

Guidelines on Management of Prostate Cancer

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Introduction

Prostate cancer is the most common non-cutaneous cancer in American men and the third most common cancer in Singapore men.¹ The incidence has increased in the last decade, with an age-standardised rate of 24.1 per 100,000 noted during the period 2004 to 2008.^{2,3}

This guideline represents a multidisciplinary effort at harmonising the practical management of prostate cancer in our community. The guidelines were discussed, presented and debated, with contribution from practising urologic oncologists, medical oncologists and radiation oncologists. The guideline is structured using simple flowcharts with explanatory paragraphs to facilitate the description of the roles of different treatment modalities in different risk groups.

The evidence highlighted is based on well-conducted systemic review of subjects and randomised phase 3 trials. Where this is not available, other non-randomised trials are considered. For systemic therapy, phase 3 clinical trials with regimen modification based on local experience on tolerability of the regimen were included. Other available international guidelines were also reviewed. However, evidence grading used in these guidelines and listing of all available publications and trials were not repeated in our guidelines. This serves to shorten the text and emphasises the working algorithm for the practising clinician that is adapted for our local community. This is preferred over reworking the guidelines into a scholastic repeat of other available text-based guidelines.

Therapeutic options for localised prostate cancer are outlined based on a risk-stratified approach. The detailed explanation of established surgical (radical prostatectomy) and radiation therapies are included as these treatments have been available for more than 10 years. In some risk groups, there are several therapeutic strategies because there is no uniform consensus on a single optimal treatment and each

therapeutic option has different risk-benefit profiles. Hence the rationale, indications, risks and benefits are presented to assist the clinician in his discussion with his patient. The committee favours this open discussion strategy over explicit and potentially dogmatic emphasis on certain therapeutic strategies. Other novel therapies currently used in Singapore are also included and specifically highlighted for selective risk groups only. A detailed statement as to the investigative nature of these therapies is also included.

Published data on cost-benefit issues for prostate cancer in Singapore are currently lacking and cost discussions differ in different institutions with varying extent of government subsidies and service grants. Hence cost considerations were not included in this set of guidelines.

Definition of Terms

Early Prostate Cancer

This refers to clinically localised prostate cancer without evidence of regional lymph node and distant metastasis. Treatment is mainly with curative intent in patients with longer life expectancy and minimal comorbidity.

Locally Advanced Prostate Cancer

This refers to clinically locally advanced prostate cancer ($\geq T3b$) with or without lymph node invasion within the pelvis. Treatment requires aggressive local multimodality therapy with surgery and/or definitive radiation therapy, combined either with or without androgen deprivation therapy.

Metastatic Prostate Cancer

This refers to prostate cancer with lymph node invasion beyond the pelvis and/or bony or visceral spread. Treatment

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is mainly with palliative intent in patients with the aims of symptom relief, improving quality of life and prolongation of survival.

Castrate Resistant Prostate Cancer

This is previously known as hormone refractory prostate cancer or androgen independent prostate cancer. It refers to the state where prostate cancer no longer responds clinically and biochemically to androgen suppression monotherapy alone.

The definition used in our current guideline is 3 consecutive rises in serum PSA (prostate specific antigen) from a nadir PSA. There must be adequate androgen suppression as confirmed by a castrate level of serum testosterone.

Biochemical Failure

Biochemical failure after radical prostatectomy is commonly defined as 2 consecutive rises of PSA >0.2 ng/mL after definitive primary surgical therapy.⁴ Biochemical failure after radiation therapy (Phoenix criteria) is defined as a PSA level greater than nadir PSA + 2.0 ng/mL.⁵

Risk Stratification

Risk stratification is an important step in the management of early prostate cancer as it helps to identify aggressive prostate cancer suitable for more intensive treatment and allows options of active surveillance for less aggressive ones. Serum PSA done before prostate biopsy, digital rectal examination (DRE) findings, and prostate biopsy histology are common parameters used to prognosticate prostate cancer.

Many risk stratification tools are available for clinical use. Amongst them, the more clinically useful models include the nomogram from Memorial-Sloan Kettering Cancer Center, D'Amico risk classification and Partin's Table.⁶⁻¹⁰

D'Amico classification has found the widest clinical application because of its ease of use in clinical practice. With its established prognostic role, this classification has also been incorporated into the National Comprehensive Cancer Network (NCCN) guidelines. Although not every patient will fit into the classical D'Amico risk groups, most clinicians will be able to risk-stratify the majority of their patients.

