptor and no overexpression of <i>HER2neu</i>) in women younger than 50 has been evaluated as a cost-effectiveness strategy for mutation detection. • 2% to 12% of high risk families may harbour a large genomic alteration	• Individuals without linkages to families or groups with known mutations receive more comprehensive testing. Testing should begin with a relative who has breast or ovarian cancer to determine if affected family members have a clinically significant mutation		

GI: Gastrointestinal; MRI: Magnetic resonance imaging

Supplementary Table 1. International Guidelines Reviewed for Hereditary Breast and Ovarian Cancer Syndrome (Con't)

Familial Breast Cancer: Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer						
Guideline Title	Genetic/Familial High Risk Assessment: Breast and Ovarian	Breast Cancer Treatment Guidelines	BRCA in Breast Cancer: ESMO Clinical Recommendations	Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility	Breast Cancer Follow-up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update	Breast Cancer Screening
	- Clinical judgement should be used to determine if the patient has reasonable	• Young onset bilateral breast cancer; and breast and ovarian cancer in the same person • Presence of medullary carcinoma and triple negative phenotype (estrogen receptor, progesterone receptor and no over expression of <i>HER2neu</i>) in women younger than 50 years.				
Member Votes	Unanimous					
GI: Gastrointestinal; MRI: Magnetic resonance imaging						

Supplementary Table 2. International Guidelines Reviewed for Lynch Syndrome

Guideline Title	Recommendations from the EGAPP Working Group: Genetic testing Strategies in Newly Diagnosed Individuals with Colorectal Cancer Aimed At Reducing Morbidity and Mortality from Lynch Syndrome in Relatives	Genetic/Familial High Risk Assessment: Colorectal	American College of Gastroenterology Guidelines for Colorectal Cancer Screening 2008	Revised Guidelines for the Clinical Management of Lynch Syndrome (HNPCC): Recommendations by a Group of European Experts	ACMG Technical Standards and Guidelines for Genetic Testing for Inherited Colorectal Cancer (Lynch Syndrome, Familial Adenomatous Polyposis, and MYH-associated Polyposis)
Date Released	January 2009	2014	2009	December 2012 (Revised January 2013)	September 2013
Guideline Developer	Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group - Independent Expert Panel	NCCN	American College of Gastroenterology - Medical Specialty Society	Vasen et al	Working Group of the American College of Medical Genetics and Genomics (ACMG) Laboratory Quality Assurance Committee
Reference	Genetics In Medicine. 2009 Jan;11(1):35-41	NCCN: National Comprehensive Cancer Network (US) Guidelines. Genetic/Familial High-Risk Assessment: Colorectal. 2015 Version 1. Page 10	Am J Gastroenterol 2009;104:739-750	Gut 62.6 (2013):812-823	Genetics In Medicine. 2014 Jan;16(1):101-116
Description of Method of Guideline Validation	Recommendations concerning laboratory and genetic testing in colorectal cancer from the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncologists (ASCO) were reviewed	The NCCN Guidelines are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to cancer treatment	This guideline has been reviewed and approved by the Practice Parameters Committee of the American College of Gastroenterology (ACG) and by the ACG Board of Trustees	External peer review. The guidelines were discussed during 2 workshops and all authors were involved in the discussion.	These technical standards and guidelines were approved by the ACMG Board of Directors on 20 May 2013.
MSI Testing	All CRC patients or CRC patients diagnosed at <70 years and also those ≥70 who meet the Bethesda guidelines	All CRC patients who meet the Bethesda criteria should undergo microsatellite instability testing of their tumour or a family member's tumour and/or tumour immunohistochemical staining for mismatch repair proteins	Patients who meet the Bethesda criteria should undergo microsatellite instability testing of their tumour or a family member's tumour and/or tumour immunohistochemical staining for mismatch repair proteins	All CRC (or individuals with CRC <70 years) and all EC (or individuals with EC <70 years) by immunohistochemistry of the 4 MMR proteins or MSI. These tests should be accompanied by methods that identify MLH1 promotor methylation.	MSI testing: 1. CRC diagnosed <50 2. Presence of synchronous or metachronous CRC or other hereditary non-polyposis CRC-related tumour, regardless of age 3. CRC in an individual <60 years of age exhibiting tumour-infiltrating lymphocytes 4. CRC at any age, plus CRC or hereditary non-polyposis CRC-related tumour diagnosed <50 years in at least one first-degree relative

CRC: Colorectal cancer; EC: Endometrial cancer; LS: Lynch syndrome; MSI: Microsatellite instability
 *4 of 5 members voted not to include universal screening in the current SCAN guidelines.

Supplementary Table 2. International Guidelines Reviewed for Lynch Syndrome (Con't)

Guideline Title	Recommendations from the EGAPP Working Group: Genetic Testing Strategies in Newly Diagnosed Individuals with Colorectal Cancer Aimed At Reducing Morbidity and Mortality from Lynch Syndrome in Relatives	Genetic/Familial High Risk Assessment: Colorectal	American College of Gastroenterology Guidelines for Colorectal Cancer Screening 2008	Revised Guidelines for the Clinical Management of Lynch Syndrome (HNPCC): Recommendations by a Group of European Experts	ACMG Technical Standards and Guidelines for Genetic Testing for Inherited Colorectal Cancer (Lynch Syndrome, Familial Adenomatous Polyposis, and MYH-associated Polyposis)
MSI Testing					5. CRC at any age, plus CRC or hereditary non-polyposis CRC-related tumour diagnosed <50 years in 2 or more first- or second-degree relatives -If an MSI unstable tumour harbours the BRAF gene <i>p.V600E</i> mutation, it is most likely sporadic and germline testing is not necessary
Member Votes					Unanimous
Genetic Testing	Offer genetic testing for LS to individuals with newly diagnosed CRC	[LS testing - clinical] Meets revised Bethesda guidelines or Amsterdam criteria Endometrial cancer <50 years or Known LS in family or Consider testing individuals with $\geq 5\%$ risk of LS on any mutation model (e.g. MMRpro, PREMM, MMRpredict)	Patients who test positive for MSI should undergo genetic testing If evaluation for HNPCC not indicated Patients with: Single first-degree relative with CRC or advanced adenoma diagnosed at age ≥ 60 years Single first-degree with CRC or advanced adenoma diagnosed at age <60 years or 2 first-degree relatives with CRC or advanced adenomas	Molecular screening of EC, sebaceous adenomas and carcinomas have been effective	CRC patient <50 including; - Colorectal cancer diagnosed in one or more first-degree relatives with a Lynch-related tumour, one who was diagnosed <50 years of age - Colorectal cancer diagnosed in 2 or more relatives of regardless of age
Member Votes*					Unanimous

CRC: Colorectal cancer; EC: Endometrial cancer; LS: Lynch syndrome; MSI: Microsatellite instability

*4 of 5 members voted not to include universal screening in the current SCAN guidelines.

