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"The wise man doesn't give the right answers, he poses the right questions."

Claude Levi-Strauss (1908 – 2009)
French anthropologist

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Editorial

World Cancer Day

Min Han Tan, [1,2,3] *MBBS, FRCP, PhD*

World Cancer Day is a global event in the fight against cancer. Falling annually on 4 February, it is an initiative by the Union for International Cancer Control to raise international awareness and education, so as to save millions of preventable deaths.

To pen this editorial, I reread my 2012 editorial marking the same event.[1] In writing this follow-up editorial 6 years later, more perspectives are available now to me as a physician, a researcher and perhaps most importantly, as a caregiver. Additional experience in both the public and private sectors—together with deeper industry involvement—have also yielded additional dimensions.

Globally, cancer remains one of the major scourges of humanity, and is one of the top causes of deaths. Major disparities in access to effective preventive and treatment measures for cancer continue, driven primarily by socioeconomic differences between countries. New therapies and diagnostics continue to emerge from the pipeline of industry, mainly deployed in the developed world.

Many themes of cancer control remain as true in 2018 as they were when first written about in 2012. Wider availability of vaccines for cancer prevention, the disparities of cancer care between developed and developing countries, tobacco control as a cornerstone for cancer prevention, remain key global issues. Cancer is still a deeply feared disease that we can prevent and cure sometimes, relieve often and to comfort always. At the same time, real changes certainly have occurred globally and in Singapore, altering the landscape for patients and physicians. While the themes of 2012 remain as important as ever, this editorial will focus on how key immediate past events and upcoming trends may affect cancer prevention and access to care in the current landscape.

Perhaps the most important milestone in recent years for the cancer community here was the implementation of Medishield Life in 2015. Medishield Life is a universal national healthcare insurance scheme for Singapore citizens and permanent residents, with enhanced coverage benefits. For the majority of cancer patients, the significant increases in coverage for outpatient treatments have led to vastly greater accessibility of costly outpatient treatments including targeted therapies and enhanced radiation techniques. The notorious "financial toxicity" of cancer care has truly been substantially alleviated by the introduction of Medishield Life. At the same time, a new generation of dramatically more expensive anticancer therapies are now entering clinical use.

The 2015 decision by the Ministry of Health to set up its Agency of Care Effectiveness (ACE) to focus on health technology assessment (HTA) serves as a signal to the clinical and pharmaceutical community that prudence is still needed especially for treatments of more marginal clinical value. National healthcare expenditure is projected to continue a relentless rise over the next few decades, together with the silvering of Singapore's population. To fund this, the inevitable consequence is that government revenues need to be increased through measures such as taxes.[2]

Clinical frameworks such as the Singapore Cancer Network (SCAN) guidelines developed by almost all public and private oncologists in a common effort (declaration: including myself) allow a helpful reference for clinical standard for patient management across a wide range of cancer types.[3] The SCAN guidelines covering mainly systemic treatment of cancer (but also extending to cancer genetics)[4] are a positive sign that the medical community here can efficiently and independently establish practice approaches, providing guidance to public funding direction. Future funding is likely to require ever more complex cost-effectiveness HTA analysis. Preserving meaningful access to a wider range of expensive cancer therapies and vaccines through collaboration between payers and industry certainly remains a key challenge.

While patient access is an important question, cancer prevention is a top priority for public health professionals and policymakers. Eliminating cancer begins from reducing exposure to the most important preventable causes including tobacco control, and vaccination to cancer-causing viruses. Tobacco control remains the most important element

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of cancer prevention, as smoking is the single most important preventable cause of cancer. However, one of the most interesting public health questions raised in recent years has centred on the role of electronic cigarettes ('e-cigarettes') in smoking cessation. An expert committee of the United States' National Academies of Sciences, Engineering, and Medicine recently concluded that there is substantial evidence that these e-cigarettes—while not harmless—do considerably reduce carcinogen intake relative to conventional smoking.[5] At the same time, the same committee concluded there is also good evidence that e-cigarettes may act as a gateway to traditional cigarettes among youth.[5] A total ban on e-cigarettes in Singapore has taken effect on 1 February 2018, making Singapore's rules the strictest in the region.[6] Together with the increasing minimum age of smoking from 18 to 21 over the next few years, antitobacco legislation in Singapore remains among the toughest from a global perspective.

New attention has also fallen on obesity as a preventable cause of cancer in the last few years.[7] It is estimated that up to 8% of cancers may be attributed to excess body weight.[8] This is likely to increase as a key contributor to cancer in Singapore. Like all lifestyle-related causes of cancer, this is likely to prove difficult to manage. In this effort, it is essential to recognise that everyone can play a part. The war against cancer is not just fought in hospitals and laboratories, but is also affected by the lifestyle decisions we make on a daily basis. Whether the interventionist approach commonly seen in Singapore policymaking will be able to limit the apparently inexorable rise of obesity remains to be seen.

In addition to these more widely known factors predisposing to cancer, an "Angelina Jolie effect" in 2013 single-handed catalysed a global interest in genetic testing for cancer risk.[9] Ms Jolie, a prominent Hollywood movie actor, announced her decision for risk-reducing mastectomy and ovarian surgery following a positive test for a BReast CAncer (BRCA)-mutated gene. A worldwide tsunami of publicity ensued. Here in Singapore, genetic counselling visits were reported to have increased by 3 times between 2011 and 2014 at the National Cancer Centre.[10] With increasing awareness and availability of genetic testing among the medical community, understanding genetic risks will play an increasingly prominent role in cancer prevention.

Beyond such key cancer prevention approaches, technological advances continue to provide hope to the community. While there are certainly improvements in cancer diagnosis and treatment, cures have remained elusive, despite no shortage of pronouncements in the media. In terms of hard numbers on mortality and morbidity, progress remains painfully slow. We should, however, celebrate even the small but hard-won advances. These tell us that we are better off today than in the past. We see these advances in the faces of the lung cancer patient who can now manage her disease with pills instead of weekly injections, the metastatic breast cancer patient who remains alive after 10 years, and patients who are no longer affected by chemotherapy-induced nausea and vomiting through side-effect management.

One day, the former things shall pass away, and cancer shall be no more. Each World Cancer Day is an opportunity to remember that we all have a part to play in that effort, no matter who we are or what we do.

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Editorial

New Approaches to the Treatment of Tuberculosis

Nicholas I Paton,[1,2] *MD, FRCP*

Tuberculosis (TB) remains one of the world's most important infectious diseases, with an estimated 10 million cases and 1.7 million deaths per year—the leading cause of death globally from a single infectious agent.[1] It is an especially important disease in Asia, accounting for almost 60% of the global cases. Multidrug-resistant TB (MDR-TB) —characterised by resistance to rifampicin and isoniazid, 2 of the key firstline drugs—affects around 500,000 people annually. Extensively drug-resistant TB (XDR-TB)—where resistance to 2 of the key secondline drugs is also present—is now emerging as an important threat to TB control as the extensive resistance profile makes it almost impossible to construct an effective treatment regimen. TB is the leading cause of death related to antimicrobial resistance. Although incidence rates have been declining globally, the overall rate of decrease is just 2% per year and in Singapore, rates have fluctuated around 40 per 100,000 for the last decade, with no suggestion of a declining trend.

In response to this recalcitrant problem, the World Health Organization (WHO) launched a new strategy in 2015. The End TB Strategy aims to accelerate the rate of decline of new cases to 10% per year by 2025, and to 17% per year thereafter with the ultimate goal of ending the TB epidemic by 2035.[2] Whilst these targets are clearly aspirational, and rely heavily on "intensified research and innovation" which is only just beginning to bear fruit, there are reasons to hope that there will be significant advances made through ongoing clinical research that could possibly be game-changing.

Improving firstline treatment for drug-sensitive disease is a high priority and this is one area in which there have been significant research-led advances in recent years. Standard "short-course" chemotherapy was established in the 1980s and has changed little since then. It comprises 6 months' treatment with a combination of drugs, each of which may cause side-effects. Adherence to long courses of treatment is challenging for many patients and poor adherence promotes the development of drug resistance. Identifying curative firstline treatment regimens that are shorter in duration—preferably 2 months or less—is an important objective for decreasing the failure rate of treatment in a programme setting, and for reducing the pressure for development of drug-resistant TB.

One approach to shortening treatment is to find new drugs that have improved activity against the persistent forms of TB bacilli—these bacilli are hard to eradicate with standard treatment and drive the need for the current protracted courses of treatment. As with antibiotic research and development in general, pharmaceutical industry investment is constrained by the perceived lack of financial return that would follow the successful development of a new TB drug. Nonetheless, after a hiatus of 40 years, 2 new drugs have been developed —bedaquiline[3] and delamanid[4]—that have recently received (accelerated) licences for the treatment of TB. Bedaquiline in particular appears to have potent activity against persistent bacilli, and also has the potentially attractive property of a very long half-life. The drug was evaluated in trials in MDR-TB but studies are now underway examining its role in combinations for the treatment of drug-sensitive TB.

Aside from the expensive quest to develop new drugs specific for TB, there has been considerable interest in repurposing drugs, i.e. finding drugs (usually antibiotics) that have been shown to be effective for other diseases (usually infections) that fortuitously have activity against TB. One class of drugs with particular promise is the beta-lactams. Penicillins, the first drugs to be identified in this class, are known to be inactive against TB because they are inactivated by penicillinase (beta-lactamase) produced by TB bacteria. However, when co-administered with clavulanic acid (a beta-lactamase inhibitor), penicillins may retain some anti-TB activity. Several studies evaluating carbapenems in a mouse model of TB infection have found evidence of efficacy, with improved survival and decreased bacterial load.[5,6] A recent 14-day trial showed that meropenem—an injectable carbapenem widely used in serious hospital-acquired infections—reduced TB bacterial counts when used as monotherapy.[7] A further impetus to this approach of repurposing beta-lactams for TB came with the recent identification of synergistic activity between beta-lactams and rifampicin,[8] one of the standard TB drugs. There are now several early-phase studies underway looking at various

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beta-lactam and rifampicin combinations as potential treatment-shortening approaches for drug-sensitive TB.

An even more straightforward approach than evaluating repurposed drugs would be to make changes to enhance the efficacy of drugs in the standard TB treatment regimen. Rifampicin is the most important sterilising drug in standard combination therapy, but the usual clinical dose of 10 mg/kg is known to lie at the lower end of the dose-response curve. Recent studies have tested increased doses of rifampicin (up to a dose of 35mg/kg) and shown substantial improvements in bacterial clearance in the first 8 weeks of treatment.[9] This increase in dose may be accompanied by higher rates of gastro-intestinal intolerance, but it does not appear to be associated with higher incidence of hepatotoxity, which was initially raised as a theoretical concern. Further trials are underway testing high dose rifampicin in short-duration treatment combinations.

Another previously neglected treatment approach that is now receiving substantial attention is the use of immunomodulatory drugs to enhance TB clearance. The human immune system is capable, in the majority of cases, of controlling TB infection even without the assistance of antibiotics. Given the limitations of standard TB drugs in clearing persistent organisms, pharmacologic enhancement of the immune response to TB could be beneficial as an adjunct that may allow shortening of the duration of antibacterial treatment.[10] This is similar to the approach that has transformed oncology treatment in recent years and several trials are now underway evaluating host-directed therapies in TB. In one such study conducted in Singapore, pascolizumab (a monoclonal antibody directed against interleukin-4) is being tested for safety and efficacy as an adjunct to standard therapy in drug-sensitive TB.

In summary, although TB remains an apparently intractable problem, there are encouraging advances in clinical research that may lead to significant improvements in TB treatment in the coming few years. Equally important for the control of TB will be: advances in diagnostic approaches that allow more people with clinical TB (or with latent TB at high risk of clinical progression) to be identified and subsequently offered effective treatment; and advances in preventive approaches including vaccines, as well as innovative ways to deliver treatment in programme settings, that may increase treatment adherence and retention in care.

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Original Article

Optical and Tectonic Corneal Transplant Outcomes in a Tertiary Hospital in Singapore within the Singapore Corneal Transplant Registry

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Abstract

Introduction: This study aimed to describe and compare corneal graft survival and optical outcomes following deep anterior lamellar keratoplasty (DALK) and Descemet's stripping automated endothelial keratoplasty (DSAEK) with penetrating keratoplasty (PK), and to document tectonic success of patch grafts. Materials and Methods: This was a retrospective, non-randomised, comparative and descriptive cohort study. A total of 139 eyes that underwent primary keratoplasty between 2000 and 2016 were included, and the following data was extracted: demographics, clinical diagnosis and primary indication, pre- and intraoperative risk factors, postkeratoplasty outcomes, and complications. Optical success was defined as good graft clarity and best corrected visual acuity (BCVA) of 6/12 or better. Graft failure was defined as irreversible corneal oedema and loss of clarity. Tectonic success in patch grafts was defined as tectonic integrity with no repeat tectonic surgical procedure required in the postoperative period. Results: The mean follow-up duration was 3.24 ± 3.47 years in the PK group (n = 16), 1.89 ± 0.86 years in the DALK group (n = 37), 2.36 ± 1.24 years in the DSAEK group (n = 53), and 2.17 ± 1.09 years in the patch graft group (n = 33). The 3-year probabilties of survival for PK, DALK, DSAEK and patch graft were 60.9%, 94.1%, 89.9%, and 67.1%, respectively. The overall percentage of complications was significantly higher for PK (81.3%), compared to DALK (48.6%), DSAEK (49.1%), and patch graft (21.2%). In the PK and DALK groups, 100% achieved BCVA of 6/12 or better, while in the DSAEK group, 96.43% achieved BCVA of 6/12 or better. Conclusion: From a similar study cohort of Asian eyes, graft survival was superior and complications were reduced for DALK and DSAEK compared to PK, but optical outcomes were comparable. Graft survival for patch graft was expectedly lower, but the incidence of complications was low.