Since prostate cancer has a continuum of prognostic risk, a comparison on the use of nomograms with individualised cancer-risk had been shown to be more accurate in predicting outcome.¹¹ This is easily obtained and calculated online by either the patient or clinician. However, nomograms alone do not give treatment recommendation. Clinicians still need to decide on their personal threshold when using

the nomogram results to discuss the optimal management options for each patient.

In setting the current Singapore guidelines, we adopted the D'Amico risk stratification strategy because its easier application also directs the clinicians towards risk-specific treatment options. This is especially useful for localised prostate cancer, where clinicians can determine the prognostic risks of their patients and proceed to decide on the appropriate investigations and treatment.

Diagnosis and Staging

Diagnosis

The most common confirmatory diagnostic test is histological diagnosis via transrectal ultrasound guided needle biopsy of the prostate. Other less common methods of histological diagnoses are from transurethral resection of prostate, biopsies from metastatic sites or incidentally found during radical cystoprostatectomy surgery done for advanced bladder cancer.

Staging and Grading

Staging is divided into clinical staging and pathological staging. Clinical assessments include digital rectal examination and radiologic imaging for loco-regional or metastatic disease. Staging is performed using the AJCC TNM staging system (Table 1). Histological grading is performed using the Gleason grading system. The Gleason score is the sum of the primary and secondary Gleason grades reported in biopsy and radical prostatectomy specimens. If tertiary grade is found in the pathological specimen after radical prostatectomy, it is commented upon, and not included in final Gleason score.¹²

The outline of the staging workup and risk stratification is shown in Figure 1. For patients with low-risk prostate cancer, radiological staging is optional because of the low yield.

In intermediate- and high-risk prostate cancer, radiological staging is recommended to exclude loco-regional spread and distant metastasis. Loco-regional spread is commonly assessed using cross-sectional imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) pelvic scans. MRI prostate offers better resolution to determine locally advanced extra-prostatic extension and seminal vesicle invasion, including detection of local cancer recurrence after radical prostatectomy.¹³⁻¹⁶ Distant metastasis is usually screened using Technetium^{99m} bone scans.

In locally advanced and metastatic prostate cancer, bone scan and cross-sectional imaging such as CT or MRI abdomino-pelvic scans are recommended for assessment of metastatic bony or visceral lesions.

Additional imaging, including CT-PET and functional

Table 1. TNM Staging (adapted from AJCC 7th edition, 2010)

Primary tumour	
Clinical (cT)	Pathologic (pT)
TX Primary tumor cannot be assessed	pT2 Organ confined
T0 No evidence of primary tumor	pT2a Unilateral, one-half of one side or less
T1 Clinically inapparent tumor neither palpable nor visible by imaging	pT2b Unilateral, involving more than one-half of side but not both sides
T1a Tumor incidental histologic finding in 5% or less of tissue resected	pT2c Bilateral disease
T1b Tumor incidental histologic finding in more than 5% of tissue resected	pT3 Extraprostatic extension
T1c Tumor identified by needle biopsy (for example, because of elevated PSA)	pT3a Extraprostatic extension or microscopic invasion of bladder neck
T2 Tumor confined within prostate	pT3b Seminal vesicle invasion
T2a Tumor involves one-half of one lobe or less	pT4 Invasion of rectum, levator muscles, and/or pelvic wall
T2b Tumor involves more than one-half of one lobe but not both lobes	
T2c Tumor involves both lobes	
T3 Tumor extends through the prostate capsule	
T3a Extracapsular extension (unilateral or bilateral)	
T3b Tumor invades seminal vesicle(s)	
T4 Tumor is fixed or invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall	

Regional Lymph Nodes (N)	
Clinical	Pathologic
NX Regional lymph nodes were not assessed	pNX Regional nodes not sampled
N0 No regional lymph node metastasis	pN0 No positive regional nodes
N1 Metastasis in regional lymph node(s)	pN1 Metastases in regional node(s)

Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

Gleason grading system
 Gleason ≤6: Well differentiated
 Gleason 7: Moderately differentiated
 Gleason 8 to 10: Poorly differentiated