Supplementary Table 3. International Guidelines Reviewed for Familial Adenomatous Polyposis

Guideline Title	Genetic/Familial High Risk Assessment: Colorectal	American College of Gastroenterology Guidelines for Colorectal Cancer Screening 2008	ACMG Technical Standards and Guidelines for Genetic Testing for Inherited Colorectal Cancer (Lynch Syndrome, Familial Adenomatous Polyposis, and MYH-associated Polyposis)
Date Released	2014	2009	September 2013
Guideline Developer	NCCN	American College of Gastroenterology - Medical Specialty Society	Working Group of the American College of Medical Genetics and Genomics (ACMG) Laboratory Quality Assurance Committee
Reference	NCCN: National Comprehensive Cancer Network (US) Guidelines. Genetic/Familial High-Risk Assessment: Colorectal. 2015 Version 1. Page 21	Am J Gastroenterol 2009; 104:739-750	Genetics In Medicine 2014 Jan;16(1):101-116
Description of Method of Guideline Validation	The NCCN Guidelines are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to cancer treatment	This guideline has been reviewed and approved by the Practice Parameters Committee of the American College of Gastroenterology (ACG) and by the ACG Board of Trustees	These technical standards and guidelines were approved by the ACMG Board of Directors on 20 May 2013
Genetic Testing	APC Testing Criteria: 1. Personal history of >10 adenomas 2. Personal history of desmoid tumour 3. Known deleterious mutation of APC in family	1. Patients with classic FAP (>100 adenomas) should be advised to pursue genetic counselling and genetic testing, if they have siblings or children who could potentially benefit from this testing 2. Patients with classic FAP, in whom genetic testing is negative, should undergo genetic testing for bi-allelic MYH mutations. Patients with 10 – 100 adenomas can be considered for genetic testing for attenuated FAP and if negative, MYH-associated polyposis	Indications for testing: 1. CRC diagnosed <40 years 2. CRC diagnosed in ≥1 first-degree relatives 3. Other adenomas and cancers FAP testing criteria: 1. Presence of 100 or more polyps 2. Autosomal dominant inheritance 3. Possible additional findings, such as congenital hypertrophy of retinal pigment epithelium, osteomas, supernumerary teeth, odontomas, desmoids, epidermoid cysts, duodenal and other small-bowel adenomas, gastric fundic gland polyps AFAP testing criteria: 1. Presence of <100 adenomas* 2. Frequent right-sided distribution of polyps 3. Adenomas and cancers at an age older than that for classic FAP and other gastrointestinal manifestations
Member Votes	Unanimous		

AFAP: Attenuated familial adenomatous polyposis; APC: Adenomatous polyposis coli; CRC: Colorectal cancer; FAP: Familial adenomatous polyposis

*Average 30 polyps. Individuals with 100 or more polyps occurring at older ages (35 – 40 years or older) may be found to have AFAP.

Singapore Cancer Network (SCAN) Guidelines for Referral for Genetic Evaluation of Common Hereditary Cancer Syndromes

The Singapore Cancer Network (SCAN) Cancer Genetics Workgroup

Abstract

Introduction: The SCAN cancer genetics workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for referral for genetic evaluation of common hereditary cancer syndromes. **Materials and Methods:** The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. **Results:** To formulate referral guidelines for the 3 most commonly encountered hereditary cancer syndromes to guide healthcare providers in Singapore who care for cancer patients and/or their family members, 7, 5, and 3 sets of international guidelines respectively for hereditary breast and ovarian cancer (HBOC) syndrome, Lynch syndrome (LS), and familial adenomatous polyposis (FAP) were evaluated. For each syndrome, the most applicable one was selected, with modifications made such that they would be appropriate to the local context. **Conclusion:** These adapted guidelines form the SCAN Guidelines 2015 for referral for genetic evaluation of common hereditary cancer syndromes.

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Key words: Familial breast cancer, Hereditary cancer syndromes, Referral guidelines

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Introduction

Mutations in high penetrance genes account for approximately 3% to 5% of all cancers. In the last 2 decades, there has been better characterisation of an ever growing list of hereditary cancer syndromes, largely due to the identification of causative genes. Formal management guidelines, including testing, screening and preventive options, have been established for many of these syndromes.^{1,2} Identification of these patients and families who are at extremely high risk of developing cancer for specialised management is crucial to reduce cancer occurrence and mortality. Formal cancer genetics programmes have been established in Singapore in both tertiary cancer centres in Singapore (National University Cancer Institute [NCIS], National Cancer Centre [NCCS]) since 2001.³ However, there are no formal local guidelines providing guidance to general practitioners, physicians or surgeons on who should be referred for cancer genetic assessment.

The SCAN Guidelines for Referral for Genetic Evaluation of Common Hereditary Cancer Syndromes

The SCAN Guidelines are clinical practice guidelines for referral for genetic evaluation of common hereditary cancer syndromes.

These first edition guidelines are intended to serve as recommendations by members of this working group reflecting their views on current existing international guidelines for the referral for genetic evaluation of common hereditary cancer syndromes. While it hopes to harmonise the management of such syndromes, it is not intended to serve as a standard or to replace good judgment and individualisation.

Target Users of the Guidelines

The guidelines will be of interest to healthcare providers in Singapore who care for cancer patients and/or their family members.

Address for Correspondence: A/Prof Lee Soo Chin, Department of Haematology-Oncology, National University Cancer Institute, Singapore, 1E Lower Kent Ridge Road, Level 7, NUHS Tower Block, Singapore 119228.
Email: csilsc@nus.edu.sg

Guideline Recommendations/Development

The SCAN Cancer Genetics Workgroup comprises a panel of 4 medical oncologists and 1 colorectal surgeon from Singapore with special interests in the management of hereditary cancer syndromes. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead with input from the workgroup members. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, high quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available.

The workgroup members shared a common view that referral guidelines represented a key issue that is both pressing and relevant to the medical community at large. In contrast, testing and management guidelines are less relevant as pre- and post-test genetic counselling, surveillance and preventive recommendations, test result interpretations, and the social and ethical implications of genetic testing would be most appropriately delivered by trained specialists, preferably in the setting of a specialised cancer genetics clinic in a tertiary cancer centre. Currently, only 2 such clinics exist in the 2 tertiary cancer centres in restructured hospitals in Singapore: NCIS and NCCS, to serve the entire

Singapore population of ~5.5 million. Both clinics are led by medical oncologists trained in cancer genetics, assisted by a cancer genetics counsellor. In addition, there are a few specialists in private medical centres who are trained to provide cancer genetics evaluation and counselling.

The workgroup decided to focus on the following 3 hereditary cancer syndromes most commonly encountered in practice:

1. Hereditary Breast and Ovarian Cancer (HBOC) Syndrome,
2. Lynch Syndrome (LS), and
3. Familial Adenomatous Polyposis (FAP).

Considering that at-risk patients may be referred from a diverse group of healthcare providers with different levels of knowledge on hereditary cancer syndromes, ranging from family physicians to specialists from different disciplines who may manage cancer patients or their families, it was decided that risk criteria chosen as referral guidelines should be clinical criteria that can be readily understood and assessed in the clinic. In addition, it was noted that while genetic evaluation and counselling is a health service that can be subsidised by the government, genetic tests are specialised tests that are self-paid by patients in Singapore and typically cost ~USD \$1500 to \$2000. High test cost has been cited as a barrier to genetic testing in Singapore.⁴ Recognising this and the fact that medical resources are limited in Singapore with only 2 specialised cancer genetics clinics in the restructured hospitals serving the entire nation, it was decided to set the referral threshold at a sensitivity level equivalent to an a priori probability of diagnosing hereditary cancer syndrome of $\geq 10\%$ to 20% , so as not to overwhelm the healthcare system.