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Key words: Cornea, Keratoplasty, Survival

Introduction

Penetrating keratoplasty (PK), which involves full-thickness replacement of a diseased cornea with an allograft donor cornea, has long been a well accepted and highly successful procedure, with numerous reports of short-term graft success of 90% or higher.[1] However, allograft endothelial rejection rates are as high as 18% based on a Cochrane review,[2] with rejection rates of primary grafts ranging from 9% to 42% in randomised controlled trials (RCT).[3] Graft rejection usually leads to loss of graft clarity and optical graft failure.[4] In recent years, new data on long-term graft survival has emerged,[1] suggesting more disappointing survival rates. This is largely due to an exponential loss in endothelial cell density over time, resulting in graft failure and ongoing irreversible allograft rejection.[5]

There has been an increasing trend in recent years towards partial-thickness replacement of the diseased cornea, namely deep anterior lamellar keratoplasty (DALK) and

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Descemet's stripping automated endothelial keratoplasty (DSAEK), for various corneal pathologies.

DALK involves replacement of diseased anterior corneal stroma, while preserving unaffected Descemet's membrane and endothelium, most commonly for keratoconus, anterior stromal dystrophies or for other forms of anterior stromal scarring.[6] Compared to PK, it allows the conservation of the host endothelium, thus removing the risk of endothelial rejection and reducing risks of intraocular complications, which translates to better long-term outcomes. Stromal or epithelial rejection is much less common and less severe than endothelial rejection, and can usually be successfully reversed by topical steroids, with preservation of graft optical quality. In addition, unlike PK, DALK surgery avoids an open-sky surgical procedure, hence avoiding intraocular complications and the major risk of intraoperative expulsive haemorrhage, which is usually blinding. However, it is technically more demanding and if imperfectly performed, may result in suboptimal visual outcomes because of interface and refractive irregularities.

Corneal endothelial disorders such as Fuchs' endothelial dystrophy and pseudophakic bullous keratopathy (PBK) or aphakic bullous keratopathy (ABK) are among the commonest indications for corneal transplantation, with PBK accounting for the majority of corneal transplants in Singapore. PK has long been the traditional transplant procedure of choice for endothelial dysfunction, but has recently been supplanted by endothelial keratoplasty (EK) procedures, which offer better graft survival, fewer complications, and better visual outcomes compared to PK.[7] DSAEK is the commonest form of EK surgery, and has now become the "gold standard" for endothelial dysfunction, comprising a closed eye, small incision procedure where only the posterior lamella of a diseased cornea is replaced, while retaining the host cornea stromal tissue.[8] DSAEK has several advantages over PK. For example, it avoids an open-sky procedure, requires minimal sutures, thus minimising induced astigmatism with a smoother anterior corneal surface, and prevents suture-related graft complications. DSAEK also provides enhanced tectonic integrity with only a 5 mm or less beveled incision—this results in fewer complications with regard to ocular surface conditions and a neurotrophic state in PK surgery, where severed corneal nerves take many months to regenerate in the donor cornea. Finally, early visual recovery and quality are greatly enhanced, with minimal refractive shifts or astigmatism, unlike what occurs in PK surgery which usually requires sequential corneal suture removal over many months.[8]

It is recognised that although PK offers patients similar visual improvement in the long-term,[8] DALK and DSAEK are superior to PK in terms of visual rehabilitation, refractive stability (surgically-induced astigmatism), graft rejection, wound dehiscence, suture-related problems, and intraocular complications.[8,9]

Corneal patch grafting, which includes PK, lamellar, or peripheral grafts of various shapes and sizes, is a useful tectonic and/or therapeutic option in selected cases of corneal thinning and perforations because it effectively restores the integrity of the globe.[10] In the Singapore Corneal Transplant Study (SCTS), graft survival rates following tectonic keratoplasty by PK were lower than optical graft survival rates, at 68.3% and 41.7% at 1 and 3 years, respectively. DALK has shown to offer a significant advantage over PK in terms of graft rejection and endothelial cell loss,[11] but for the purpose of this paper, we will only document the long-term tectonic success of patch grafts in general.

Many studies have looked at baseline risk factors for graft failure, including patient demographics and clinical diagnosis, preoperative recipient corneal tissue status, and donor corneal tissue status, as well as short-term outcomes. Most studies have demonstrated favourable short-term outcomes of DALK and DSAEK over PK, but with comparable visual acuity outcomes to PK.[4,8] A Cochrane review also concluded that there was no strong evidence in terms of visual outcome and graft survival, to suggest that EK is superior to PK. However, various techniques of EK such as deep lamellar EK, Descemet's stripping EK, DSAEK and femtosecond laser-assisted EK were employed in this review, which may have a bearing on the findings.[9] Still, relatively few studies have studied long-term outcomes such as graft survival and visual acuity. Apart from the SCTS,[1] there is no other local corneal transplant data available.

The SCTS is an ongoing prospective cohort study designed to prospectively track corneal transplant outcomes in Singapore.[12,13] Initiated in Singapore, SCTS has tracked over 5000 transplants mainly performed at the Singapore National Eye Centre (SNEC) since its inception in 1991. SCTS prospectively captures preoperative clinical data, donor tissue data, operative data, and yearly postoperative updates for all corneal transplant patients at SNEC and its related subsidiary units from Changi General Hospital (CGH), Kandang Kerbau Hospital (KKH) (paediatric patients), and at SNEC faculty practice (SNEC Eye Associates) and Gleneagles Hospital. At the National University Hospital (NUH) Department of Ophthalmology, the Corneal Service developed its corneal transplantation in tandem with the SNEC Corneal Service since 2000, and both institutions perform all forms of corneal transplantation procedures including PK, DALK, DSEK and corneal patch grafts, utilising jointly developed surgical protocols. In coordination with the Singapore Eye Bank (SEB), which tracks SCTS, and the Singapore Eye Research Institute, NUH has adopted the SCTS database and is currently its second major clinical institution for corneal transplants.

The current SCTS database has now been expanded into a formal registry, and renamed the Singapore Corneal Transplant Registry (SCTR). SCTR currently tracks corneal transplants performed at SNEC, CGH, KKH, NUH and also involves the majority of corneal transplants performed at Gleneagles Hospital by corneal surgeons within the SNEC faculty practice (SNEC Eye Associates) and Eye & Cornea Surgeons (a division of the Eye & Retina Surgeons private group practice). Collectively, SCTR currently tracks approximately 85% of all corneal transplants performed in Singapore—in 2016, SCTR tracked 420 out of a total of 490 transplants performed.

This study analyses primary graft outcomes, complications and survival rates between the 3 main forms of optical transplants performed at the NUH Corneal Service, with direct comparison of conventional PK surgery to DALK and DSAEK, in terms of graft survival, optical outcomes and complication rates, as well as analysis of tectonic success in corneal patch grafts over a15-year period. All surgeries were performed by 3 NUH corneal surgeons (DT, AT, MR) utilising similar surgical transplant protocols.

Materials and Methods

Corneal Donor Tissue Acquisition

The acquisition of corneal donor tissue in Singapore and within this study is from the SEB. The SEB is the sole provider for corneal tissue in Singapore since 1991. With the exception of grafts performed for emergency therapeutic or tectonic reasons, internal guidelines within the SEB releases grade A corneal tissue with endothelial cell counts exceeding 2200 cells/mm^2 and a death-to-surgery time generally not exceeding 7 days for elective keratoplasty for optical indications.[1]

Methodology

A total of 218 eyes that underwent keratoplasty at a single tertiary instutition, NUH, between 2000 and 2016 were identified from Computerised Patient Support System (CPSS) or Medical Records Office (MRO). Consecutive patients who underwent either a primary PK, DALK, DSAEK, or patch graft for optical (surgery performed primarily for visual recovery), tectonic (surgery performed to restore globe integrity of eyes with abnormally thin or perforated corneas), or therapeutic (surgery performed to eradicate corneal infection or neoplasia) reasons were included. This left a total of 139 primary grafts, including 9 bilateral cases, after excluding 66 grafts with follow-up of less than 1 year and 13 repeat grafts.

Case records were retrospectively reviewed and the following data extracted: demographics (age at time of keratoplasty, sex, and race); type of keratoplasty (PK, DALK, DSAEK, or patch graft); clinical diagnosis and primary indication; duration of follow-up; preoperative risk factors (pre-existing glaucoma, cataract or uveitis, active inflammation or infection, ocular surface disease, lid disease, and globe perforation at time of surgery); additional intraoperative procedures at the time of keratoplasty; and postkeratoplasty best-corrected visual acuity (BCVA), immunosuppression regime, complications, subsequent surgeries or procedures, and graft failures.

Outcomes were measured at 1 month, 3 months, 6 months, and yearly thereafter. The main outcome measures were graft failure, defined as irreversible oedema and loss of clarity, and optical outcomes, determined by graft clarity and BCVA.

All grafts were performed by 1 of our 3 corneal surgeons (DT, AT, MR) from NUH over the same period (2000-2016) utilising unified surgical protocols.

The study adhered to the tenets of the Declaration of Helsinki and received approval from the Institutional Review Board.

Long-Term Outcomes and Graft Failure

Long-term outcomes included glaucoma or raised intraocular pressure (IOP), allograft rejection, postoperative anterior synechiae at graft, late graft failure, epithelial problems, microbial keratitis, activation of herpes simplex virus (HSV) keratitis, suture-related infection, endophthalmitis, recurrence of primary disease, and other complications.

Graft failure was defined as irreversible oedema and loss of clarity in a graft that was previously documented to be thin and clear, with the date of onset of corneal clouding selected as the time-point of graft failure, with the precise clinical cause of graft failure as recorded by the surgeon in the case notes.

Clinical Diagnosis and Primary Indications for Keratoplasty

Cases were classified based on the International Classification of Disease (ICD-10) into 9 major clinical diagnoses: infectious keratitis, postinfectious scars, pseudophakic bullous keratopathy or aphakic bullous keratopathy (PBK/ABK), Fuchs' endothelial dystrophy (FED), keratoconus, corneal trauma, postglaucoma corneal endothelial decompensation, regrafts, and other diagnoses. In addition to clinical diagnosis, cases were classified into 3 primary indications: optical, therapeutic, and tectonic.

Statistical Analysis

Statistical analysis was performed by a statistician using the Statistical Package for the Social Sciences (SPSS) software version 19.0 (SPSS, Inc, Chicago, Illinois, USA).

Kaplan-Meier survival analysis was used to estimate the cumulative probability of survival of PK, DALK, DSAEK, and patch graft groups. Other statistical analysis included descriptive statistics, where the mean values and standard deviations were calculated for continuous variables, and frequency distribution and percentages were calculated for categorical variables. Comparisons between categorical variables were conducted by Fisher's Exact tests, whereas 1-way analysis of variance was used for continuous variables. Statistical significance was defined as a <0.05.

Results

Patient Data

A total of 218 corneal grafts, comprising PK (n = 29), DALK (n = 62), DSAEK (n = 73), and patch graft (n = 54), were initially identified. The eyes underwent keratoplasty between 2000 and 2016.

Overall mean age at the time of operation was 52.33 +/- 23.24 (0.22-89.24) (mean +/- standard deviation [SD] range) years. Mean age of PK, DALK, DSAEK, and patch graft groups were 47.16 +/- 24.50 (0.56-88.10) years, 33.75 +/- 18.39 (0.22-81.28) years, 61.79 +/- 20.63 (0.69-89.24) years, and 63.65 +/- 15.93 (5.80-82.66) years respectively. There were 15 paediatric recipients (recipients ≤ 16 years).

63.8% of patients were males. There were more males across PK, DALK, DSAEK, and patch graft groups. The difference in gender was not significant ($P = 0.285$).

The ethnic ratio of our Asian cohort approximated the ethnic ratio in Singapore, with Chinese being the predominant race (61.9%), and Malays (11.9%), Indians (16.1%), and other races (10.1%) making up the remaining cohort. Chinese was the predominant race across PK, DSAEK, and patch graft groups, except in DALK group, where Indians were the predominant race due to the predominance of keratoconus in this ethnic group.