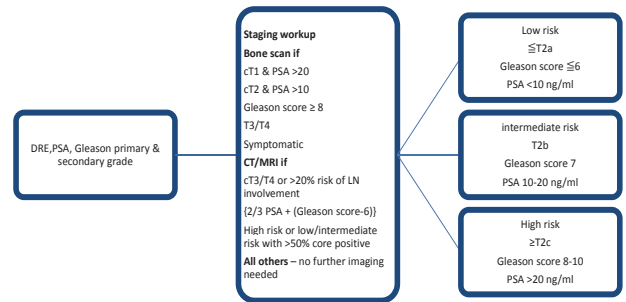
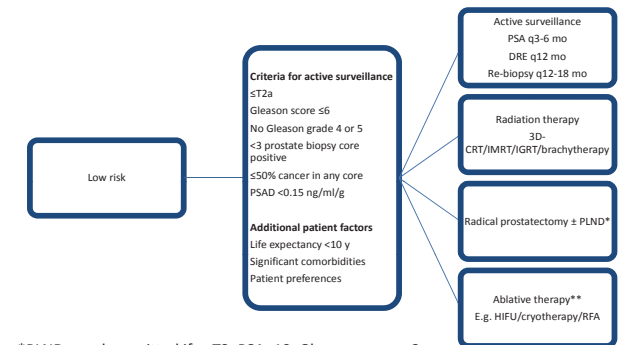


Fig. 1. Staging workup and risk stratification.



*PLND may be omitted if <cT2, PSA<10, Gleason score ≤6
 **currently offered as an option in selected patients

Fig. 2. Localised prostate cancer—low risk.

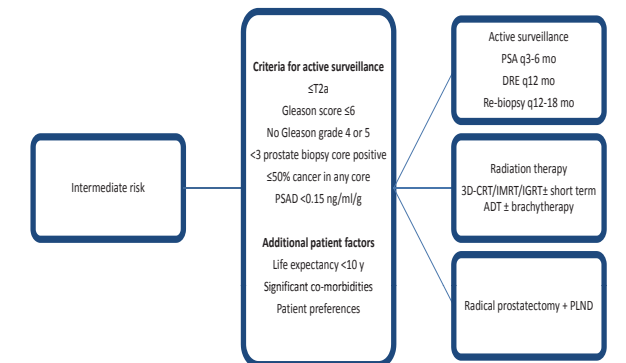


Fig. 3. Localised prostate cancer—intermediate risk.

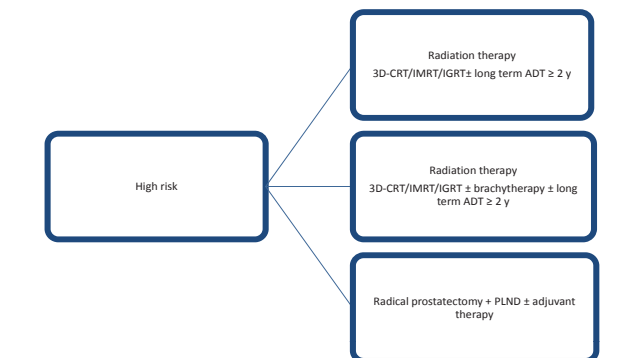


Fig. 4. Localised prostate cancer—high risk.

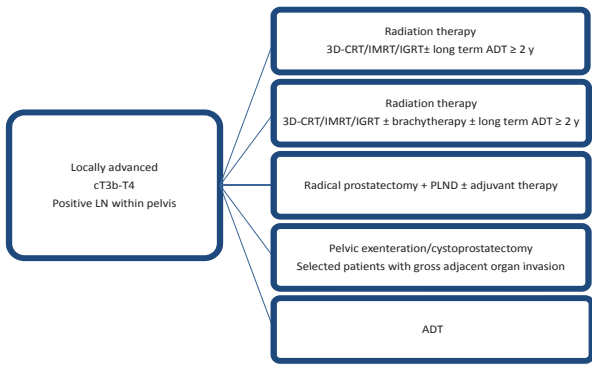
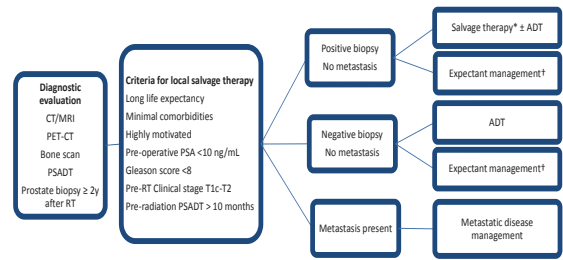
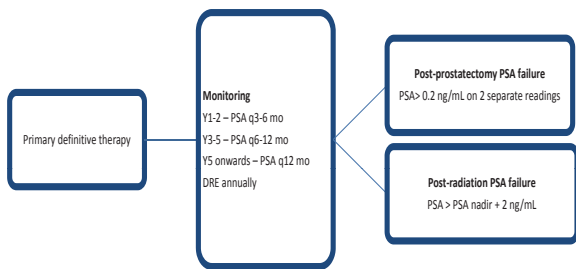


Fig. 5. Locally advanced prostate cancer.