Table 1 lists the guidelines that were reviewed, the details of which are summarised in Supplementary Tables 1-3. Guidelines were selected from various representative international professional bodies, excluding those that were published more than 10 years ago. Seven, 5, and 3 sets of international guidelines were reviewed for HBOC,⁵⁻⁸ LS,⁹⁻¹² and FAP^{10,12} respectively. The workgroup reviewed the guidelines and selected the most applicable one for each syndrome with modifications made for them to be appropriate to the local context (Table 2).

1. Hereditary Breast and Ovarian Cancer (HBOC)

International guidelines for HBOC typically divided the recommendations into 2 categories: for women with and without a personal history of cancer. All members elected to streamline the guidelines into a single category using the family as a unit and modify the wordings to include salient aspects of both personal and family histories. Most of the guidelines (NICE, Canadian Saskatchewan, USPSTF, ASCO,

Table 1. International Guidelines Reviewed for Common Hereditary Cancer Syndromes by the SCAN Cancer Genetics Workgroup

Hereditary Cancer Syndrome	International Guidelines Reviewed
Hereditary Breast and Ovarian Cancer Syndrome	National Comprehensive Cancer Network (NCCN, United States), 2014 United States Preventive Services Task Force (USPSTF), 2013 ⁵ National Institute for Health and Care Excellence (United Kingdom), 2013 American Society of Clinical Oncology (ASCO), 2012 ⁶ Saskatchewan Cancer Agency (Canada), 2012 European Society for Medical Oncology (ESMO) Guidelines Working Group, 2011 ⁷ The American College of Obstetricians and Gynaecologists (ACOG), 2011 ⁸
Lynch Syndrome	National Comprehensive Cancer Network (NCCN, United States), 2014 European revised guidelines for the management of Lynch syndrome, 2013 ⁹ American College of Medical Genetics (ACMG), 2013 ¹⁰ The Evaluation of Genomic Applications in Practice and Prevention working Group (EGAPP) Working Group, 2009 ¹¹ American College of Gastroenterologists, 2008 ¹²
Familial Adenomatous Polyposis	National Comprehensive Cancer Network (NCCN, United States), 2014 American College of Medical Genetics (ACMG), 2013 ¹⁰ American College of Gastroenterologists, 2009 ¹²

ESMO) were similar in recommending that women with young breast cancer, multiple family members with breast cancers, bilateral breast cancers, breast and ovarian cancers, male breast cancers, and multiple other related cancers (pancreatic, prostate, etc.) be included. In concordance with these recommendations, one local study showed that the highest risk group is families with breast and ovarian cancer.¹³

After reviewing the 7 sets of international guidelines, the committee decided to adopt the guidelines by the European Society for Medical Oncology (ESMO) Guidelines Working Group (2011) as the backbone guidelines,⁷ as they were most encompassing, recommending 4 broad categories of patients to be referred: family history of breast or ovarian cancer, young onset cancer, male breast cancer, and multiple tumours. The workgroup built upon these general guidelines and added specific information to make the guidelines easy for referring physicians to follow. Of note, the age threshold for 'young onset cancer' was specified to be less than 40, while 'family history of breast or ovarian cancer' was further divided into 'family history of breast and ovarian cancer' and 'family history of 2 or more breast cancers, with at least one diagnosed below age 50' (adopted from the 2014 NCCN guidelines). In addition, members added a special note for clinicians to ask for a family history of young onset pancreatic and prostate cancer (diagnosed below age 50) in patients and/or families with breast cancer, and to consider referring these patients/families to a cancer genetics clinic for further evaluation (adopted from the 2014 NCCN guidelines). Recognising that patients with certain histological subtypes of breast and ovarian cancer have up to 10% to 20% chance of carrying a *BRCA1/2* mutation, patients with triple negative breast cancer diagnosed below age 50 (adopted from the 2014 NCCN guidelines with age

threshold added to increase the specificity for referral)¹⁴ and patients with epithelial ovarian cancer diagnosed at any age (adopted from the 2012 ASCO guidelines), in particular those with high-grade serous ovarian cancer,¹⁵ were included in the referral criteria for HBOC.

The concept of population-based screening for *BRCA1/2* has been proposed recently.¹⁶ However, given the high test cost that has to be borne by the patients as well as our currently limited medical resources to handle pre- and post-test genetic counselling and test interpretations required from large scale genetic testing, all members of the workgroup agreed not to include universal screening for HBOC syndrome in the guidelines, recognising that genetic testing administered without appropriate counselling may result in misinterpretation and harm.¹⁷

2. Lynch Syndrome (LS) or Hereditary Non-Polyposis Colorectal Cancer

Colorectal cancer (CRC) is a major public health problem, being the third most common cancer in men and women.¹⁸ It is the second and third commonest cause of cancer-related deaths in men and women respectively and is largely preventable with recommended population screening.^{18,19} It is estimated that approximately 3% of CRCs are attributable to LS.²⁰⁻²² This autosomal dominant genetic disorder is associated with greatly increased risks of developing colorectal, endometrial, gastric and other cancers.²⁰⁻²³ Despite the increased risk of cancers seen in LS patients, long-term follow-up studies show that compliance with current surveillance recommendations is highly successful. LS patients show no increase in cancer-related mortality when compared to mutation-negative family members on long-term follow-up.²⁴ Unfortunately, unless

Table 2. Singapore Cancer Network (SCAN) Guidelines for the Referral for Genetic Evaluation of Common Hereditary Cancer Syndromes