Of the 218 corneal grafts, the majority was for optical indications (n = 149), followed by tectonic indications (n = 61), and therapeutic indications (n = 8). The common clinical diagnoses were PBK/ABK (n = 6, 20.7%), traumatic scarring (n = 6, 20.7%), and bacterial keratitis (n = 4, 13.8%) for PK, keratoconus (n = 34, 54.8%) and traumatic scarring (n = 8, 12.9%) for DALK, PBK/ABK (n = 33, 45.2%) and FED (n = 15, 20.5%) for DSAEK, and prior glaucoma surgery with glaucoma drainage implant (GDI) tube, plate exposure or scleral melting (n = 41, 75.9%) for patch graft.

A total of 139 out of 218 consecutive primary corneal grafts, comprising PK (n = 16), DALK (n = 37), DSAEK (n = 53), and patch graft (n = 33), were included for analysis of long-term outcomes. Of the 139 corneal grafts, 99 were for optical indications, 36 for tectonic indications, and 4 for therapeutic indications. The eyes underwent keratoplasty between 2000 and 2016 and were followed up for 2.29 +/- 1.59 (mean +/- SD) years (range 0.00-15.19 years). Mean follow-up period was 3.24 +/- 3.47 years in the PK group (n = 16), 1.89 +/- 0.86 years in the DALK group (n = 37), 2.36 +/- 1.24 years in the DSAEK group (n = 53), and 2.17 +/- 1.09 years in the patch graft group (n = 33).

Graft Survival

Overall graft survival time for tectonic and therapeutic grafts compared to optical grafts were expectedly lower (2.99, 2.26, and 4.52 years, respectively) (Fig. 1), attributed to higher severity of disease, infection, inflammation, glaucoma, corneal vascularisation, ocular surface instability or limbal stem cell deficiencycompared to optical cases, and this difference was significant (log rank $P = 0.02$).

Comparing PK, DALK, DSAEK, and patch graft groups, overall graft survival time for PK, DALK, DSAEK, and patch graft were 3.97 (+/- 0.50) mean [+/- standard error), 3.67 (+/- 0.12), 4.36 (+/- 0.23), and 2.91 (+/- 0.28) years, respectively. A subgroup analysis revealed significant differences for DALK versus patch graft ($P = 0.009$) and DSAEK versus patch graft ($P = 0.007$). However, PK versus DALK, DSAEK, and patch graft, and DALK versus DSAEK were insignificant ($P = 0.105$, 0.221, 0.498, and 0.687, respectively).

The Kaplan-Meier (KM) probabilities of survival for PK were 93.8%, 85.2%, and 60.9% at 1, 2, and 3 years respectively, compared to 94.1%, 94.1%, and 94.1% for DALK, 94.2%, 94.2%, and 89.9% for DSAEK, and 78.8%, 71,6%, and 67.1% for patch graft (Table 1). Lower probabilities of survival for patch graft were expected due to its tectonic indications. There were no differences in probabilities of survival comparing PK, DALK, and DSAEK

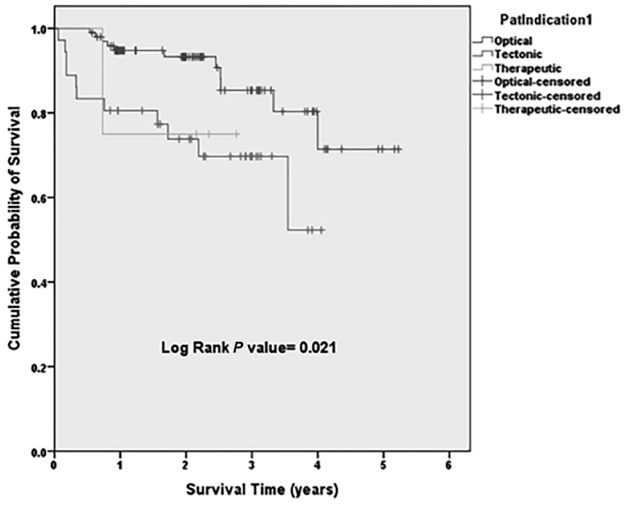

Fig. 1. Graft survival curves by optical, tectonic and therapeutic outcomes.

Table 1. Cumulative Kaplan-Meier Graft Survival Probabilities Comparing PK, DALK, and DSAEK

Year	PK		DALK		DSAEK	
	n	Survival Rate	n	Survival Rate	n	Survival Rate
1	15	93.8%	31	94.1%	48	94.2%
2	10	85.2%	31	94.1%	48	94.2%
3	5	60.9%	31	94.1%	21	89.9%
4	5	60.9%			5	68.7%
5	5	60.9%				

DALK: Deep anterior lamellar keratoplasty; DSAEK: Descemet's stripping automated endothelial keratoplasty; PK: Penetrating keratoplasty

at 1 year (93.8% vs 94.1% vs 94.2%). However, we note a drop in probability of survival for PK at 2 years (93.8% vs 85.2%), while probabilities of survival for DALK and DSAEK did not change at 2 years. There was a significant drop in probability of survival for PK at 3 years, while that for DALK remained unchanged and DSAEK dropped more modestly.

The KM probabilities of survival (Fig. 2) demonstrate that the best long-term survival was seen in the DALK group (Fig. 3), followed by the DSAEK group (Fig. 4), and lastly by the PK group. Statistical significance compared to PK was not achieved due to the small sample size.

Complications

Overall percentage of complications was significantly higher for the PK group (81.3%) compared to the DALK group (48.6%) and the DSAEK group (49.1%). Of note, the patch graft had a significantly lower percentage of complications (21.2%), which could be attributed to smaller grafts and no need for long-term immunosuppression.

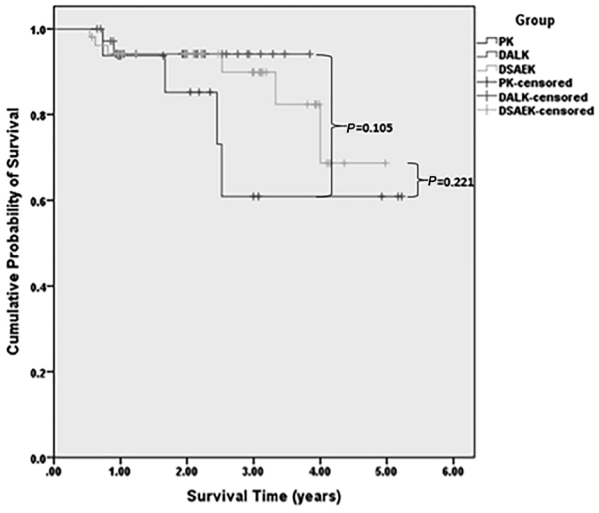

Fig. 2. Graft survival curves comparing PK, DALK and DSAEK. PK: Penetrating keratoplasty; DALK: Deep anterior lamellar keratoplasty; DSAEK: Descemet's stripping automated endothelial keratoplasty.

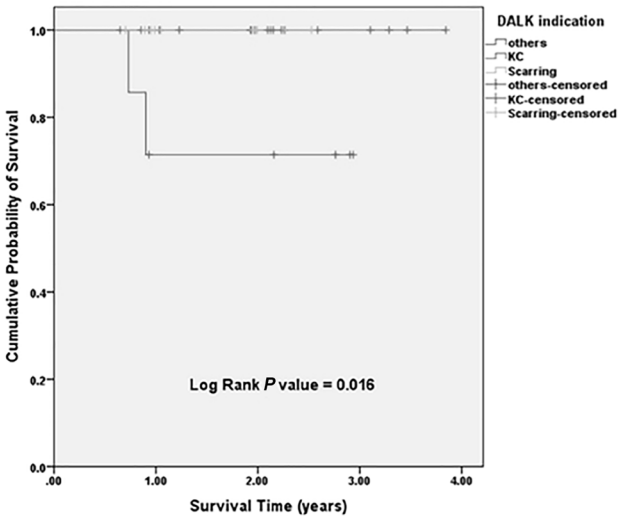

Fig. 3. Graft survival curves of DALK by primary clinical diagnoses. DALK: Deep anterior lamellar keratoplasty; KC: Keratoconus.

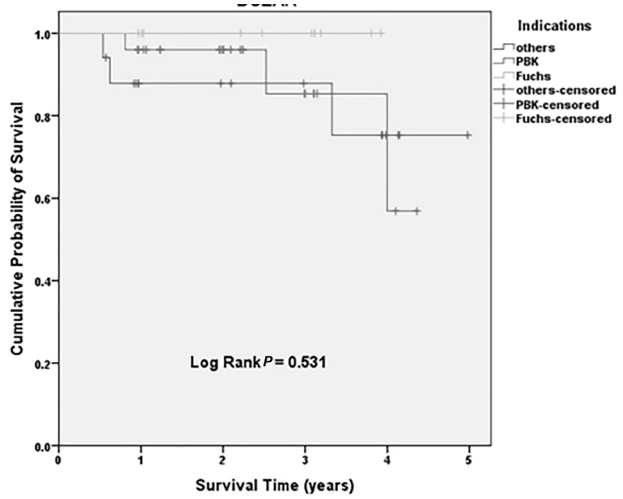

Fig. 4. Graft survival curves of DSAEK by primary clinical diagnoses. DSAEK: Descemet's stripping automated endothelial keratoplasty; PBK: Pseudophakic bullous keratopathy.

Raised IOP (n = 28), epithelial problems (n = 14) and allograft rejection (n = 11) were the most common complications (Table 2). In our study, 29 eyes had pre-existing glaucoma, comprising 5 eyes from the DSAEK group and 24 eyes from the patch graft group. The most frequent complications were glaucoma or raised IOP (31.3%), allograft rejection (18.8%) and epithelial problems (18.8%) for the PK group, glaucoma or raised IOP (29.7%) and epithelial problems (10.8%) for the DALK group, glaucoma or raised IOP (20.8%), allograft rejection (9.4%) and epithelial problems (9.4%) for the DSAEK group, and epithelial problems (6.1%) and microbial keratitis (6.1%) for the patch graft group.

Table 2. Complications Comparing PK, DALK, DSAEK, and Patch Graft Groups over the Follow-up Period

Complication	PK (n = 16)	DALK (n = 37)	DSAEK (n = 53)	Patch Graft (n = 33)
Glaucoma or raised IOP	5	11	11	1
Allograft rejection	3	2	5	1
Late graft failure	0	0	2	0
Epithelial problems	3	4	5	2
Microbial keratitis	1	1	0	2
Activation of HSV keratitis	1	0	3	1
Suture-related infection	1	2	0	0
Endophthalmitis	0	0	0	1
Recurrence of primary disease	0	1	0	3
Other complications	1	3	1	10

DALK: Deep anterior lamellar keratoplasty; DSAEK: Descemet's stripping automated endothelial keratoplasty; HSV: Herpes simplex virus; IOP: Intraocular pressure; PK: Penetrating keratoplasty

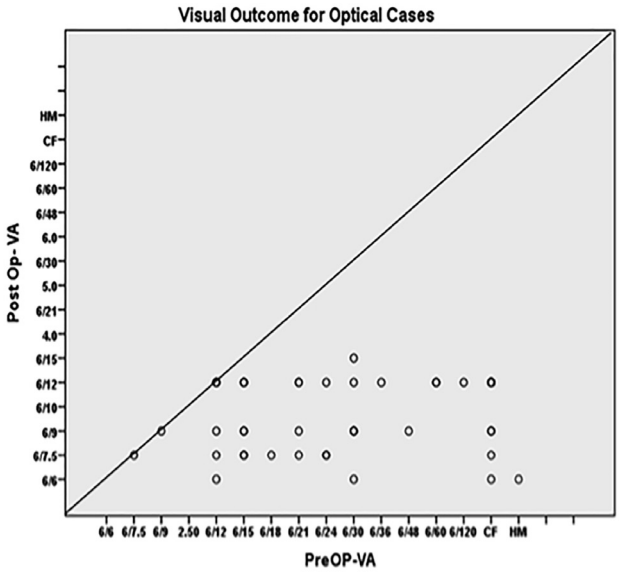

Fig. 5. Comparison of best-corrected visual acuity of optical cases preoperatively and 1 year postoperatively. VA: Visual acuity

Late graft failure occurred in only 2 cases of DSAEK (3.8%). Of note, there was a higher incidence of allograft rejection in the PK group (18.8%) compared to the DALK group (5.4%), DSAEK group (9.4%) and patch graft group (3.0%).

Optical Outcomes

BCVA was measured using a Snellen chart. For the purpose of this outcome measure, only cases with optical indications were included. Of these optical cases, failed grafts and eyes with pre-existing comorbidities (cloudy graft, ambylopia, glaucoma, cataract, retinal or macular disease) were excluded, leaving a total of 48 preoperative eyes and 52 postoperative eyes at 1 year for comparison, based on the available data at the time-point (Table 3, Fig. 5).