*Salvage therapy may include salvage RP, cryotherapy, HIFU, brachytherapy.
 †Expectant management may be considered in older patients with short life expectancy, multiple comorbidities, long PSADT, patients willing to have close monitoring.

Fig. 9. Post-radiation recurrence.



AUA guidelines: Cookson et al. J Urol 2007
 Phoenix criteria: Roach et al. Int J Radiat Oncol Biol Phys 2006

Fig. 6. Localised prostate cancer—monitoring.

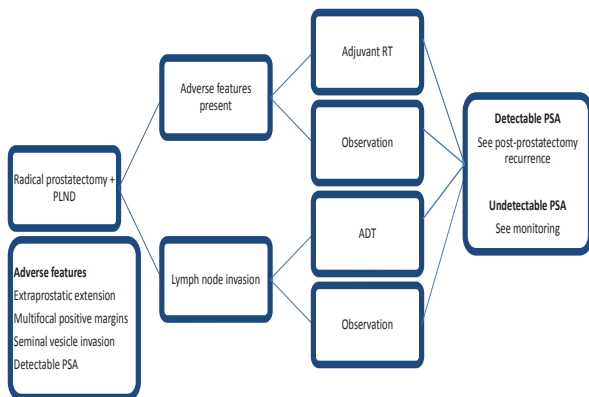
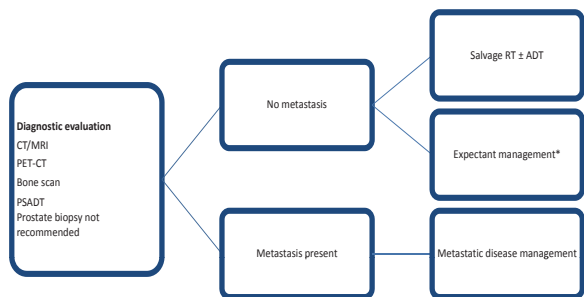


Fig. 7. Radical prostatectomy—adjuvant therapy.



*Expectant management may be considered in older patients with short life expectancy, multiple comorbidities, long PSADT, patients willing to have close monitoring.

Fig. 8. Post-prostatectomy recurrence.

MRI scans, may be considered as adjunctive staging tests in selected patients.

Treatment

Figures 2 to 9 outlines the management algorithms for clinically localised and locally advanced prostate cancer.

Active Surveillance with Selective Delayed Intervention

Active surveillance is a strategy of close monitoring for carefully selected patients with localised prostate cancer who are most likely to be safely watched, and for deferred treatment when necessary. It represents an alternative to initial treatment for men with low risk, clinically localised prostate cancer. The intent of active surveillance is not to have treatment unless disease progresses or when the patient chooses treatment, in which the treatment should be one with curative intent.

Rationale

The rationale for this approach stems from the growing concern of the over-detection and over-treatment of prostate cancer.^{17,18} In many countries, the mortality rates for prostate cancer has remained relatively stable or shown only slight decreases (USA, some parts of Europe) even though the rate of diagnosis have sharply increased over the last few decades, which suggests over diagnosis.^{19,20} Worldwide autopsy data have shown the presence of prostate cancer in about one-third of men (up to 70% in US men) between 60 and 70 years of age and about 31% to 58% in men between 70 and 80 years of age (up to 83% in US men) (Haas et al).¹⁹ In spite of this, the number of men who actually die from prostate cancer remains low.²¹

Inclusion Criteria

There is currently no uniform consensus on inclusion criteria, but typically may include some combination of

the factors listed below:²²

- PSA <10 ng/mL
- Clinical stage \leq T2a
- Gleason score \leq 6
- No Gleason grade 4 or 5
- Positive cores <33% of total cores
- Maximum core involvement <50%
- PSAD <0.15
- Good patient compliance

The typical patient who may benefit from active surveillance is usually one who fits the D'Amico criteria for low-risk disease and has low volume of disease found in his prostate biopsy (e.g. fewer than 3 positive biopsy cores or less than 33% of total cores, with no core having >50% involvement, in an adequately sampled prostate biopsy, as described by Epstein²³). However, older men (e.g. >70 years), particularly with comorbidity, who have a PSA greater than 10 ng/mL or minor elements of a Gleason 4 pattern may still be appropriate active surveillance candidates.²⁴ In addition, patient age, family history of prostate cancer, and medical comorbidities should be taken into account when counseling and selecting patients for active surveillance.