Suspected Hereditary Cancer Syndrome	Patients Who Should be Referred for Cancer Genetic Risk Assessment	Guidelines Adapted From
Hereditary Breast and Ovarian Cancer Syndrome	- Personal or family history of breast cancer diagnosed <40 years of age; - Personal or family history of male breast cancer, any age; - Personal or family history of epithelial ovarian cancer, any age; - Personal or family history of triple negative breast cancer diagnosed <50 years of age - Family with 2 or more breast cancers, at least one aged <50 years of age; - Family with both breast and epithelial ovarian cancers; - Two or more tumours in the same patient (bilateral breast cancer; multiple breast cancers; breast and ovarian cancer); - Known <i>BRCA1/2</i> mutation in family. An a priori $\geq 10\%$ probability of finding a mutation based on predictive models such as BRCAPRO, BOADICEA or Manchester Score* (Special note: <i>BRCA1/2</i> mutation carriers are also at risk for pancreatic and prostate cancer and clinicians should additionally ask for these cancers in taking the family history. Physicians should consider referring families with breast cancer and young onset pancreatic or prostate cancer diagnosed before age 50.)	European Society for Medical Oncology (ESMO) Guidelines Working Group (2011)
Lynch Syndrome (LS)	Tumour microsatellite instability (MSI) and/or immunohistochemical (IHC) staining for mismatch repair (MMR) proteins should be considered in:† 1. Patient with CRC diagnosed <50; 2. Patient with synchronous or metachronous CRC or other LS-related tumours,‡ regardless of age; 3. Patient with CRC diagnosed <60 years of age with the MSI-H histology (presence of tumour infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet ring differentiation, or medullary growth pattern); 4. Patient with CRC diagnosed at any age, and who has at least 1 first-degree relative diagnosed with CRC or LS-related tumour diagnosed <50 years; 5. Patient with CRC at any age, and who has 2 or more first- or second-degree relatives with CRC or LS-related tumour at any age. (Special note: If an MSI unstable tumour harbours the BRAF gene <i>p.V600E</i> mutation, it is most likely sporadic and germ line testing for mismatch repair genes is not necessary.) When referral for clinical germline testing for mismatch repair genes should be considered: 1. Meets Amsterdam criteria§ or any of the above 5 listed criteria for tumour MSI or IHC testing for MMR proteins; 2. Endometrial cancer <50 years; 3. Known LS mutation in family; (Special note: Consider testing individuals with $\geq 10\%$ risk of LS on any mutation model³⁹⁻⁴² (e.g., MMRpro, PREMM, MMRpredict)*	National Comprehensive Cancer Network Guidelines - Genetic/Familial High Risk Assessment Colorectal (2014)
Familial Adenomatous Polyposis (FAP)	1. Patients with classic FAP (>100 adenomas) should be advised to pursue genetic counselling and genetic testing, particularly if they have siblings or children who could potentially benefit from predictive testing. 2. Patients with classic FAP, in whom APC genetic testing is negative, should undergo genetic testing for bi-allelic MYH mutations. 3. Patients with 10 – 100 adenomas can be considered for genetic testing for attenuated FAP and if negative, for MYH-associated polyposis. (Special note: It should be highlighted that the number of adenomas is the cumulative number of adenomas seen in a patient's lifetime.)	American College of Gastroenterology - Medical Specialty Society 2009

APC: Adenomatous polyposis coli; CRC: Colorectal cancer; MSI-H: Microsatellite instability (high)

*This assessment should be made by a trained cancer genetics specialist.

†Alternatively, patients fulfilling these criteria may be referred to a cancer genetics clinic for genetic evaluation and workup.

‡LS-related cancers include cancers of the endometrium, stomach, pancreas, small intestine, ovary, kidney, brain, ureters, or bile duct.

§Amsterdam criteria: At least 3 family members affected with cancer, spanning 2 generations, with at least 1 affected family member diagnosed below age 50 years; the 3 affected family members have to be first-degree relatives of each other. In the Amsterdam I criteria, all 3 affected family members must have colorectal cancer; in Amsterdam II criteria, the affected family members may have colorectal, uterine, small bowel, ureteric or renal pelvis cancer.

there is strong clinical suspicion, many cases of LS are missed.²³ Furthermore, standard population CRC screening guidelines fail to provide early detection or prevention for most LS colon cancers as they tend to occur at young ages.²⁰⁻²³ There is hence a clear need for better ways to detect patients at risk of LS.

The challenge in diagnosing LS, in contrast to FAP, is that it does not have pathognomonic clinical features of polyposis that distinguish it from a sporadic cancer. Guidelines for LS testing comprise one for screening of resected tumour specimens and another that targets germline genetic testing (usually blood) of at-risk individuals. Germline genetic testing by sequencing with or without multiplex ligation-dependent probe amplification is cost-effective in individuals who are of sufficient risk.²⁵

Unfortunately, a high proportion of patients are missed when clinicians rely only on high risk clinical and/or pathological features.^{21,26} Indeed, the revised Bethesda guidelines are now known to be inadequate for LS screening when family cancer history is not available. A universal screening paradigm greatly increased the rate of LS detection,²⁷ and the approach of universal screening for mismatch repair defect (MMR), the hallmark feature in LS,^{20,26} in all colorectal cancer specimens, with either tumour microsatellite instability (MSI) testing with or without BRAF testing, or immunohistochemistry (IHC) staining of MMR proteins, has been proposed.²⁸ For screening, IHC is thought to be almost equally sensitive as MSI but more readily available.²⁶ Either MSI and/or MMR IHC as a screening tool to identify candidate LS cases for further workup are available in both tertiary cancer centres (NCIS and NCCS). However, while universal screening has been shown to be cost-effective,²⁹⁻³² infrastructure comprising trained medical staff, pathologists and workflows is required for effective implementation.³³⁻³⁵ As such, there is disagreement within the workgroup with regard to universal screening, with 4 of 5 members voting not to include it in the current SCAN guidelines, given the lack of clear data and untested assumption in cost-effectiveness analysis studies that multiple family members will be tested following the identification of gene mutation in the proband in the local context.

The guidelines for LS were divided into criteria for tumour screening for MSI or IHC for MMR proteins, and criteria for referral for germline genetic testing. The 2013 American College of Medical Genetics (ACMG) guidelines¹⁰ and the 2014 NCCN guidelines were adopted as the backbone guidelines for tumour screening and germline genetic testing respectively. Tumour screening guidelines were largely based on the revised Bethesda criteria,³⁶ and were included as there are specialists who have access to tumour screening and sufficient expertise to interpret results in at-

risk individuals. However, the workgroup acknowledged that not all physicians are willing or able to order tumour screening tests, and added a special note that physicians may refer patients who fulfill criteria for tumour screening to a cancer genetics clinic for further workup, rather than arrange tumour testing themselves.

3. Familial Adenomatous Polyposis (FAP)

Classic FAP with its carpeting of adenomatous polyps throughout the colon and rectum is an easily recognisable phenotype and should prompt clinicians to initiate confirmatory genetic testing. More challenging would be the recognition of attenuated FAP or MYH-associated polyposis which has a less florid polyposis phenotype. The workgroup felt that an addendum to existing guidelines should be made to highlight that the number of adenomas (10-100) that would trigger consideration for attenuated FAP or MYH-associated polyposis refers to the cumulative incidence of adenomas over a patient's lifetime.

Pre-test Genetic Counselling and Test Interpretation by Trained Specialists

All members in the committee agreed that genetic counselling and informed consent is required before genetic testing.³⁷ In our local setting, this is provided by trained specialists with the recognition that erroneous interpretation of genetic tests results can cause harm.¹⁷ Moreover, many primary care physicians may be unprepared or unable to interpret genetic tests information.³⁸

Conclusion

The systematic development of guidelines will be helpful in the development of cancer genetics in Singapore. Inevitably, the increasing availability of genetic testing will allow greater opportunities for detecting patients with inherited disorders, while also increasing risks from indiscriminate utilisation. These adapted guidelines constitute best practice recommendations on the evaluation of at-risk individuals based on consensus and experience of trained clinical cancer geneticists familiar with the Singapore setting and its unique healthcare system. These guidelines also allow for dissemination of experience and education in Singapore for improving referral and interpretation of genetic tests results.

Of note, the workgroup eventually selected recommendations from multiple source guidelines developed by a variety of organisations, with additional calibration based on local data and experience. This bears testimony to the unique practice setting in Singapore, while also indicating that no single international organisation's

guidelines may be transplanted here as ideal practice. There was general consensus in the selection of relevant recommendations, with only one dissenting opinion in the development of LS guidelines, suggesting that there is a common view of how cancer genetics may be best developed in Singapore.