There was an overall significant improvement in visual acuity after keratoplasty. All eyes had better BCVA postoperatively compared to preoperatively. By 1 year postoperatively, all but 1 eye (98.08%) achieved BCVA of 6/12 or better.

Table 3. Best Corrected Visual Acuity of Optical Cases Preoperatively and 1 Year Postoperatively

Visual Acuity	Preoperative		Postoperative	
	n	%	n	%
6/12 or better	9	18.75	51	98.08
6/15 – 6/48	25	52.08	1	1.92
6/60 – 6/120	3	6.25	0	0
CF or worse	11	22.92	0	0
Total	48	100	52	100

CF: Counting fingers

Preoperative and postoperative BCVA in the PK, DALK, and DSAEK groups were individually analysed and compared (Table 4). In the PK and DALK groups, 100% achieved BCVA of 6/12 or better, while in the DSAEK group, 98.08% achieved BCVA of 6/12 or better. However, the difference in the percentage of patients achieving BCVA of 6/12 or better at postoperative year 1 between the PK, DALK, and DSAEK groups was not significant.

Of note, 100% of the patients in the PK group had preoperative BCVA of counting fingers (CF) or worse, compared with 23.81% in the DALK group and 16.00% in the DSAEK group. This generally reflects the higher visual compromise in eyes requiring total corneal replacement with disease involvement of both corneal stroma and corneal endothelium, in the PK group, as opposed to the DALK group with only stromal disease, or DSAEK group with primarily only endothelial dysfunction.

Discussion

PK has been the gold standard graft for corneal transplantation for over a century. However, in the last decade, the evolution of corneal transplant surgery has seen the emergence of modern techniques in selective lamellar replacement of corneal tissue, in the form of anterior lamellar (DALK) or posterior lamellar (DSAEK) transplantation, as important watersheds to the field.[12] Still, the major goals of keratoplasty, which are visual improvement and prolonged

Table 4. Best Corrected Visual Acuity of PK, DALK, and DSAEK Groups Preoperatively and 1 Year Postoperatively

Visual Acuity	PK		DALK		DSAEK	
	Preoperative n (%)	Postoperative n (%)	Preoperative n (%)	Postoperative n (%)	Preoperative n (%)	Postoperative n (%)
6/12 or better	0 (0)	3 (100)	4 (19)	21 (100)	5 (20)	27 (96.4)
6/15 – 6/48	0 (0)	0 (0)	11 (52.4)	0 (0)	14 (56)	1 (3.6)
6/60 – 6/120	0 (0)	0 (0)	1 (4.8)	0 (0)	2 (8)	0 (0)
CF1 or worse	2 (100)	0 (0)	5 (23.8)	0 (0)	4 (16)	0 (0)
Total	2 (100)	3 (100)	21 (100)	21 (100)	25 (100)	28 (100)

CF: Counting fingers; DALK: Deep anterior lamellar keratoplasty; DSAEK: Descemet's stripping automated endothelial keratoplasty; PK: Penetrating keratoplasty

graft survival, remain unchanged, and in this study, we evaluated graft survival, postoperative complications, and optical outcomes of the various techniques of keratoplasty, and compared the outcomes of PK with DALK and DSAEK.

A review of literature reveals heterogeneous conclusions of graft success.[8,11,14,15,16] While numerous clinical studies specifically evaluating success rates in DALK and DSAEK compared with PK have shown the superiority of these lamellar procedures in terms of visual outcomes, graft survival, and complication rates, most of these studies were efficacy studies involving limited numbers of surgeons and specific or controlled indications, often with exclusion of high-risk comorbidities. The Australian Corneal Graft Registry (ACGR) has recently suggested that the survival of DALK and DSAEK may in fact be worse than the survival of PK performed over the same time frame, when analysed in a "real world" clinical situation, involving major cohort registry with many surgeons at different stages of the learning curve and varied indications.[17] In the ACGR, most of the DSAEKs that failed were the results of primary graft failure, and the majority of DSAEKs failed within the first 12 months after surgery, suggesting that the surgical technique rather than the PK, DALK, or DSAEK procedure itself may be an important factor for graft survival.

At NUH, graft survival for PK, DALK, and DSAEK was comparable at 1 year, but subsequently, the graft survival of PK was poorer than that of DALK and DSAEK. The poor graft survival of PK may be attributed to the fact that the majority of patients who underwent PK had endothelial disease (ABK/PBK), and the SCTS had previously demonstrated that corneal endothelial health was an important overall predictor of graft survival. In DALK surgery, however, host endothelial function was generally normal, and was not replaced. In the study, endothelial indications (PBK/ABK, FED, and regraft) represented the 3 disease groups with the lowest graft survival, where the most common cause of graft failure was immunologic rejection (29.15%) (with endothelial rejection as the dominant form), followed by late endothelial failure (21.36%).[1] Similar findings have been reported in other studies.[7] Our findings mirror the results seen in other SCTS publications, where DALK and DSAEK were seen to have longer graft survival compared with PK.[6,7,11,15]

Our study also supports the advantage of DALK and DSAEK over PK in terms of a lower incidence of complications, although the PK group had a smaller sample size compared to the DALK and DSAEK groups and hence may not be a fair comparison. This is a conceivable finding, because PK is an intraocular procedure, in contrast to DALK, which is essentially extraocular and non-penetrating.[4] While DSAEK—as an essentially small incision procedure—results in less suture-related and wound-related complications as compared to PK. Of significance, the incidence of allograft rejection was significantly higher with PK (18.8% vs 9.4% and 5.4% in DSAEK and DALK, respectively). In DSAEK, less donor corneal tissue is transplanted, which results in less antigenicity challenge, while in DALK, the obviation of the possibility of endothelial rejection with DALK is a major advantage over PK,[4] and we have demonstrated that the incidence of allograft rejection is indeed significantly reduced with DALK. As anterior lamellar and endothelial keratoplasty techniques improve, we expect further improvements in clinical outcomes tacking on to its recognised advantages, but more definitive studies are needed.

Of note, we notice that glaucoma or raised IOP was the overall most common complication, and recognise that it would be important to ascertain if these patients have an underlying history of glaucoma, which will have a bearing on the findings. Many of our patients experienced only a transient rise in IOP that was largely steroid-induced. Few patients progressed to chronic glaucoma. However, the incidence of transient elevated IOP or glaucoma after DALK or DSAEK compared with PK seems to be comparable, or even reduced. One study comparing PK and DSAEK found no significant difference in the 5-year incidence of postoperative glaucoma.[7] In our study, the 5-year cumulative incidence of transient elevated IOP was 22.4 +/- 4.1

(cumulative incidence +/- 95% confidence interval) for the PK group and 23.6 +/- 4.1 for the DSAEK group (P = 0.689). All PK and DSAEK patients in this study received a standard postoperative relatively high-dose steroid regimen. Another study comparing PK and DALK found a higher incidence of postoperative glaucoma in the PK group.[4] As a result of the lower risk of allograft rejection, DALK patients in this study required a shorter postoperative steroid regimen than PK patients, which may contribute to the lower rate of glaucoma. This is further suggestive that postoperative steroid is an important cause of glaucoma after keratoplasty. A targeted study evaluating steroid-induced glaucoma after PK reported a significant overall frequency of 73% and 60.3% in eyes with keratoconus and Fuchs dystrophy, respectively.[18] Yet another study found steroid-induced IOP elevation as the most frequent cause of the incidence of IOP elevation, compared with other risk factors such as pre-existing glaucoma, preoperative lens status, preoperative diagnosis, age, preoperative IOP, preoperative synechiae, and combined surgery.[19] In conclusion, IOP may be elevated after ketatoplasty. However, the elevated IOP is commonly steroid-induced, often benign and transiently elevated, and do not all progress to chronic glaucoma. Moreover, steroid-induced transient elevated IOP can normally be treated effectively by antiglaucoma medications, tapering steroids, or changing steroids. Of note, postoperative administration of steroids is effective in reducing postoperative inflammation and preventing the development of peripheral anterior synechiae,[19] which has shown to be one of the main complications of elevated IOP after keratoplasty.[20] Further studies are needed to investigate the optimal medication schedule after keratoplasty.

PK currently remains the most common form of corneal transplantation in the world at present, although it is increasingly being replaced by lamellar keratoplasty in various conditions, especially in more developed countries with well established corneal transplant programmes.[21] It also appears that the rate of adoption of lamellar keratoplasty is highly variable between geographic regions, and between developed and less developed countries. This dichotomy is attributed to many factors, such as the availability of surgical training in the newer procedures, access to appropriately dissected donor tissue including appropriate instrumentation, relative cost issues for performing the procedures, and the inherent variability in the types and severity of corneal diseases pertinent to specific populations.[6]

Conclusion

Our study shows that corneal transplantation remains a highly successful vision-restoring procedure. All the patients achieved good postoperative BCVA at the level of 6/12 or better. It should be noted that the baseline BCVA of patients who subsequently underwent PK was generally worse than those who underwent DALK and DSAEK, and this may be attributed to PK being selected as the procedure of choice for later stage disease involving multiple corneal layers, but nonetheless the optical success of PK in our series remains comparable to DALK and DSAEK.

The main drawback of this study is its retrospective nature, resulting in limited long-term follow-up data due to patients who were lost to follow-up. However, the KM analysis generally takes into account the length of follow-up of approximately 3 years.

We also recognise the smaller sample size of our PK group as our centre shifted mainly to lamellar surgery in the later years. Previous randomised controlled trials (RCTs) comparing DALK with PK have had small sample sizes and short follow-up periods. One RCT comparing EK with PK encountered incomplete enrolment as EK techniques changed rapidly.[22] Still, we are aware that interpreting outcomes between different studies can be difficult when outcome definitions vary, preoperative characteristics are not well defined, and outcome assessments are not standardised.[22] Hence we believe that evaluating a relatively newer surgical technique should be performed under standardised conditions to identify specific differences in outcomes of interest. This is what we aimed to achieve in our corneal transplant study.

Future long-term, large-cohort studies are definitely needed to assess and compare the advantages of the various techniques of keratoplasty. Baseline risk factors and clinical indications must also be analysed to understand the interplay between preoperative factors and choice of keratoplasty technique. However, we acknowledge that this corneal transplant study at NUH is at a relative early stage, and as the database continues to mature, we anticipate additional data relevant to prospective, nested studies in a larger cohort. We propose further prospective cohort studies or retrospective nested cohort studies based on the database as the next best alternatives. We believe that such a registry that is under annual audit at NUH provides the advantages of a large prospective cohort to minimise selection bias in a controlled setting of multiple surgeons with varying degrees of surgical experience, and at the same time utilising standardised surgical techniques and postoperative management. This will hence continue to provide valuable insights into the long-term outcomes of the various techniques of keratoplasty in the same study population.[7] Finally, this study validates the development of a national corneal transplant programme across Singapore with similar surgical protocols and training standards within the SCTR. It also confirms the feasibility of adopting national surgical transplant protocols and standards across clinical institutions, and with many surgeons at different stages of training. More

importantly, SCTR data analysis enables us to evaluate the ongoing development of newer surgical techniques and transplant procedures in selective lamellar keratoplasty as they are being adopted and also as younger generations of corneal surgeons are trained and accredited. Our study confirms that with unified and updated surgical protocols and techniques, excellent visual outcomes and graft survival rates are achievable in selective lamellar keratoplasty that continues to largely replace conventional PK.

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Original Article

Complications and Pain in Obstructive Sleep Apnoea – Comparing Single and Multilevel Surgery

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Abstract

Introduction: This study aimed to investigate differences in the complication rate and postoperative pain score between single and multilevel surgery performed on patients with obstructive sleep apnoea. Materials and Methods: A retrospective analysis was performed on patients with obstructive sleep apnoea who underwent surgery in a tertiary referral centre over 3 years. Patients who underwent single-level nasal, palatal or tongue surgery were compared with patients who underwent concurrent multilevel surgery of 2 or 3 levels. Complications and the postoperative Visual Analogue Scale pain score were recorded and the outcomes between single and multilevel groups were compared. Results: The overall complication rate for patients was 12.6%, 6.7% if only patients requiring intervention were considered. The adjusted odds ratio (OR) for complication rate for patients undergoing multilevel surgery and single-level surgery was 2.76. It was not statistically significant (P = 0.053) after adjusting for confounders. There was more pain in patients who underwent multilevel surgery than in the single-level surgery group. Conclusion: Concurrent multilevel surgery is a feasible option in patients with multilevel obstruction, especially if they are undergoing palate and tongue surgery, nose and palate surgery or nose and tongue surgery. There may be more complications, though it is not statistically significant. Further studies are required to investigate the differences between single-level nasal surgery and 3-level multilevel surgery. More patients undergoing multilevel surgery than single-level surgery experienced pain. Multilevel surgery patients should have their analgesia reviewed regularly and titrated accordingly.