Active Surveillance Protocol

While there is no uniform consensus on monitoring parameters, most active surveillance protocols have similar approaches. They include (i) selecting appropriate patients with low-risk localised prostate cancer, (ii) reassuring and educating the patient, (iii) close monitoring with periodic PSA measurements, physical examination including digital rectal examination and repeat prostate biopsies, and (iv) treat with curative intent if the prostate cancer develop more aggressive features but are still amenable to definitive therapy.

A common protocol is to have 3 to 6 monthly PSA testing and physical examination, and a repeat prostate biopsy within the first 12 to 18 months. If no adverse features are seen after 2 years, the interval between follow-up consultations and repeat biopsies may be increased.

Some common triggers for intervention may include²²:

- Increase in Gleason score \geq 7
- Any Gleason grade 4 or 5
- >2 Cores involved on 1 side on repeat biopsy
- >50% core involvement on repeat biopsy
- Abnormal or change in DRE
- Patient preference

Risks/benefits

The main benefit of active surveillance is in minimising the risk of overtreatment of insignificant cancer with its attendant treatment side effects. However, it does have potential limitations such as the patient being chronically anxious over an 'untreated' cancer, having to undergo multiple periodic examinations and tests, and the risk of under-treating a significant but under-sampled cancer.²⁵ The results of several observational cohorts of active surveillance have been promising, but follow-up has been relatively short. Overall, approximately up to one-third of patients will be reclassified as higher risk for progression or show evidence of progression, and are treated.^{22,24} In the intermediate timeframe (5 to 15 years), prostate cancer mortality is low.²⁴

Watchful Waiting

Watchful waiting generally refers to prostate cancer patients who are observed and treated only when symptoms or metastases occurs. This is an option for minimally symptomatic or asymptomatic men with limited life expectancy (e.g. age >75 years or those with extensive comorbidity).

Radical Prostatectomy

Surgery in the form of radical prostatectomy is an established treatment modality in early prostate cancer.

Rationale

Radical prostatectomy is the primary treatment modality with complete surgical extirpation of the cancerous prostate and adjacent pelvic lymph nodes. The technical steps are well established and the oncological and functional outcomes have improved over the years.²⁶⁻²⁹ With the introduction of laparoscopic and robot-assisted approaches, the short-term perioperative parameters have improved with comparable medium term oncological outcomes in experienced high volume centres.³⁰⁻³²

Criteria

The patient most likely to benefit from surgery would have a clinically organ-confined disease, a relatively long life expectancy, no significant surgical risk factors and a preference to undergo surgery. Surgery in men with locally advanced prostate cancer may be considered as part of a multimodality treatment protocol.

Technique

Radical prostatectomy may be performed using an open,

laparoscopic or robotic approach. PLND is recommended for men with intermediate and high-risk early prostate cancer undergoing surgery. In men with low-risk prostate cancer, the risk of lymph node metastasis is less than 5% and PLND may be omitted.³³ The role and benefit of extended PLND is not optimally defined and there is no consensus on routine EPLND.

Risks/benefits

Short-term benefits in the form of smaller wounds, less blood loss and less analgesic use are common in the minimal access approaches. Long-term cancer control is similar in few studies with long-term follow-up. The main complications include post-prostatectomy urinary incontinence and impotence. These functional outcomes depend on the surgical approach as well as preoperative functional status and tumour profile.

Ablative Therapy

Ablative therapy is used here as a general term for minimally invasive treatment of prostate cancers involving the use of different energy sources for whole gland or focal ablation.

Rationale

Common energy ablative therapies include cryotherapy and high intensity focused ultrasound (HIFU) ablation, which have been offered as minimally invasive primary therapy options for localised prostate cancer.³⁴ These treatments offer the potential for a middle ground between active surveillance and radical therapy.

Technique

Cryotherapy has been in use as an alternative primary therapy to completely ablate the prostate. A number of series show encouraging efficacy in terms of biochemical control (49% to 90%), over a range of short term to 12 years' follow-up duration.^{34,35} It has also been the most utilised for focal therapy of prostate cancer, in the form of hemiablation and targeted focal therapy in several trials. While the initial results from these trials appear promising in terms of oncologic control and reduced morbidity, further investigation of this technique with prospective randomised trials are still required.³⁶

HIFU has also been used widely in Europe for the whole-gland treatment of prostate cancer.³⁷ The reported oncologic efficacy in terms of biochemical control ranges from 56% to >90%, with short to intermediate-term follow-up.³⁴ It uses hyperthermic energy focused on a specific point in the prostate, thus providing the rationale for its use for

focal therapy. Limited data exist for such use, but newer HIFU devices and real-time imaging techniques are being developed which can enhance its use for focal prostate cancer ablation.