In conclusion, we have developed best practice recommendations surrounding referral for patients at risk of common hereditary cancer syndromes in Singapore. These recommendations are aimed at improving the identification and evaluation of such patients, and would be relevant to all physicians involved in caring for patients who may have or are at risk for cancer.

Conflicts of Interest

Dr Ang reports receiving lecture fees from Myriad Genetics; Dr Tan reports receiving grant support from Pfizer, and holding the following pending patents: "A Multigene Assay for Prognosis and Drug Response Prediction in Clear-Cell Renal Cell Carcinoma Patients that Identifies Distinct Biological Subtypes", "Method for Predicting Clinical Toxicities and Outcomes in Patients Receiving Sunitinib Using Gene Polymorphisms", "Self-Assembled Micellar Nanocomplexes Comprising Polyethylene Glycol-Epigallocatechin-3-Gallate Conjugates and Anticancer Drugs", "Antibody Specific for Parafibromin, a New Marker of Parathyroid Carcinoma", licensed to Santa Cruz Biotechnology, and "Method for Determining Mutation Status in Colorectal Cancer Patients Using Allele-Specific PCR", licensed to AIT Biotech; Dr Ngeow, Dr Koh and Dr Lee have nothing to disclose.

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Workgroup Members

The Members of the SCAN Cancer Genetics Workgroup are Section Lead and Workgroup Chairperson: Soo Chin Lee, MBBS, MRCP (UK), M Med (Int Med), Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore; Workgroup Members (Voting): Peter Ang, MBBS (S'pore), MMed (S'pore), MRCP (UK), Oncocare Cancer Centre, Singapore; Poh Koon Koh, MBBS (Spore), MMed (Surg), FRCS (Gen), Colorectal Surgical Oncology & Cancer Genetics Service, Fortis Surgical Hospital, Singapore; Joanne YY Ngeow, MBBS (Melbourne), MMed (Int Med), MRCP (UK), Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Min-Han Tan, MBBS, FRCP, PhD, Department of Medical Oncology, National Cancer Centre Singapore, Singapore.

Reviewers

Invited reviewers were Shirley Hodgson, BSc, BMBCh, FRCP, Department of Clinical Genetics, St Georges Hospital, UK; Ignacio Blanco, MD, PhD, Genetic Counseling and Clinical Genetics Program, Hospital Universitari Germans Trias i Pujol, Germany. An additional invited reviewer chose to be anonymous.

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Guideline Title	Genetic/Familial High Risk Assessment: Breast and Ovarian	Familial Breast Cancer: Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer	Breast Cancer Treatment Guidelines	BRCA in Breast Cancer: ESMO Clinical Recommendations	Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility	Breast Cancer Follow-up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update	Breast Cancer Screening
Date Released	2014 Version 1	June 2013	March 2012	January 2011	December 2013	November 2012	August 2011
Guideline Developer	NCCN: National Comprehensive Cancer Network (US)	NICE: National Institute for Health and Care Excellence (UK)	Saskatchewan Cancer Agency (Canada)	European Society for Medical Oncology (ESMO) Guidelines Working Group	US Preventive Services Task Force (USPSTF)	American Society of Clinical Oncology (ASCO)	The American College of Obstetricians and Gynecologists (ACOG)
Reference	NCCN: National Comprehensive Cancer Network (US) Guidelines. Genetic/Familial High-Risk Assessment: Breast and Ovarian. 2015 Version 1. Page 8.	NICE: National Institute for Health and Care Excellence (UK) Guideline 164. June 2013. Pages 24 – 28.	Saskatchewan Cancer Agency (Canada). Breast Cancer Treatment Guidelines. Page 2.	Annals of Oncology 22 (Supplement 6): vi31-vi34, 2011.	Ann Intern Med 2014; 160 (4):271-281.	Journal of Clinical Oncology 31.7 (2013):961-965.	Obstetrics and Gynecology (2011) Vol 118: Issue 2 – Part 1. Pages 372 – 382.
Who to Refer: Breast Cancer Screening for Women Without Personal History of Breast or Ovarian Cancer	• A known mutation in a breast cancer susceptibility gene within the family • ≥2 breast primaries in a single individual • ≥2 individuals with breast primaries on the same side of the family • ≥1 ovarian cancer primary from the same side of the family • First- or second-degree relative with breast cancer ≤45 years	People who should be offered a referral to a specialist genetic clinic: • At least the following female breast cancers only in the family: - Two first- or second-degree relatives diagnosed with breast cancer at younger than an average age of 50 years (at least 1 must be a first-degree relative) or - Three first- or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years (at least 1 must be a first-degree relative) or	• Age greater than 60 • A history of lobular carcinoma in situ (LCIS), ductal carcinoma in situ (DCIS), or atypical proliferative lesion of the breast (atypical ductal or lobular hyperplasia) • Women between 35 and 59 years of age with an estimated risk of breast cancer of 1.66% or higher over 5 years from the Gail model • Individuals with <i>BRCA 1</i> and <i>BRCA2</i> mutations	• Family history of breast or ovarian cancer • Young age at onset • Male breast cancer • Multiple tumours (bilateral breast cancer or breast and ovarian cancer in the same patient)	Family history factors associated with increased likelihood of potentially harmful BRCA mutations include • Breast cancer diagnosis <50 years • Bilateral breast cancer, family history of breast and ovarian cancer • Presence of breast cancer in ≥1 male family member • Multiple cases of breast cancer in the family	Women at high risk for familial breast cancer syndromes should be referred for genetic counselling in accordance with clinical guidelines recommended by the US Preventive Services Task Force. Criteria to recommend referral include the following: • Ashkenazi Jewish heritage • History of ovarian cancer at any age in the patient or any first- or second-degree relatives • Any first-degree relative with a history of breast cancer diagnosed before the age of 50	Relative risk >4.0 • Female • Age (65+ vs <65 years, although risk increases across all ages until age 80) • Certain inherited genetic mutations for breast cancer (<i>BRCA1</i> and/or <i>BRCA2</i>) • Two or more first-degree relatives with breast cancer diagnosed at an early age

GI: Gastrointestinal; MRI: Magnetic resonance imaging

Supplementary Table 1. International Guidelines Reviewed for Hereditary Breast and Ovarian Cancer Syndrome (Con't)