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Key words: Bleeding, Infection, Nose, Palate, Sleep surgery, Snoring, Tongue

Introduction

Obstructive sleep apnoea (OSA) is a chronic medical problem with potentially serious consequences—increased cardiovascular risk, hypertension and sudden death.[1,2] Lifestyle modification and continuous positive airway pressure (CPAP) are the mainstay of treatment. Many OSA patients have CPAP compliance issues and often undergo surgery as a salvage procedure. As most OSA patients have multilevel obstruction, multilevel surgery (MLS) gives improved outcomes.[3] MLS can be staged to address the obstruction one level at a time, or performed concurrently, where many levels of obstruction are addressed in the same operative setting. The advantages of concurrent MLS are: 1) single anaesthesia, 2) decreased total length of hospital stay, 3) decreased time away from work, 4) lower cost and 5) shorter postoperative recovery time.[4] However, there is concern that patients will experience increased pain and postoperative complications.[5]

The available literature comparing single-level surgery (SLS) and MLS is difficult to interpret. Firstly, surgical techniques such as lateral pharyngoplasty, transoral robotic tongue base reduction (TORS) and genial tubercle

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advancement (GTA) are often excluded. Secondly, inclusion criteria are different. Some groups only include OSA patients while others have both OSA and non-OSA patients.[4,5] Thirdly, the outcome measures are different. Some studies analysed patients based on the total number of procedures, instead of the number of levels of intervention. There is also limited data comparing postoperative pain in SLS and MLS patients. A literature search using the keywords 'OSA' and 'pain' did not yield any results. We are of the opinion that complications should be analysed according to levels as patients are treated based on their levels of obstruction. Therefore, the objective of this retrospective study is to investigate the differences in postoperative complications and Visual Analogue Scale (VAS) pain score between SLS and MLS performed on patients with OSA.

Materials and Methods

Study Design

We performed a retrospective review of all patients who underwent elective sleep surgery from January 2011 to December 2013 in an academic tertiary referral centre—the largest hospital in the country with 1597 beds and an annual average of 80,859 surgical operations. Only patients diagnosed with OSA were included and all had either declined or failed CPAP use. Diagnosis of OSA was made following a level 1 in-laboratory attended polysomnogram performed according to the American Association of Sleep Medicine guidelines for overnight polysomnogram. The criteria for apnoea and hypopnoea were defined according to the American Academy of Sleep Medicine guidelines and scoring manual.[6] The following information was collected from the cohort: age, gender, type of anaesthesia, race, body mass index, systolic and diastolic blood pressure, smoking history, alcohol consumption, lowest level of saturation during sleep study, apnoea-hypopnoea index, the immediate postoperative VAS pain score, surgical procedure/s performed, and complications occurring within the first 30 days of surgery. The review of medical records was approved by the Institutional Review Board.

Surgical Procedure

The level of obstruction was determined after in-office oral and nasoendoscopic examination. Following this, counselling was performed and the type of surgery and levels of surgical intervention decided upon. The surgical procedures were classified into nasal, palatal, and tongue base levels. Nasal surgeries included inferior turbinoplasty, septoplasty, adenoidectomy, radiofrequency of inferior turbinates, and functional endoscopic sinus surgery. Palatal reconstructive surgeries included uvulopalatal flap, lateral pharyngoplasty, tonsillectomy, and radiofrequency of soft palate. Tongue-base surgeries included TORS, GTA, radiofrequency of tongue-base, midline glossectomy, and hyoid suspension.

After surgery, all patients who underwent general anaesthesia were admitted to the surgical intensive care unit or high-dependency care unit for overnight observation before being transferred to the general ward on postoperative day 1 or 2. Patients with surgical procedures performed under local anaesthesia were discharged on the same day. All patients who underwent TORS, GTA, and palatal reconstructive surgery received intravenous antibiotics, intravenous dexamethasone sodium phosphate, intravenous omeprazole, analgesia, and lozenges. All patients who underwent nasal surgery received oral antibiotics, nasal douche, and analgesia. All admitted patients were discharged when their airway was adequate and they were able to achieve oral feeding. They were taught to recognise complications and advised to return to the hospital if these complications occurred. Patients returned for consultation within 2 weeks of discharge.

Classification and Grouping

The patients were divided into SLS and MLS groups (Fig. 1). The SLS group was subdivided into patients who only had nasal surgery (Group N), palatal surgery (Group P), or tongue surgery (Group T). The MLS group was subdivided into patients with 2- or 3-level surgery. MLS patients who underwent 2-level surgery were further classified into nasal and palatal surgery (Group NP), nasal and tongue surgery (Group NT), or palatal and tongue surgery (Group PT). Patients in 3-level surgery had nasal, palatal and tongue surgery (Group NPT). Patients who underwent multiple surgeries at the same level (for example bilateral inferior turbinoplasty, septoplasty and adenoidectomy) belonged to the same SLS subgroup.

The complication rate and VAS pain score were compared between SLS and MLS groups, with the SLS patients as controls.

Further subgroup analysis was also performed. Patients who underwent single-level nasal surgery (Group N) were in the control group and were compared with patients who underwent nasal and palatal surgery (Group NP) or nasal and tongue surgery (Group NT). Group N patients were also compared with those who underwent nasal, palatal and tongue surgery (Group NPT). Group NPT patients were then compared with Group NP or Group NT patients.

None of the patients who underwent palatal surgery alone (Group P) had complications. Hence, we could not compare SLS and MLS using Group P patients as controls. However, patients who underwent nasal and palatal surgery (Group NP) or palatal and tongue surgery (Group PT) were compared with those who underwent nasal, palatal and tongue surgery (Group NPT).

Similarly, patients who underwent single-level tongue surgery (Group T) were controls and were compared with

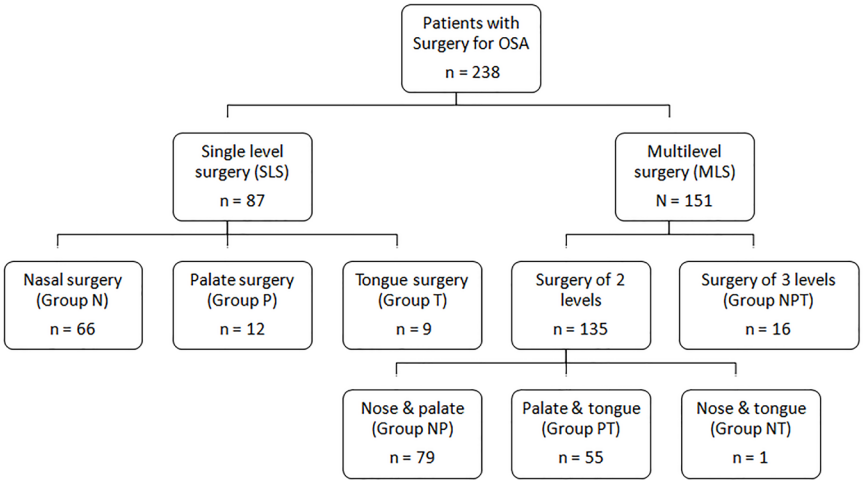

Fig. 1. Classification and distribution of patients who underwent surgery for OSA. n: patient number.

patients who had nasal and tongue surgery (Group NT) or palatal and tongue surgery (Group PT). Group T patients were also compared with patients who underwent nasal, palatal and tongue surgery (Group NPT). Group NPT patients were then compared with Group NT or Group PT patients.

Complication Rate and Pain Score

Complications were tracked using emergency department visit records, hospital admission records and operative procedure records. Complications were defined as events needing additional medical attention within the first 30 days of surgery. These included nasal packing, cautery in the outpatient setting, hospitalisation, need for return to the operating theatre, and emergency department visits. Early complications were those that occurred in the first 24 hours after surgery and late complications were those that occurred after 24 hours. Patients who had either early or late complications, regardless of the number, were recorded to have an event in the analysis. Complications were also classified into minor and major complications. Minor complications were defined as those without haemodynamic compromise, such as cases managed with digital pressure, electrocautery in the clinic, and examination under anaesthesia with haemostasis. Major complications were defined as those with haemodynamic instability, bleeding requiring transfusion, unplanned reintubations, or mortality. Postoperative VAS pain scores were obtained immediately after surgery when the patient first reached the ward.

Statistical Analysis

Continuous variables were summarised as means ± standard deviation and analysed using the simple t-test. Categorical variables were summarised as counts (percentages) and analysed using chi-squared test or the Fisher's Exact test as appropriate. Univariable analysis was performed for all variables. Variables with $P < 0.20$ or deemed to be clinically relevant were inserted into multivariable logistic regression model. The adjusted odds ratios (OR), 95% confidence intervals and P values comparing complication rate and pain score between SLS and MLS were presented.

The pain scores were grouped into binary outcomes: no pain (score = 0), and pain (score = 1).

P values <0.05 were considered statistically significant. Statistical analysis was performed using SAS 9.3 (SAS Institute, Cary, NC, USA).

Results

There were 238 OSA patients who had undergone a total of 426 procedures; 194 were men and 44 were women. Patient demographics and severity of OSA were similar between the SLS and MLS groups (Table 1). There was a difference between the number of single-level and multilevel palatal surgery patients. There was also a difference between the number of single-level and multilevel tongue surgery patients ($P < 0.05$), which suggests more patients underwent multilevel tongue or palatal surgery than single-level tongue or palatal surgery. Mean hospital stay was 3.4 ± 0.9 days. Eighty-seven patients underwent SLS and 151 underwent MLS, of which 135 had surgery of 2 levels and 16 had surgery of 3 levels (Fig. 1). All patients were seen at least once in the first 30 days following surgery and 86.6% were seen twice.

After adjusting for apnoea-hypopnoea index, age, gender, blood pressure, lowest oxygen saturation level, smoking and alcohol consumption, there was an almost statistically significant difference in complication rate between the SLS and MLS groups (adjusted OR = 2.76, P value = 0.053).

Table 1. Patient Demographics

	Overall (n = 238)	Single-level Surgery (n = 87)	Multilevel Surgery (n = 151)	*P* Value*
Age, year	44.1 (11.4)	45.1 (10.8)	43.6 (11.8)	0.315
BMI, kg/m^2	28.7 (5.2)	28.8 (5.7)	28.6 (4.9)	0.823
SBP, mmHg	130.3 (13.8)	129.7 (13.0)	130.6 (14.3)	0.661
DBP, mmHg	79.2 (10.1)	79.4 (10.3)	79.2 (10.1)	0.860
Gender, male	194 (81.5)	71 (81.6)	123 (81.5)	0.977
Race				
Chinese	183 (76.9)	68 (78.2)	115 (76.2)	0.980
Malay	27 (11.3)	10 (11.5)	17 (11.3)	
Indian	22 (9.2)	7 (8.1)	15 (9.9)	
Others	6 (2.5)	2 (2.3)	4 (2.7)	
Smoking	53 (22.4)	17 (19.5)	36 (24.0)	0.427
Alcohol consumption	28 (11.9)	9 (10.5)	19 (12.7)	0.615
AHI	28.7 (14.4 – 59.0)	30.0 (13.2 – 59.3)	27.1 (14.8 – 59.0)	1.000
LSAT	79.0 (70.0 – 86.0)	79.0 (69.0 – 84.0)	79.5 (71.0 – 86.0)	0.412
Surgery site				
Nose	162 (68.1)	66 (75.9)	96 (63.6)	0.050
Tongue	81 (34.0)	9 (10.3)	72 (47.7)	< 0.001
Palate	162 (68.1)	12 (12.8)	150 (99.3)	< 0.001
Pain reported	125 (53.0)	36 (41.9)	89 (59.3)	0.010
Complications, n = 31				
Early	3 (1.3)	1 (1.1)	2 (1.3)	0.488
Late	28 (11.8)	5 (5.7)	23 (15.2)	
Minor	30 (12.6)	6 (6.9)	24 (15.9)	1.000
Major	1 (0.4)	0 (0.0)	1 (0.7)	

AHI: Apnoea-hypopnoea index; BMI: Body mass index; DBP: Diastolic blood pressure; LSAT: Lowest oxygen saturation during polysomnogram; SBP: Systolic blood pressure; SD: Standard deviation

*Compares single and multilevel surgery, and was calculated by simple t-test for continuous variable or chi-squared test/Fisher's Exact test for categorical variables. A value of P <0.05 was considered statistically significant.

Continuous variables (age, BMI, SBP and DBP) were presented as mean standard deviation (SD) and apnoea-hypopnoea index (AHI) and lowest oxygen saturation during polysomnogram (LSAT) were presented in median (interquartile range).

Categorical variables (gender, race, smoking, alcohol consumption, surgical site, pain and complications) were presented in counts (percentages).

The SLS and MLS groups were further analysed in their nasal, palatal and tongue subgroups (Table 2). After adjusting for the same confounders, there was no statistical difference in complication rate between Group N (SLS) and Groups NP or NT (2-level MLS) and between Group NPT (3-level MLS) and Groups NP or NT (2-level MLS). There was an almost statistically significant difference between Group N (SLS) and Group NPT (3-level MLS, adjusted OR 4.51, P = 0.059).