Focal therapy for localised prostate cancer is a controversial new area of research. It involves minimally invasive organ-sparing approaches in an attempt to achieve effective cancer control whilst reducing treatment burden and morbidity. Several techniques that have the potential for focal ablation of prostate cancer include cryotherapy, HIFU, vascular-targeted photodynamic therapy, interstitial laser thermotherapy and stereotactic radio-surgery.³⁶

Criteria

Ablative therapy may be considered an option in the treatment of selected patients with low risk localised prostate cancer. In other risk categories, it is not generally viewed as a standard option and should be considered investigational.

Risk/benefits

As the long-term outcomes of whole gland energy ablative therapies for localised prostate cancer are not as established as radical prostatectomy and radiation therapy, the recommendation is for treatment be offered to those who desire such treatment having understood its limitations compared to other standard therapies or under a research protocol until longer term data are available. The main complications of concern in whole gland ablative therapies may include urinary incontinence, impotence, bladder neck contracture and recto-urethral fistulae. Techniques for focal therapy for prostate cancer are constantly evolving and still need further evaluation in clinical trials to determine its true risk-benefit ratio, and they should therefore be considered investigational.

Radiation

Radiotherapy (RT) is an effective alternative for patients who do not wish to undergo or are unsuitable for surgery. Modern RT and surgical series show similar progression free survival. Radiotherapy is commonly delivered via external beam radiotherapy (EBRT), treating the prostate alone or in the case of patients with high-risk disease, the regional lymph nodes as well.³⁸ Other modalities include brachytherapy where radioactive sources are implanted permanently in the prostate (low dose rate brachytherapy, LDR) or as a temporary implant (high dose rate, HDR). Both LDR and increasingly HDR can be used as an alternative to EBRT as monotherapy in low risk patients or as a boost in intermediate risk patients (LDR or HDR) and high-risk patients (HDR only) in order to safely allow for dose escalation.

Adjuvant radiotherapy should be considered post prostatectomy in patients at high risk of local recurrence i.e. detectable PSA postoperation, margins positive, extracapsular extension or seminal vesicle involvement.^{39,40} In patients with high-risk features but whose PSA is undetectable postoperative, it is unknown whether close monitoring and salvage radiotherapy at the time of failure is better than upfront adjuvant radiotherapy. However patients should still be referred for discussion of adjuvant radiotherapy.

Hormonal therapy (neoadjuvant and concurrent with or without adjuvant) combined RT has been shown to delay recurrence and lead to improve survival in intermediate (4 to 6 months of hormonal therapy) and high-risk groups (2 to 3 years of hormonal therapy).^{41,42}

RT avoids many surgical complications such as bleeding and infection. Bowel side effects and sexual side effects are the main long-term complication of EBRT, while urinary side effects e.g. urinary stenosis are the main concern with brachytherapy.⁴³ In order to reduce the risk of radiation toxicity, image guidance with cone beam CT scans and/or fiducial markers are recommended especially when doses above 74Gy are used.

External Beam Radiation

EBRT should minimally be delivered using at least 3-dimensional planning techniques in order to reduce the risk of radiation toxicity and allow for higher dose of RT to be given. Intensity-modulated radiotherapy (IMRT), which uses second generation of 3D planning, is considered standard of care.

Recent results of numerous randomised controlled trials have demonstrated that dose escalation (>70Gy) is associated with improved biochemical outcomes.^{38,44} If doses above 75Gy are being considered, use of IMRT with daily image guidance (IGRT) is mandatory.

Dose recommendations are (i) 75.6 to 79.2Gy in 1.8Gy/fractions for patients with low-risk disease, and (ii) 75.6 to 81.0Gy for patients with intermediate and high-risk disease.

The planning target volume (PTV) is the whole prostate with 1 cm margin all around except posterior where the margin can be reduced to between 0.5 cm and 1 cm. If IGRT is being used, the PTV margin can be reduced to between 0.5 cm and 1 cm. Pelvic lymph nodes should be treated in patients with high-risk cancers. Patients with intermediate risk cancers should be considered for pelvic node irradiation if the risk of lymph node metastasis is greater than 15% while patients with low risk disease should not have their pelvic nodes treated. Non-enlarged pelvic nodes should receive 45 to 48.6Gy. Nodes enlarged by CT criteria (>1 cm in size) should receive 54 to 79.2Gy, depending on proximity to small bowel, rectum and bladder.