Guideline Title	Genetic/Familial High Risk Assessment: Breast and Ovarian	Familial Breast Cancer: Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer	Breast Cancer Treatment Guidelines	BRCA in Breast Cancer: ESMO Clinical Recommendations	Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility	Breast Cancer Follow-up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update	Breast Cancer Screening
	• ≥ 1 family member on the same side of the family with a combination of breast cancer and ≥ 1 of the following (especially if early onset): - Pancreatic cancer - Prostate cancer (Gleason score ≥ 7) - Sarcoma - Adrenocortical carcinoma - Brain tumours - Endometrial cancer - Leukaemia/lymphoma - Thyroid cancer - Dermatologic manifestations and/or macrocephaly - Hamartomatous polyps of GI tract - Diffuse gastric cancer • Male breast cancer	- Four relatives diagnosed with breast cancer at any age (at least 1 must be a first-degree relative) or • Families containing 1 relative with ovarian cancer at any age and, on the same side of the family: - One first-degree relative (including the relative with ovarian cancer) or second-degree relative diagnosed with breast cancer at younger than age 50 years or - Two first- or second-degree relatives diagnosed with breast cancer younger than an average age of 60 years or - Another ovarian cancer at any age or • Families affected by bilateral cancer - One first-degree relative with cancer diagnosed with cancer in both breasts at younger than an average age 50 years or - One first- or second-degree relative diagnosed with bilateral cancer and one first- or			• ≥ 1 or more family member with 2 primary types of BRCA-related cancer • Ashkenazi Jewish ethnicity • Several familial risk stratification tools are available to determine the need for in-depth genetic counselling, such as the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, and FHS-7 -Referral Screening Tool and FHS-7 are the simplest and quickest to administer	• Two or more first- or second-degree relatives diagnosed with breast cancer at any age • Relative with diagnosis of bilateral breast cancer • History of breast cancer in a male relative	• High breast tissue density • Biopsy-confirmed atypical hyperplasia 2.1 – 4.0 • One first-degree relative with breast cancer • High-dose radiation to chest • High bone density (postmenopausal) 1.1 – 2.0 Factors That Affect Circulating Hormones • Late age at first full-term pregnancy (>30 years) • Early menarche (<12 years) • Late menopause (>55 years) • No full-term pregnancies • Never breastfed a child • Recent oral contraceptive use

GI: Gastrointestinal; MRI: Magnetic resonance imaging

Supplementary Table 1. International Guidelines Reviewed for Hereditary Breast and Ovarian Cancer Syndrome (Con't)

Guideline Title	Genetic/Familial High Risk Assessment: Breast and Ovarian	Familial Breast Cancer: Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer	Breast Cancer Treatment Guidelines	BRCA in Breast Cancer: ESMO Clinical Recommendations	Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility	Breast Cancer Follow-up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update	Breast Cancer Screening
		second-degree relative diagnosed with bilateral cancer and one first- or second-degree relative diagnosed with breast cancer at younger than an average age of 60 years or • Families containing male breast cancer at any age and, on the same side of the family, at least: - One first- or second-degree relative diagnosed with breast cancer at younger than 50 years or - Two first- or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years. • If their combined <i>BRCA1</i> and <i>BRCA2</i> mutation carrier probability is 10% or more and an affected relative is unavailable for testing • A formal risk assessment has given risk estimates of:					• Recent and long-term use of estrogen and progestin • Obesity (postmenopausal) Other Factors • Personal history of endometrial or ovarian cancer • Alcohol consumption • Height (tall) • High socioeconomic status • Ashkenazi Jewish heritage <u>Others</u> • Women with a personal history of high risk breast biopsy results, including atypical hyperplasia and lobular carcinoma in situ

GI: Gastrointestinal; MRI: Magnetic resonance imaging

Supplementary Table 1. International Guidelines Reviewed for Hereditary Breast and Ovarian Cancer Syndrome (Cont'd)

Familial Breast Cancer: Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer					
Guideline Title	Genetic/Familial High Risk Assessment: Breast and Ovarian	Breast Cancer Treatment Guidelines	BRCA in Breast Cancer: ESMO Clinical Recommendations	Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility	Breast Cancer Follow-up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update
					Breast Cancer Screening
Who to Refer: Breast Cancer BRCA Screening for Women With Personal History of Breast or Ovarian Cancer	• A known mutation in a breast cancer susceptibility gene within the family				
	• Early age onset breast cancer				
	• Triple negative (ER-, PR-, HER2-) breast cancer				
	• Two breast primaries in a single individual				
	• Breast cancer at any age, and - ≥1 close blood relative with breast cancer ≤50 years, or - ≥1 close blood relative with epithelial ovarian cancer at any age, or - ≥2 close blood relatives with breast cancer and/or pancreatic cancer at any age - From a population with increased risk (requirements for inclusion may be modified, e.g. of Ashkenazi Jew descent with breast/ovarian/pancreatic cancer at any age)				• Patient with diagnosis of bilateral breast cancer

GI: Gastrointestinal; MRI: Magnetic resonance imaging

Supplementary Table 1. International Guidelines Reviewed for Hereditary Breast and Ovarian Cancer Syndrome (Con't)

Familial Breast Cancer: Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer						
Guideline Title	Genetic/Familial High Risk Assessment: Breast and Ovarian	Breast Cancer Treatment Guidelines	BRCA in Breast Cancer: ESMO Clinical Recommendations	Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility	Breast Cancer Follow-up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update	Breast Cancer Screening
Mutation Detection	• ≥1 family member on the same side of the family with a combination of breast cancer and ≥1 of the following (especially if early onset): - Pancreatic cancer - Prostate cancer (Gleason score ≥7) - Sarcoma - Adrenocortical carcinoma - Brain tumours - Endometrial cancer - Leukaemia/lymphoma - Thyroid cancer - Dermatologic manifestations and/or macrocephaly - Hamartomatous polyps of GI tract - Diffuse gastric cancer • Ovarian cancer • Male breast cancer					
	• Individual from a family with a known deleterious <i>BRCA1/BRCA2</i> mutation • Personal history of breast cancer and 1 of more of the following: - Diagnosed ≤45 years - Diagnosed ≤50 years with:	• Tests aimed at mutation finding should first be carried out on an affected family member where possible • If possible, the development of a genetic test for a family should usually start with the testing of an affected individual	• Three or more breast and/or ovarian cancer family cases - With at least one <50 years - Two breast cancer cases <40 years - Male breast cancer and ovarian cancer or early onset female breast cancer	• Testing for BRCA mutations should only be done when: - An individual has personal or family history that suggests an inherited cancer susceptibility - An individual has access to a health professional who is trained to provide		Family history to be considered: • Breast cancer cases, ovarian cancer cases, prostate cancer cases, and other types of cancer cases in first-, second- and third-degree relatives, including the age of onset for the family members with cancer