There was no statistical difference in complication rate between Group NPT (3-level MLS) and Groups NP or PT (2-level MLS, adjusted OR 2.05, P = 0.275). We could not compare Group P (SLS) with NP, PT or NPT as there was no complication in Group P.

There was no statistical difference in complication rate between Group T (SLS) and Groups NT or PT (2-level MLS), between Group T (SLS) and Group NPT (3-level MLS), and between Group NPT (3-level MLS) and Groups NT or PT (2-level MLS).

There was more postoperative pain in the MLS group than the SLS group; 41.9% of SLS patients had pain while 59.3% of MLS patients had pain (adjusted OR 2.09, P = 0.008) (Tables 1 and 3).

Thirty of the 238 patients (12.6%) had complications, of which 1 patient had early and late complications (counted as 2 complications). Six underwent SLS, 20 underwent MLS of 2 levels and 4 underwent MLS of 3 levels. The subgroup complication rate was 7.6% for Group N, 0% for

Table 2. Association between Postoperative Complication and Surgery on Patients with Obstructive Sleep Apnoea

	Adjusted Odds Ratio	95% Confidence Interval	*P* Value
Multilevel vs single-level, n = 204	2.76	0.99 – 7.73	0.053
Multilevel vs SLS nose, n = 137	2.35	0.70 – 7.86	0.166
Multilevel vs SLS tongue, n = 71	1.19	0.12 – 12.33	0.882
Nose, n = 137			
NP or NT vs N	1.89	0.53 – 6.77	0.329
NPT vs N	4.51	0.94 – 21.54	0.059
NPT vs NP or NT	2.39	0.58 – 9.76	0.226
Palate, n = 127			
NPT vs NP or PT	2.05	0.57 – 7.43	0.275
Tongue, n = 71			
NT or PT vs T	0.96	0.09 – 10.49	0.972
NPT vs T	1.98	0.16 – 25.04	0.596
NPT vs NT or PT	2.07	0.46 – 9.36	0.345

N: Single-level nasal surgery, NP: Nasal and palatal surgery, NT: Nasal and tongue surgery, NPT: Nasal, palatal and tongue surgery, PT: Palatal and tongue surgery, SLS: Single-level surgery; T: Single-level tongue surgery

*Adjusted for apnoea-hypopnoea index, age, gender, systolic blood pressure, lowest oxygen saturation during polysomnogram, smoking, drinking. None of them were statistically significant in the multivariable models.

Table 3. Association between Pain and Surgery on Patients with Obstructive Sleep Apnoea (n = 234)

	Adjusted Odds Ratio	95% Confidence Interval	*P* Value
Multilevel vs. single-level surgery	2.09	1.21 – 3.62	0.008
Gender (female vs male)	0.54	0.27 – 1.07	0.079
Smoking (yes vs no)	0.62	0.32 – 1.19	0.149
Drinking (yes vs no)	1.20	0.52 – 2.74	0.668

Group P, 11.1% for Group T, 13.9% for Group NP, 0% for Group NT, 18.2% for Group PT and 25% for Group NPT.

There were 3 early and 28 late complications. Thirty complications were minor and 1 was major. The main complication was bleeding (27 cases, 87.1%). The other 4 complications consisted of 2 infections, 1 flap dehiscence and 1 case of dehydration due to poor oral intake. Fifteen complications resolved following conservative management. Six required intervention in the ward or clinic. Of the 10 who returned to the operating theatre, there were 6 post-tonsillectomy bleeds, 1 post-turbinoplasty bleed, 1 post-TORS bleed, 1 postmidline glossectomy bleed and 1 post-GTA infection. The major complication occurred in a patient who resumed smoking immediately after TORS SLS. He had intermittent bleeding from the tongue base. Examination under anaesthesia and haemostasis was uneventful. However, while changing the orotracheal tube to a nasotracheal tube intraoperatively, he experienced transient desaturation, therefore needing intubation and observation in the intensive care unit for presumed aspiration. He was extubated successfully the next day and discharged well with no permanent sequelae. There was no airway complication nor mortality.

Discussion

The overall complication rate is 12.6%, which is within the range quoted by other studies (7.1 to 14.6%).[3,7,8] If only patients requiring intervention were considered, the complication rate would be 6.7%. Patients undergoing MLS may have a higher possibility of developing complications compared to patients undergoing SLS (adjusted OR 2.76), but this is not of statistical significance. More patients undergoing MLS had pain compared to patients undergoing SLS.

Complication Rate

There are 2 main reasons for a relatively high complication rate; firstly, complications occurring up to the first 30 postoperative days were included. In contrast, other studies had shorter follow-up periods. Secondly, our inclusion criteria encompassed a wide range of minor complaints, such as epistaxis which resolved with digital pressure.

Multilevel versus Single-level Surgery – Complication Rates

The literature comparing complication rates in SLS and MLS is diverse, with different patient selection criteria, different definitions of single and multi-level surgery and only specific types of surgery were analysed. There were contradicting results. Kezirian et al[9] found concurrent uvulopalatopharyngoplasty (UPPP) and nasal surgery to be safe, while simultaneous UPPP and non-nasal upper airway

procedures were significantly associated with higher risk of serious complications. A review of 347 OSA patients showed higher complications with multiple nasal procedures (septoplasty and inferior turbinate reduction) and concurrent UPPP.[10] In 91 OSA patients who underwent nasal and palatal surgery in a synchronous or staged fashion, there were 3 complications in the synchronous surgery group and 1 complication in the staged surgery group. The authors concluded the complication rate was comparable in both groups and synchronous surgery was safe, but no statistical analysis was performed.[11]

The aim of our study was to include a wide repertoire of surgical procedures, including a significant number of TORS and GTA patients and a study of our surgical practice for OSA. This is because there has been an increasing number of such surgeries being performed in recent years and comparative information on complication rates should be obtained. After adjusting for confounders, our data shows that the difference in complication rate between SLS and MLS is near statistical significance ($P = 0.053$). Upon further analysis of the data in subgroups, the difference between Group N and Group NPT was close to statistical significance as well ($P = 0.059$). Surgery involving the other levels of obstruction (palate and tongue), as well as comparing NT and NP with NPT had similar complication rates.

Interpreting the data in a straightforward manner is difficult because it is close to statistical significance. Concurrent MLS is mostly safe for OSA patients, especially if they are undergoing palate and tongue surgery, nose and palate surgery, or nose and tongue surgery. Concurrent surgery in this group of patients avoids higher complications while reaping the benefit of single anaesthesia, reduced hospitalisation, shorter postoperative recovery time, and decreased time away from work.[4]

While it seems advisable for a patient who requires 3-level surgery to undergo nasal surgery separately from palate and tongue surgery because NPT vs N is almost statistically significant, the converse is not true. A patient who is undergoing both palate and tongue surgery has the same complication rate as a patient undergoing 3-level surgery. In view of this, and that the overall complication rate is low with minor complications, it is still reasonable for a patient needing 3-level surgery to have concurrent surgery of all the levels in the same sitting after being adequately counselled on the risks and possible alternatives. Further study may be able to yield data to suggest whether there is a true statistical difference between these 2 groups.

Multilevel versus Single-level Surgery – Postoperative Pain

MLS results in a larger proportion of patients with postoperative pain than SLS. Logically, the presence of pain is higher in the group that had undergone more levels of surgery as they had more operations and surgical wounds; our results confirm this. Importantly, the pain scores were obtained with analgesia on board. Therefore, we recommend regular review of VAS pain scores and analgesia in MLS patients. The managing team should consider starting postoperative MLS patients immediately on a cocktail of analgesics. Our current regime includes a combination of paracetamol and COX-2 inhibitor. Patients undergoing palatal and tongue-base surgeries are also given topical pain relief in the form of lozenges and sprays. If pain control is poor or if the patient is allergic to either medication, an opioid is sometimes prescribed, with particular attention paid to respiratory rate and oxygen saturation.

Limitations and Areas of Improvement

We acknowledge that this study has limitations. Firstly, the number of patients in the 3-level surgery group is relatively small compared with those in the 2-level and SLS groups. This retrospective study can be improved by increasing the period of study to recruit more patients in the SLS and 3-level surgery groups, thereby reducing the disparity in number of patients between the groups. A larger number of patients may be able to give more information on whether there is truly a difference in the complication rate between the single-level nasal surgery group and the 3-level surgery group. Alternatively, conducting a prospective study with the same objectives will enable the recruitment of an equal number of patients in each group.

Secondly, long-term complications were not captured in our study. A longer follow-up period, or a prospective study with longer follow-up will enable us to capture this data.

Thirdly, a wide variety of procedures were performed in our patients, ranging from minor procedures such as radiofrequency of the tongue-base to major procedures such as midline glossectomy and GTA. Our study analyses the levels of surgery but does not differentiate between minor or major surgeries. As major procedures tend to have higher complication rates than minor procedures, a matched study may help analyse surgery-specific outcomes between single and multilevel surgery groups.

In addition, in our study, we were unable to compare single-level palatal surgery with multilevel palatal surgery because none of the patients in the single-level palatal surgery group had complications. Increasing the cohort size has a higher likelihood of a single palatal surgery patient with a complication and will allow us to perform this comparison.

Lastly, none of the patients defaulted during the follow-up period. However, the complications detected were based on hospital records. Some patients with complications may not be captured if they presented to another clinic or hospital. To prevent this, we advised our patients—prior

to discharge—to return to our hospital if they experienced difficulties or complications. Another solution would be to have a follow-up teleconsult with each patient after 30 days to capture out-of-hospital treatments.

Conclusion

Our study has shown single-level surgery and multilevel surgery to have similar complication rates, although single-level nasal surgery may have a lower complication rate than 3-level multilevel surgery. As the overall complication rate remains low, even for 3-level surgery, patients may still proceed with multilevel surgery following adequate counselling and informed consent. Patients can safely undergo concurrent multilevel surgery if they are undergoing palate and tongue surgery, nose and palate surgery, or nose and tongue surgery. There is more postoperative pain in the multilevel group of patients and they may require more analgesia titration than single-level surgery patients.

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Commentary

General Practitioner's Attitudes and Confidence in Managing Patients with Dementia in Singapore

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Abstract

The number of people living with dementia is increasing globally as a result of an ageing population. General practitioners (GPs), as the front-line care providers in communities, are important stakeholders in the system of care for people with dementia. This commentary describes a study conducted to understand GPs' attitudes and self-perceived competencies when dealing with patients with dementia and their caregivers in Singapore. A set of study information sheet and survey questionnaires were mailed to selected GP clinics in Singapore. The survey, comprising the "GP Attitudes and Competencies Towards Dementia" questionnaire, was administered. A total of 400 GPs returned the survey, giving the study a response rate of 52.3%. About 74% of the GPs (n = 296) were seeing dementia patients in their clinics. Almost all the GPs strongly agreed or agreed that early recognition of dementia served the welfare of the patients (n = 385; 96%) and their relatives (n = 387; 97%). About half (51.5%) of the respondents strongly agreed or agreed that they felt confident carrying out an early diagnosis of dementia. Factor analysis of the questionnaire revealed 4 factors representing "benefits of early diagnosis and treatment of patients with dementia", "confidence in dealing with patients and caregiver of dementia", "negative perceptions towards dementia care" and "training needs". GPs in Singapore held a generally positive attitude towards the need for early dementia diagnosis but were not equally confident or comfortable about making the diagnosis themselves and communicating with and managing patients with dementia in the primary care setting. Dementia education and training should therefore be a critical first step in equipping GPs for dementia care in Singapore. Shared care teams could further help build up GPs' knowledge, confidence and comfort in managing patients with dementia.

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Key words: Communication, Diagnosis, Management

Dementia is a syndrome characterised by a deterioration in memory, thinking, behaviour and the ability to perform daily activities.[1] As it is a major cause of disability and dependence, it not only affects the person with dementia, but also the carers, the wider community and other health and social providers. Studies suggest that the age standardised prevalence of dementia for those aged 60 years and above varies within 5% to 7% in most world regions[2] while in terms of absolute numbers, it is estimated that worldwide, 47.5 million people have dementia.[1] The worldwide cost of dementia, including medical expenditure and informal care, was estimated at US$604 billion in 2010.[3]

Early diagnosis of dementia is important as this allows people with dementia and their family to engage with support services and plan for the future. With the increasing prevalence of dementia, healthcare systems are shifting the care of dementia patients to primary care[4,5] and a majority of caregivers regard the general practitioner (GP) as the key person in managing care for dementia patients.[6] Thus, GPs are important stakeholders in the system of care for

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people with dementia. Their roles include early identification and diagnosis of dementia, providing information about the diagnosis, prognosis and services available in the community as well as referring the person for specialist care when appropriate.