Adjuvant therapy should be considered for patients after prostatectomy with high-risk features such as positive margins, extracapsular extension, seminal vesicle involvement or persistently elevated PSA readings postoperation. Evidence from 3 randomised trials has demonstrated that upfront adjuvant therapy improves local control rates, risk of metastasis and in one trial, overall survival, when compared to observation. Whether upfront adjuvant therapy is superior to salvage radiotherapy after close surveillance at the first instance of PSA failure is unknown. Patients undergoing adjuvant therapy should start within 4 months of surgery, allowing time for improvement of urinary symptoms and before PSA >1.5 ng/mL. Dose recommendation is 64Gy in 2 Gy fractions. IMRT should also be used to reduce the risk of radiation toxicity. The treatment volume is the surgical bed with a 0.5 cm to 1 cm margin. For patients undergoing salvage RT, the dose recommendation is 66.6 to 70.2Gy to the tumour bed with a boost to 79.2Gy to any sites of gross disease recurrence. If a dose of more than 75Gy is being considered, the use of daily image guidance is mandatory.

Brachytherapy

Brachytherapy involves the placement of the radioactive sources within the prostate tissue. Presently, 2 forms of brachytherapy exist, low dose rate (LDR) brachytherapy in which radioactive sources e.g. Iodine 125 are permanently implanted within the patients and high dose rate (HDR) brachytherapy where an Iridium 192 sources is temporarily placed within the prostate for 2 to 4 treatments.

The advantages of brachytherapy over EBRT are that there is less radiation exposure to the bladder and rectum and hence a low risk of radiation toxicity due to the short range of irradiation emitted from these sources, lower rates of impotency and a savings in time as the brachytherapy can be completed in 1 to 3 days as compared to the 8 weeks of EBRT.⁴⁵ Disadvantages of brachytherapy are the need for general or spinal anaesthesia, radiation protection issues of patients and staff with the use of LDR and higher rates of irritative voiding symptoms. Patients with symptoms of bladder outlet obstruction and previous TURP are not suitable for brachytherapy.

Prostate brachytherapy has been used as monotherapy for patients with low-risk cancer.⁴⁶ The bulk of the evidence has been with the use of LDR brachytherapy although recently more studies have been published demonstrating the effectiveness of HDR monotherapy as well. Recommended dose for LDR monotherapy are 145Gy for Iodine 125 and 125 Gy for Palladium 103. Post implant dosimetry is mandatory. For HDR monotherapy the recommended doses are 31.5 to 38Gy in 3 to 4 fractions respectively.^{47,48}

For patients with intermediate disease, there is emerging

evidence that prostate monotherapy, either LDR or HDR, can be used. However at present, the recommendation is that for intermediate- and high-risk disease, prostate HDR brachytherapy as a boost (19 to 21Gy in 2 fractions) can be combined with EBRT (45Gy) in order to achieved dose escalation whilst minimising radiation side effects. In published data, this approach appears to be more effective than even ultra high dose EBRT (81Gy).⁴⁹

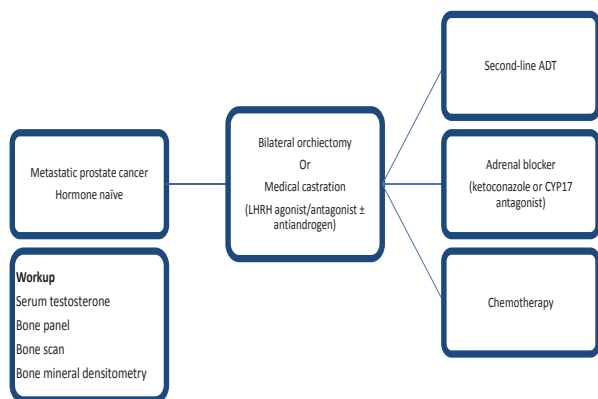


Fig. 10. Metastatic hormone naïve prostate cancer.