GI: Gastrointestinal; MRI: Magnetic resonance imaging

Guideline Title	Genetic/Familial High Risk Assessment: Breast and Ovarian	Familial Breast Cancer. Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer	Breast Cancer Treatment Guidelines	BRCA in Breast Cancer: ESMO Clinical Recommendations	Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility	Breast Cancer Follow-up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update	Breast Cancer Screening
	- An additional primary - ≥ 1 close blood relative with breast cancer at any age - An unknown or limited family history - Diagnosed ≥ 60 years with: - ≥ 1 close blood relative with breast cancer diagnosed ≤ 50 years - ≥ 2 close blood relatives with breast cancer diagnosed at any age - ≥ 1 close blood relative with epithelial ovarian cancer - ≥ 2 close blood relatives with pancreatic cancer and/or prostate cancer (Gleason score ≥ 7) at any age - A close male blood relative with breast cancer - For an individual with ethnicity associated with higher mutation frequency (e.g. Ashkenazi Jewish), no additional family history may be required • Personal history of epithelial ovarian cancer	(mutation searching/screening) to try to identify a mutation in the appropriate gene (such as <i>BRCA1</i>, <i>BRCA2</i> or <i>TP53</i>) • Genetic testing for a person with no personal history of breast cancer but with an available affected relative - Offer genetic testing in specialist genetic clinics to a relative with a personal history of breast and/or ovarian cancer if that relative has a combined <i>BRCA1</i> and <i>BRCA2</i> mutation carrier probability of 10% or more • Genetic testing for a person with no personal history of breast cancer and/or ovarian cancer if that relative has a combined <i>BRCA1</i> and <i>BRCA2</i> mutation carrier probability of 10% or more • Genetic testing for a person with no personal history of breast cancer and no available affected relative to test - Offer genetic testing in specialist genetic clinics to a person with no personal history of breast or ovarian cancer if their combined <i>BRCA1</i> and <i>BRCA2</i> mutation carrier probability is 10% or more and an affected relative is unavailable for testing	• Three or more breast and/or ovarian cancer family cases - With at least one <50 years - Two breast cancer cases <40 years - Male breast cancer and ovarian cancer or early onset female breast cancer • Ashkenazi Jew with breast cancer <60 years • Young onset bilateral breast cancer; and breast and ovarian cancer in the same person • Presence of medullary carcinoma and triple negative phenotype (estrogen receptor, progesterone receptor and no over expression of <i>HER2neu</i>) in women younger than 50 years • Three or more breast and/or ovarian cancer family cases - With at least one <50 years - Two breast cancer cases <40 years	• Three or more breast family cases - With at least one <50 years - Two breast cancer cases <40 years - Male breast cancer and ovarian cancer or early onset female breast cancer • Ashkenazi Jew with breast cancer <60 years • Young onset bilateral breast cancer; and breast and ovarian cancer in the same person • In some countries, the criterion for testing is based on an a priori 10-20% probability of finding a mutation based on predictive models such as <i>BRCA</i>PRO, <i>BOADICEA</i> or Manchester Score, while less specific criteria include a potential benefit in the medical or surgical management of the individual or his/her relatives	• Testing for <i>BRCA</i> mutations should only be done when: - An individual has personal or family history that suggests an inherited cancer susceptibility - An individual has access to a health professional who is trained to provide genetic counselling and interpret test results - Test results will aid in decision-making • Initial testing of a family member with breast or ovarian cancer is the preferred strategy in most cases, but it is reasonable to test if no affected relative is available • Type of mutation analysis required depends on family history. Individuals from families with known mutations or from ethnic groups in which certain mutations are more common (e.g. Ashkenazi Jewish women) can be tested for these specific mutations		

GI: Gastrointestinal; MRI: Magnetic resonance imaging

Supplementary Table 1. International Guidelines Reviewed for Hereditary Breast and Ovarian Cancer Syndrome (Con't)

Guideline Title	Genetic/Familial High Risk Assessment: Breast and Ovarian	Familial Breast Cancer: Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer	Breast Cancer Treatment Guidelines	BRCA in Breast Cancer: ESMO Clinical Recommendations	Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility	Breast Cancer Follow-up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update	Breast Cancer Screening
	• Personal history of male breast cancer • Personal history of pancreatic cancer or prostate cancer (Gleason score ≥ 7) at any age with ≥ 2 close blood relatives with breast and/or ovarian and/or pancreatic cancer (Gleason score ≥ 7) at any age - For pancreatic cancer, if Ashkenazi Jewish ancestry, only one additional affected relative is needed • Family history only (significant limitations of interpreting test results for an unaffected individual should be discussed): - First- or second-degree blood relative meeting any of the above criteria - Third-degree blood relative with breast cancer and/or ovarian cancer with ≥ 2 close blood relatives with breast cancer (at least one with breast cancer ≤ 50 years) and/or ovarian cancer - Clinical judgement should be used to determine if the patient has reasonable	• Genetic testing for a person with breast or ovarian cancer - Offer genetic testing in specialist genetic clinics to a person with breast or ovarian cancer if their combined <i>BRCA1</i> and <i>BRCA2</i> mutation carrier probability is 10% or more	- male breast cancer and ovarian cancer or early onset female breast cancer • Ashkenazi Jew with breast cancer <60 years • Young onset bilateral breast cancer; and breast and ovarian cancer in the same person • Presence of medullary carcinoma and triple negative phenotype (estrogen receptor, progesterone receptor and no over expression of <i>HER2neu</i>) in women younger than 50 years. • Three or more breast and/or ovarian cancer family cases - With at least one <50 years - Two breast cancer cases <40 years - Male breast cancer and ovarian cancer or early onset female breast cancer • Ashkenazi Jew with breast cancer <60 years	• The addition of pathological features of breast cancer such as medullary carcinoma and triple negative phenotype (estrogen receptor, progesterone receptor and no overexpression of <i>HER2neu</i>) in women younger than 50 has been evaluated as a cost-effectiveness strategy for mutation detection. • 2% to 12% of high risk families may harbour a large genomic alteration	• Individuals without linkages to families or groups with known mutations receive more comprehensive testing. Testing should begin with a relative who has breast or ovarian cancer to determine if affected family members have a clinically significant mutation		

GI: Gastrointestinal; MRI: Magnetic resonance imaging

Supplementary Table 1. International Guidelines Reviewed for Hereditary Breast and Ovarian Cancer Syndrome (Con't)

Guideline Title	Genetic/Familial High Risk Assessment: Breast and Ovarian	Familial Breast Cancer: Classification and Care of People At Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer	Breast Cancer Treatment Guidelines	BRCA in Breast Cancer: ESMO Clinical Recommendations	Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility	Breast Cancer Follow-up and Management After Primary Treatment: ASCO Clinical Practice Guideline Update	Breast Cancer Screening
			• Young onset bilateral breast cancer; and breast and ovarian cancer in the same person • Presence of medullary carcinoma and triple negative phenotype (estrogen receptor; progesterone receptor and no over expression of <i>HER2neu</i>) in women younger than 50 years.				
Member Votes							Unanimous
GI: Gastrointestinal; MRI: Magnetic resonance imaging							