However, the onset of dementia is often insidious and difficult to diagnose in the early stages. Research has shown that the inability of GPs to detect dementia was due to diagnostic uncertainties, concerns about their own clinical competencies, stigma, or a sense of therapeutic nihilism.[7] Boustani et al[8,9] estimated that in the United States (US), less than a third of patients with dementia were recognised by the primary care system as having dementia. The findings have been similar from studies conducted elsewhere in the world.[10,11]

Singapore is a multiethnic, developed country in Southeast Asia, with a resident population of 3.9 million people, consisting predominantly of Chinese (74.3%), Malays (13.4%) and Indians (9.1%).[12] Private general medical practitioner clinics provide 80% of the primary healthcare services in Singapore, while doctors in government polyclinics provide the remaining 20%.[13] Polyclinics provide a range of subsidised services both for acute and chronic medical conditions including outpatient medical care, screenings and immunisation, and x-ray and laboratory services, allowing them to be a one-stop health centre for the community.[13] GP practices are usually located in neighbourhoods, enabling patients and their caregivers to access care beyond regular working hours and even during weekends. These clinics comprise of solo, small group or large healthcare group practices. They usually do not possess onsite laboratory and other investigative facilities, and are not subsidised by the government. Secondary and tertiary care is provided by the national specialty centres and the public as well as private hospitals. The main difference between the polyclinics and GP clinics is that patient care is shared between all the doctors in the polyclinic and a patient can be assigned to any doctor in the polyclinic; in contrast, patients who go to a GP clinic would usually see a particular doctor.

A recent study in Singapore—the Well-being of the Singapore Elderly (WiSE)—established the prevalence of dementia to be 10% among Singapore residents aged 60 years and above.[14] However, there was a very low rate of diagnosis of dementia being made by doctors.[15] In all, 3% of the respondents in the WiSE study were diagnosed to have dementia by medical practitioners, of which 11.5% were diagnosed by GPs. The explanation for this could not be established by the study.[15]

A number of polyclinics comanage patients with mild to moderate dementia, with specialists from tertiary hospitals. These collaborative partnerships allow for training and capability building among the community-based clinicians, enabling better care for patients with dementia. The Ministry of Health, Singapore (MOH) launched its first application call in April 2017 for GPs to join the Primary Care Networks (PCNs) scheme. Under this scheme, GPs will be able to manage their patient's healthcare needs more holistically by leveraging on a team-based care model. This study is thus timely in gaining an understanding of the attitudes of GPs towards diagnosing and managing dementia, and a critical first step to the planning and development of primary care services for dementia. Unfortunately, relatively little empirical work has been done in Singapore that examines the views and perceptions of GPs in providing care for people with dementia. This study was therefore aimed at understanding GPs' attitudes and self-perceived competencies when dealing with patients with dementia and their caregivers.

Materials and Methods

GPs were recruited from a list of GP clinics (obtained from MOH) located in the whole of Singapore. The government-run polyclinics were excluded from the survey. Inclusion criteria for the study included all GPs working in clinics that were operational at the point of survey. Excluded were doctors in specialist clinics and those who were serving a 'defined' population such as staff of a specific company etc. The sample size was calculated using a single proportion formula based on the results of the study by Pathak and Montgomery[16] which found that about 46.8% of GPs reported themselves as being "somewhat confident towards the diagnosis of dementia". The sample size was thus calculated to be 383 GPs to achieve 5% precision at the 95% confidence interval. Assuming that 4% of questionnaires may have missing data, the overall sample size was calculated as 400 participants.

A cover letter along with the study information sheet and the survey questionnaire were mailed to the selected GP clinics. Participation was anonymous and the information sheet described the intent and details of the study. The cover letter provided a link to an online survey which was designed using QuestionPro. Respondents could choose to complete either the online or the paper-based survey and mail it back using the return envelope provided. The survey was estimated to take about 20 minutes to complete and this was stated in the information sheet. Each GP was assigned a unique participant identity (ID) to avoid duplication. The study was approved by the relevant ethics committee (National Healthcare Domain Specific Review Board). Consent was implied by the completion and return of the questionnaire. Respondents were each reimbursed with a voucher amounting to S$40 as an inconvenience fee sent via registered mail. The voucher was sent to the address

used for mailing the invitation letter, unless respondents indicated an alternate address at which they preferred to receive the voucher. The administration process was handled by staff who were not part of the research team and hence, confidentiality was maintained at all times.

The respondents were administered the following questionnaires:

(i) Sociodemographic questionnaire: This included questions on age, gender, ethnicity, qualifications and other relevant sociodemographic data.

(ii) Questionnaires assessing attitudes and competencies were developed by adapting questions from the instrument developed by Pentzek et al[17] and Turner et al[18] as well as based on input from local experts in dementia and a GP.

The questionnaire that assessed attitudes towards the diagnosis, management and outcomes of those with dementia comprised 11 questions which were related to the GPs' own personal views on dementia. The questions were intended to measure attitudes towards early recognition, treatment options and outcomes. Answers were measured on a 4-point Likert scale ranging from 1 (strongly agree) to 4 (strongly disagree).

The questionnaire that assessed self-perceived competencies in dealing with and managing patients with dementia (and their caregivers) comprised 9 questions. The questions were intended to measure how confident they were in diagnosing, informing patients and caregivers of the diagnosis and managing patients with dementia. Two additional questions were asked to find out whether they would feel more confident in managing patients if treatment guidelines or specific training were provided to them. Answers were on a 4-point Likert scale ranging from 1 (strongly agree) to 4 (strongly disagree).

Statistical Analysis

Descriptive analysis was conducted for the sociodemographic variables. Mean and standard deviation (SD) were presented for continuous variables while frequencies and percentages were presented for categorical variables. The factor structure was explored using exploratory factor analysis (EFA). EFA was performed using Mplus version 7.0 with the mean- and variance-adjusted weighted least square estimator, which has been recommended for the analysis of ordered categorical data.[19] To allow the correlation between factors, oblique geomin rotation was used, and the factor loading was set at 0.3 as a cutoff. Prior to EFA, we used multiple criteria including eigenvalue >1.0, scree plot, pattern of loadings on each item (e.g. cross-loading, consistently lowest loading across different models), and the interpretability to determine number of factors and items that should be retained. A parallel analysis (PA) which is arguably the current golden rule, was also used to determine how many factors should be extracted for EFA.[20,21] The PA was carried out using R software version 3.1.3. The internal reliability (Cronbach's alpha) for each factor was calculated as well. Subscores were calculated by summing the scores of the respective items in each factor, with lower scores reflecting higher level of GPs' attitudes and self-perceived competencies when dealing with patients with dementia and their caregivers. Multivariate linear regression was conducted using SAS software version 9.4 to examine the sociodemographic correlates (i.e. age, gender, ethnicity, education level, number of years spent in general practice, and type of practice for each of the identified factor scores [dependent variables]). A two-sided *P* value below 0.05 was considered as statistically significant.

A total of 1009 clinics were approached; 241 clinics were ineligible for various reasons such as they no longer provided general care but were specialist clinics. In addition, some clinics had shut down and others were in sites that were accessible only to employees of a specific company. A total of 400 respondents completed the survey, giving the study a response rate of 52.1% (Fig. 1). One of the respondents was excluded from the final analysis as there was extensive missing data (more than 50% answers were missing). Thus in all, 399 GPs were included in the final analyses. The sample comprised 27.8% female and 72.2% male respondents. The majority of the respondents were aged between 40 to 59 years (64.1%), of Chinese ethnicity (92.2%), with 20.3 (mean) years (SD = 10.7) of service

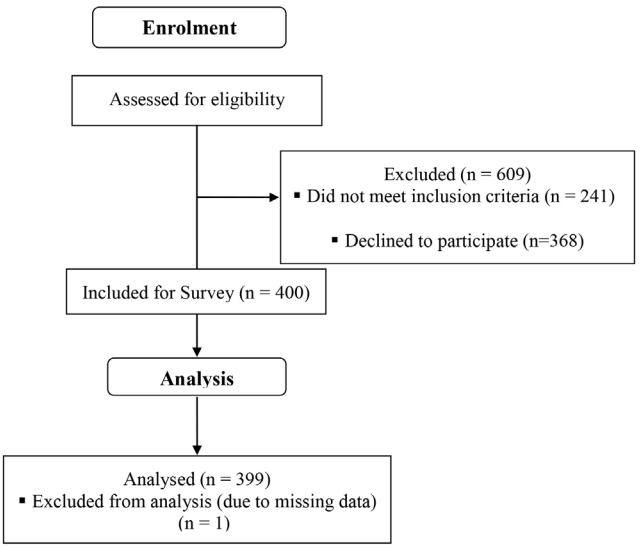

Fig. 1. Flow diagram for recruitment of general practitioners.

(Table 1). About 74.2% of the GPs (n = 296) were seeing dementia patients in their clinics.

GPs' Attitudes to Dementia Care

Responses to the items of the attitudes scale are shown in Table 2. Almost all the GPs strongly agreed or agreed that early recognition of dementia served the welfare of the patients (n = 385; 97.0%) and their relatives (n = 387; 97.5%). Slightly less than three-fourths of the GPs strongly agreed or agreed (n = 275; 70.2%) that antidementia drugs had a positive influence on the course of the disease. Almost all of the GPs strongly agreed or agreed (n = 389; 98%) that much could be done to improve the quality of life of patients with dementia and their carers. Despite strongly disagreeing or disagreeing that "the primary care has limited role to play in the care of people with dementia" (n = 313; 79%), more than half of the GPs in this sample felt that "managing dementia is usually more frustrating than rewarding" (n = 251; 64%) and that "patients with dementia can be a drain on resources with little positive outcome" (n = 225; 57.1%).

Table 1. Sociodemographic Correlates of the Sample of GPs Responding to the Survey

	n*	%
Age group (years)		
28 – 39	68	17.09
40 – 59	255	64.07
60 – 83	75	18.84
Age (mean, SD)	50.07	10.88
Education		
MBBS	224	56.14
MBBS and MMed	67	16.79
MBBS and postgraduate diploma	72	18.05
Others	36	9.02
Gender		
Male	285	72.15
Female	110	27.85
Race		
Chinese	364	92.15
Malay	7	1.77
Indian	16	4.05
Others	8	2.03
Practice		
Solo	233	58.54
Group	165	41.46
Number of years in general practice (mean, SD) (ranged from 1 to 50 years)	20.33	10.73

GP: General practitioner; MBBS: Bachelor of Medicine and Bachelor of Surgery; MMed: Master of Medicine
*Not all 399 respondents answered all the questions.

GPs' Confidence Concerning Diagnosis/Management

Responses for aspects on self-perceived competencies in dealing and managing patients with dementia and their caregivers are shown in Table 2. Only about half of the respondents strongly agreed or agreed that they felt confident carrying out an early diagnosis of dementia (item 12; 51.5%), and about half of the respondents (51.5%) did not feel comfortable about diagnosing a patient with dementia (item 16). In addition, the majority of the respondents were also not confident with the pharmacological treatment of dementia (item 14; 77.1%).

Factor Structure of the GP Attitudes and Competencies towards Dementia Questionnaire

Table 2 shows the item endorsements of the scale. The results of the initial eigenvalues and scree plot suggested that 4-, 5-, or 6-factor models were all potential solutions. Further simulation analysis using the PA indicated that a 4-factor model should be extracted from EFA analysis. Inspection of pattern of loadings on each item (e.g. cross-loading, consistently lowest loading across different models) and the interpretability of each item within extracted factors suggested the 4-factor model to provide the best solution. The model also fitted the data well (root mean square error of approximation [RMSEA] = 0.096, comparative fit index [CFI] = 0.974; Tucker-Lewis Index [TLI] = 0.960), although there was a clear need for improvement in RMSEA index.

Table 2. Item Endorsement of GP Attitudes and Competencies towards Dementia Questionnaire

Item		Agree/Strongly Agree*		Disagree/Strongly Disagree*	
		n	%	n	%
1	The early recognition of dementia usually serves the welfare of the patient	385	97.0	12	3.0
2	The early recognition of dementia usually serves the welfare of the patient's relatives	387	97.5	10	2.5
3	The present treatment option with antidementia drugs usually have a positive influence on the course of the disease	275	70.2	117	29.8
4	Much can be done to improve the quality of life of demented patients	389	98.0	8	2.0

GP: General practitioner
*Not all 399 respondents answered all the questions.