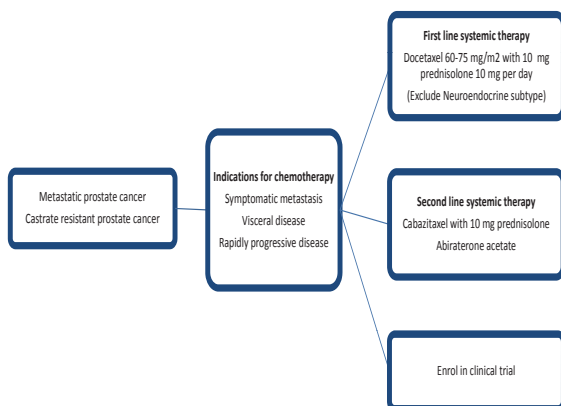


Fig. 11. Metastatic castrate-resistant prostate cancer.

Metastatic Prostate Cancer

The management algorithms for metastatic hormone naïve and castrate-resistant prostate cancer are outlined in Figures 10 and 11.

Androgen Deprivation Therapy

First Line

Surgical orchiectomy remains the standard of care. The alternative is medical castration using luteinizing hormone

releasing hormone agonist (LHRH) as monotherapy. The addition of an anti-androgen to either surgical or medical castration as combined androgen blockade (CAB) remains controversial in terms of additional disease control benefit versus additional cost and potential side effects. Pros and cons of CAB should be discussed thoroughly with the patient.

Second Line ADT and Beyond

In patients who have disease progression after first line hormonal therapy, further androgen deprivation may be offered especially in patients with low volume disease without impending organ crisis such as high-risk of fracture or paraparesis or acutely symptomatic. Second line hormonal therapy may include adding an anti-androgen agent to LHRH agonist monotherapy or withdrawal of anti-androgen therapy if patient is already on CAB. Ketoconazole is an acceptable alternative to anti-androgen.

Although abiraterone acetate is a type of hormonal therapy, its role will be discussed as a treatment option under the section of second line chemotherapy as it is approved as treatment after failed docetaxel chemotherapy.

Androgen deprivation therapy should continue even if the patient is castrate resistant. This is supported by retrospective data that showed a survival benefit of 2 to 6 months when androgen deprivation therapy is continued.⁵⁰

Chemotherapy

First Line

In patients who are castrate resistant, the option of chemotherapy should be discussed and offered as it has been shown to improve overall survival and quality of life compared to best supportive care. The standard first line regimen is docetaxel-prednisolone chemotherapy.^{51,52} Although the recommended dose of docetaxel in most western centres is 75 mg/m² per 3 weeks, we recommend starting at a lower dose of 60 mg/m² per week and increasing to 75 mg/m² if the lower dose was well tolerated. The recommended duration of treatment may be as long as 10 cycles so long as the patient shows continued disease control and tolerable side effects. The use of growth factors to decrease the risk of neutropenia is at the sole discretion of the treating physician.

Second Line

There are 2 clinical indications for second line chemotherapy:

1. Disease progression after completion of initial docetaxel treatment. Docetaxel treatment was administered as first line chemotherapy without initial evidence of progression at time of cessation.

In this situation, a repeat challenge with docetaxel chemotherapy is an acceptable option.

2. Disease progression while on docetaxel chemotherapy. In this situation, second line treatment should be considered, including cabazitaxel in combination with prednisolone or hormonal therapy using abiraterone acetate.^{53,54} There has not been any head to head comparison between these 2 options but in the clinical trial of cabazitaxel, the control arm was mitoxantrone-prednisolone which is a chemotherapy known to be relatively effective in improved pain control in more symptomatic patients compared to prednisolone alone.⁵³ Abiraterone acetate on the other hand, was compared to placebo-prednisolone. As both trials have proven improved median survival, they may be offered as an option after failing docetaxel. The pro and cons of either treatment should be discussed with the patient.

Third Line and Beyond

There is no recognised third line of treatment although reasonable options may include cabazitaxel, mitoxantrone or abiraterone acetate-prednisolone therapies. Patients should be considered for enrollment in clinical trials in this setting, failing which best supportive care would be reasonable.

Other Treatment Modalities in CRPC

Although immunotherapy such as Sipuleucel-T (Provenge) has been proven to be an effective treatment for patients with castrate resistant prostate cancer with minimal symptoms, it is currently not recommended in local setting due to lack of local experience and results.⁵⁵ In addition, the prohibitive cost of such treatment and the complex treatment delivery does not make this option feasible at present.

Conclusion

The last decade has seen a paradigm shift in the management of early and advanced prostate cancer. The improvements in treatment morbidity and functional outcomes have increased the acceptance of treatment for this disease but there remains much work to be done in advancing biomarker research for prognostication and improving the cost-benefit ratio of available treatment modalities.

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