Supplementary Table 2. International Guidelines Reviewed for Lynch Syndrome

Guideline Title	Recommendations from the EGAPP Working Group: Genetic testing Strategies in Newly Diagnosed Individuals with Colorectal Cancer Aimed At Reducing Morbidity and Mortality from Lynch Syndrome in Relatives	Genetic/Familial High Risk Assessment: Colorectal	American College of Gastroenterology Guidelines for Colorectal Cancer Screening 2008	Revised Guidelines for the Clinical Management of Lynch Syndrome (HNPCC): Recommendations by a Group of European Experts	ACMG Technical Standards and Guidelines for Genetic Testing for Inherited Colorectal Cancer (Lynch Syndrome, Familial Adenomatous Polyposis, and MYH-associated Polyposis)
Date Released	January 2009	2014	2009	December 2012 (Revised January 2013)	September 2013
Guideline Developer	Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group - Independent Expert Panel	NCCN	American College of Gastroenterology - Medical Specialty Society	Vasen et al	Working Group of the American College of Medical Genetics and Genomics (ACMG) Laboratory Quality Assurance Committee
Reference	Genetics In Medicine. 2009 Jan;11(1):35-41	NCCN: National Comprehensive Cancer Network (US) Guidelines. Genetic/Familial High-Risk Assessment: Colorectal. 2015 Version 1. Page 10	Am J Gastroenterol 2009;104:739-750	Gut 62.6 (2013):812-823	Genetics In Medicine. 2014 Jan;16(1):101-116
Description of Method of Guideline Validation	Recommendations concerning laboratory and genetic testing in colorectal cancer from the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncologists (ASCO) were reviewed	The NCCN Guidelines are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to cancer treatment	This guideline has been reviewed and approved by the Practice Parameters Committee of the American College of Gastroenterology (ACG) and by the ACG Board of Trustees	External peer review. The guidelines were discussed during 2 workshops and all authors were involved in the discussion.	These technical standards and guidelines were approved by the ACMG Board of Directors on 20 May 2013.
MSI Testing	All CRC patients or CRC patients diagnosed at <70 years and also those ≥70 who meet the Bethesda guidelines	All CRC patients or CRC patients diagnosed at <70 years and also those ≥70 who meet the Bethesda guidelines	Patients who meet the Bethesda criteria should undergo microsatellite instability testing of their tumour or a family member's tumour and/or tumour immunohistochemical staining for mismatch repair proteins	All CRC (or individuals with CRC <70 years) and all EC (or individuals with EC <70 years) by immunohistochemistry of the 4 MMR proteins or MSI. These tests should be accompanied by methods that identify MLH1 promotor methylation.	MSI testing: 1. CRC diagnosed <50 2. Presence of synchronous or metachronous CRC or other hereditary non-polyposis CRC-related tumour, regardless of age 3. CRC in an individual <60 years of age exhibiting tumour-infiltrating lymphocytes 4. CRC at any age, plus CRC or hereditary non-polyposis CRC-related tumour diagnosed <50 years in at least one first-degree relative

CRC: Colorectal cancer; EC: Endometrial cancer; LS: Lynch syndrome; MSI: Microsatellite instability
 *4 of 5 members voted not to include universal screening in the current SCAN guidelines.

Supplementary Table 2. International Guidelines Reviewed for Lynch Syndrome (Con't)

Guideline Title	Recommendations from the EGAPP Working Group: Genetic Testing Strategies in Newly Diagnosed Individuals with Colorectal Cancer Aimed At Reducing Morbidity and Mortality from Lynch Syndrome in Relatives	Genetic/Familial High Risk Assessment: Colorectal	American College of Gastroenterology Guidelines for Colorectal Cancer Screening 2008	Revised Guidelines for the Clinical Management of Lynch Syndrome (HNPCC): Recommendations by a Group of European Experts	ACMG Technical Standards and Guidelines for Genetic Testing for Inherited Colorectal Cancer (Lynch Syndrome, Familial Adenomatous Polyposis, and MYH-associated Polyposis)
MSI Testing					5. CRC at any age, plus CRC or hereditary non-polyposis CRC-related tumour diagnosed <50 years in 2 or more first- or second-degree relatives -If an MSI unstable tumour harbours the BRAF gene <i>p.V600E</i> mutation, it is most likely sporadic and germline testing is not necessary
Member Votes					Unanimous
Genetic Testing	Offer genetic testing for LS to individuals with newly diagnosed CRC	[LS testing - clinical] Meets revised Bethesda guidelines or Amsterdam criteria Endometrial cancer <50 years or Known LS in family or Consider testing individuals with $\geq 5\%$ risk of LS on any mutation model (e.g. MMRpro, PREMM, MMRpredict)	Patients who test positive for MSI should undergo genetic testing If evaluation for HNPCC not indicated Patients with: Single first-degree relative with CRC or advanced adenoma diagnosed at age ≥ 60 years Single first-degree with CRC or advanced adenoma diagnosed at age <60 years or 2 first-degree relatives with CRC or advanced adenomas	Molecular screening of EC, sebaceous adenomas and carcinomas have been effective	CRC patient <50 including: - Colorectal cancer diagnosed in one or more first-degree relatives with a Lynch-related tumour, one who was diagnosed <50 years of age - Colorectal cancer diagnosed in 2 or more relatives of regardless of age
Member Votes*					Unanimous

CRC: Colorectal cancer; EC: Endometrial cancer; LS: Lynch syndrome; MSI: Microsatellite instability
 *4 of 5 members voted not to include universal screening in the current SCAN guidelines.

Supplementary Table 3. International Guidelines Reviewed for Familial Adenomatous Polyposis (Con't)

Guideline Title	Genetic/Familial High Risk Assessment: Colorectal	American College of Gastroenterology Guidelines for Colorectal Cancer Screening 2008	ACMG Technical Standards and Guidelines for Genetic Testing for Inherited Colorectal Cancer (Lynch Syndrome, Familial Adenomatous Polyposis, and MYH-associated Polyposis)
Date Released	2014	2009	September 2013
Guideline Developer	NCCN	American College of Gastroenterology - Medical Specialty Society	Working Group of the American College of Medical Genetics and Genomics (ACMG) Laboratory Quality Assurance Committee
Reference	NCCN: National Comprehensive Cancer Network (US) Guidelines. Genetic/Familial High-Risk Assessment: Colorectal. 2015 Version 1. Page 21	Am J Gastroenterol 2009; 104:739-750	Genetics In Medicine 2014 Jan;16(1):101-116
Description of Method of Guideline Validation	The NCCN Guidelines are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to cancer treatment	This guideline has been reviewed and approved by the Practice Parameters Committee of the American College of Gastroenterology (ACG) and by the ACG Board of Trustees	These technical standards and guidelines were approved by the ACMG Board of Directors on 20 May 2013
Genetic Testing	APC Testing Criteria: 1. Personal history of >10 adenomas 2. Personal history of desmoid tumour 3. Known deleterious mutation of APC in family	1. Patients with classic FAP (>100 adenomas) should be advised to pursue genetic counselling and genetic testing, if they have siblings or children who could potentially benefit from this testing 2. Patients with classic FAP, in whom genetic testing is negative, should undergo genetic testing for bi-allelic MYH mutations. Patients with 10 – 100 adenomas can be considered for genetic testing for attenuated FAP and if negative, MYH-associated polyposis	Indications for testing: 1. CRC diagnosed <40 years 2. CRC diagnosed in ≥1 first-degree relatives 3. Other adenomas and cancers FAP testing criteria: 1. Presence of 100 or more polyps 2. Autosomal dominant inheritance 3. Possible additional findings, such as congenital hypertrophy of retinal pigment epithelium, osteomas, supernumerary teeth, odontomas, desmoids, epidermoid cysts, duodenal and other small-bowel adenomas, gastric fundic gland polyps AFAP testing criteria: 1. Presence of <100 adenomas* 2. Frequent right-sided distribution of polyps 3. Adenomas and cancers at an age older than that for classic FAP and other gastrointestinal manifestations
Member Votes	Unanimous		

AFAP: Attenuated familial adenomatous polyposis; APC: Adenomatous polyposis coli; CRC: Colorectal cancer; FAP: Familial adenomatous polyposis

*Average 30 polyps. Individuals with 100 or more polyps occurring at older ages (35 – 40 years or older) may be found to have AFAP.