Table 2. Item Endorsement of GP Attitudes and Competencies towards Dementia Questionnaire (Cont'd)

Item		Agree/Strongly Agree*		Disagree/Strongly Disagree*	
		n	%	n	%
5	Much can be done to improve the quality of life of carers of demented patients	389	98.0	8	2.0
6	A cognitive examination demands specialist expertise	209	52.8	187	47.2
7	All patients suspected of dementia should undergo a diagnostic evaluation	379	95.7	17	4.3
8	Managing dementia is usually more frustrating than rewarding	251	64.0	141	36.0
9	Patients with dementia can be a drain on resources with little positive outcome	225	57.1	169	42.9
10	There is little point in referring families to services as they do not want to use them	81	20.5	314	79.5
11	The primary care has limited role to play in the care of people with dementia	83	21.0	313	79.0
12	I usually feel confident carrying out an early diagnosis of dementia	202	51.5	190	48.5
13	I usually feel confident with the provision of care for dementia patients and their caregivers	152	38.8	240	61.2
14	I usually feel confident with the pharmacological treatment of dementia	90	22.9	303	77.1
15	I usually feel confident with the organisation of social support for patients and their relatives (e.g. support groups, ambulatory care)	172	43.9	220	56.1
16	I usually feel comfortable about diagnosing a patient with dementia	191	48.5	203	51.5
17	I usually feel comfortable informing dementia patients about their diagnosis	196	50.0	196	50.0
18	I usually feel comfortable informing the relatives about the patient's diagnosis	238	60.6	155	39.4
19	I usually feel comfortable about managing a patient with dementia	138	35.1	255	64.9
20	I usually feel confident responding to coexisting behavioural problem	143	36.3	251	63.7
21	I would feel more confident about managing patients with dementia if treatment guidelines for the diagnosis and treatment of dementia were made available to me	358	91.1	35	8.9
22	I would feel more confident about communicating with patients and caregivers if I was provided training on how to deal and speak with patients with dementia and their relatives	345	88.2	46	11.8

GP: General practitioner
*Not all 399 respondents answered all the questions.

Based on these considerations, we found that the 4-factor model fit the data best. Factor loadings from the 4-factor model are shown in Table 3. The first factor represented "benefits of early diagnosis and treatment of patients with dementia" as defined by 6 items (items 1-5 and 7). The second factor was labelled as "confidence in dealing with patients and caregiver of dementia" as defined by 11 items (items 6 and 11-20). The third factor was labelled as "negative perceptions towards dementia care" (3 items) (items 8-10) while the last factor was labelled as "training needs", as measured by 2 items (items 21 and 22). The Cronbach alpha for the 4 factors ranged from 0.64 to 0.89.

Sociodemographic Correlates

Table 4 shows the correlates of the 4-factor scores. Multivariate linear regression analyses results revealed that male GPs and those who practised without partners (i.e. solo practice) were associated with significantly higher scores i.e. lower agreement with "benefits of early diagnosis and treatment of patients with dementia". GPs with both a Bachelor of Medicine and Bachelor of Surgery (MBBS) and Master of Medicine degrees (MMed, a postgraduate academic degree awarded in Singapore) were significantly associated with higher "confidence in dealing with patients and caregivers of dementia" as compared to those with only a MBBS.

Discussion

The current research explored Singapore GPs' attitudes and self-perceived competencies towards dementia diagnosis, management and treatment. This study showed that majority of the GPs felt positively towards the early diagnosis of dementia, endorsed the need for improving the quality of life of patients and carers, and preferred more training to better equip themselves in the management of dementia. Furthermore, the study demonstrated the psychometric properties of the 22-item attitudes and self-reported competencies of GPs towards dementia care questionnaire and proposed a 4-factor structure in dealing and managing patients with dementia, namely, "benefits of early diagnosis and treatment of patients with dementia", "confidence in dealing with patients and caregiver of dementia", "negative perceptions towards dementia care", and "training needs".

Table 3. Factor Structure of GP Attitudes and Competencies towards Dementia Questionnaire

Item		Benefits of Early Diagnosis and Treatment of Patients with Dementia	Confidence in Dealing with Patients and Caregiver of Dementia	Negative Perceptions towards Dementia Care	Training Needs
1	The early recognition of dementia usually serves the welfare of the patient	**0.787**	0.256	-0.111	0.019
2	The early recognition of dementia usually serves the welfare of the patient's relatives	**0.750**	0.277	-0.109	-0.001
3	The present treatment option with antidementia drugs usually have a positive influence on the course of the disease	**0.557**	0.203	-0.058	-0.164
4	Much can be done to improve the quality of life of demented patients	**0.828**	0.294	0.067	-0.011
5	Much can be done to improve the quality of life of carers of demented patients	**0.716**	0.223	0.091	0.059
6*	A cognitive examination demands specialist expertise	0.121	**-0.460**	0.194	-0.181
7	All patients suspected of dementia should undergo a diagnostic evaluation	**0.444**	-0.063	0.068	0.096
8	Managing dementia is usually more frustrating than rewarding	0.178	-0.338	**0.738**	0.014
9	Patients with dementia can be a drain on resources with little positive outcome	-0.046	-0.177	**0.780**	0.024
10	There is little point in referring families to services as they do not want to use them	-0.084	-0.089	**0.441**	-0.157
11*	The primary care has limited role to play in the care of people with dementia	-0.119	**-0.427**	0.261	-0.232
12	I usually feel confident carrying out an early diagnosis of dementia	-0.018	**0.787**	0.047	-0.057
13	I usually feel confident with the provision of care for dementia patients and their caregivers	0.028	**0.903**	0.08	-0.141
14	I usually feel confident with the pharmacological treatment of dementia	-0.028	**0.736**	0.025	-0.106
15	I usually feel confident with the organisation of social support for patients and their relatives (e.g. support groups, ambulatory care)	0.085	**0.583**	0.031	-0.174
16	I usually feel comfortable about diagnosing a patient with dementia	-0.075	**0.853**	0.085	0.063
17	I usually feel comfortable informing dementia patients about their diagnosis	0.059	**0.849**	0.071	0.028
18	I usually feel comfortable informing the relatives about the patient's diagnosis	-0.013	**0.837**	0.067	0.089
19	I usually feel comfortable about managing a patient with dementia	-0.062	**0.903**	-0.065	-0.04
20	I usually feel confident responding to coexisting behaviour problem	-0.07	**0.737**	-0.017	-0.05
21	I would feel more confident about managing patients with dementia if treatment guidelines for the diagnosis and treatment of dementia were made available to me	-0.023	0.297	-0.039	**0.885**
22	I would feel more confident about communicating with patients and caregivers if I was provided training on how to deal and speak with patients with dementia and their relatives	0.061	0.173	0.057	**0.792**
	Fit indices				
	chi-squared (degree of freedom) = 697.263 (149)				
	RMSEA = 0.096				
	CFI = 0.974				
	TLI = 0.959				
	SRMR = 0.063				
	Cronbach's alpha	0.786	0.895	0.634	0.850

GP: General practitioner; CFI: Comparative fit index; RMSEA: Root mean square error of approximation; SRMR: Standardised root mean squared residual; TLI: Tucker-Lewis Index

*Items 6 and 11 were reverse scored.

Table 4. Sociodemographic Correlates of the Factors of GP Attitudes and Competencies towards Dementia Questionnaire

Parameter	Benefits of Early Diagnosis and Treatment of Patients with Dementia			Confidence in Dealing with Patients and Caregiver of Dementia			Negative Perceptions towards Dementia Care			Training		
	Beta	95% CI	*P* Value	Beta	95% CI	*P* Value	Beta	95% CI	*P* Value	Beta	95% CI	*P* Value
Age group												
28 – 39	0.09	-1.20 to 1.38	0.895	1.89	-1.01 to 4.79	0.201	0.32	-0.53 to 1.18	0.458	0.08	-0.53 to 0.69	0.789
40 – 59	0.20	-0.62 to 1.02	0.631	0.49	-1.35 to 2.32	0.604	0.27	-0.28 to 0.81	0.336	0.15	-0.24 to 0.54	0.451
60 – 83	Reference			Reference			Reference			Reference		
Gender												
Male	0.55	0.03 to 1.07	0.039	-0.63	-1.81 to 0.54	0.291	-0.29	-0.64 to 0.06	0.106	0.16	-0.08 to 0.41	0.193
Female	Reference			Reference			Reference			Reference		
Ethnicity												
Malay/ Indian/ Others	0.30	-0.55 to 1.15	0.488	-0.98	-2.89 to 0.93	0.313	0.47	-0.10 to 1.05	0.106	0.24	-0.15 to 0.64	0.230
Chinese	Reference			Reference			Reference			Reference		
Education												
Others	0.57	-0.28 to 1.42	0.189	-1.80	-3.71 to 0.11	0.065	0.21	-0.36 to 0.78	0.463	0.10	-0.30 to 0.50	0.627
MBBS and postgrad diploma	-0.46	-1.10 to 0.17	0.153	-1.08	-2.51 to 0.34	0.136	0.24	-0.18 to 0.66	0.263	-0.15	-0.46 to 0.15	0.312
MBBS and MMed	-0.08	-0.74 to 0.58	0.812	-1.73	-3.21 to -0.25	0.022	-0.01	-0.45 to 0.43	0.962	-0.14	-0.45 to 0.17	0.361
MBBS	Reference			Reference			Reference			Reference		
Number of years as GP	0.02	-0.02 to 0.05	0.356	0.04	-0.04 to 0.12	0.369	0.00	-0.03 to 0.02	0.865	0.01	-0.01 to 0.03	0.187
Type of practice												
Solo	0.52	0.03 to 1.00	0.036	0.16	-0.93 to 1.25	0.774	-0.15	-0.47 to 0.17	0.365	0.08	-0.15 to 0.31	0.478
Group	Reference			Reference			Reference			Reference		

CI: Confidence interval; GP: General practitioner; MBBS: Bachelor of Medicine and Bachelor of Surgery; MMed: Master of Medicine

Factor 1: Benefits of Early Diagnosis and Treatment of Patients with Dementia

The majority of the GPs agreed with the statements reflecting the benefits of early diagnosis and treatment of patients with dementia. Responses on the subscale showed that GPs strongly agreed with the need for early recognition of dementia, diagnostic evaluation, and that much could be done to improve the quality of life of patients with dementia and their carers. The item which had the lowest agreement was whether the present treatment options with antidementia drugs had a positive influence on the course of the disease, with only 70.5% agreeing with the item. Currently, both cholinesterase inhibitors (ChEIs; including rivastigmine, donepezil, and galantamine) and the N-methyl D-aspartate receptor antagonist memantine, are available in Singapore for the treatment of dementia. A review assessing the effects of ChEIs on people with Alzheimer's disease (AD) has shown small but positive treatment effects on cognitive function, activities of daily living and behaviour.[22,23] Trials for memantine similarly show benefits in terms of improvement in cognition and clinical impression among patients with AD.[24] However, concerns remain about whether the magnitude of the benefits outweighs the risks of medication.[24,25] A systematic review of the clinical- and cost-effectiveness of these drugs concluded that the results of the cost-effectiveness were uncertain and very sensitive to change and thus the implications for service provision were not very clear.[23] This ambiguity could have led to the lack of consensus about the best practice for management and to differences in clinical guidelines for treatment across countries, and thus, may be one of the reasons that GPs did not strongly endorse a positive effect of these drugs on dementia. Given the available evidence, it is important that GPs make care decisions during consultation with patients and their families based on realistic expectations of the benefits, side-effects and costs of antidementia treatment.

Factor 2: Confidence in Dealing with Dementia Patients and Their Caregivers

Our study indicates that only about half of the GPs were comfortable and confident about diagnosing a person with dementia and informing them and their caregivers of the diagnosis. Even fewer felt confident or comfortable about managing patients with dementia. These findings are similar to that of another study from Scotland and London where only one-third of the GPs expressed confidence in their diagnostic skills while two-thirds did not feel confident in the management of behaviour and other problems in dementia.[18]

Studies suggest that older adults preferred knowing about their dementia diagnosis and while some felt upset with the diagnosis, they did not regret knowing it.[26] Evidence also suggests that there were considerable advantages to the early diagnosis of dementia. It allowed the person with dementia (PWD) and relatives the opportunity to make practical and financial decisions.[27] It offered a chance for the PWD and their family to come to terms with the diagnosis,[28] and caregivers felt that they would have been more patient and understanding of the person's behaviour if they had received a diagnosis earlier.[29]

The reluctance of GPs to make and communicate the diagnosis may reflect their lack of training as well as their concerns about limited therapeutic options and the propensity of the diagnosis to cause distress to both the patient and their relatives. Studies have found that the lack of confidence and reservations towards informing patients and caregivers could stem from the diagnostic uncertainty in the early stages, patient denial,[30,31] lack of proper instruments available for diagnosis, negative view of dementia by family members and society, overlapping features with other neurological and psychiatric conditions,[16] and the belief that a diagnosis of dementia might conversely limit access to medical services because of the associated stigma and lack of dementia-specific services.[31] Although many of the GPs did not express confidence in diagnosing and managing patients with dementia, close to 80.0% of the GPs agreed that primary care played an important role in the care of people with dementia. It was also interesting to note that the majority of GPs were not confident with the pharmacological treatment of dementia (only 22.9% expressed confidence in doing so) even though 70.2% agreed that the present treatment option with antidementia drugs usually have a positive influence on the course of the disease. The MOH Clinical Practice Guidelines suggest that "pharmacotherapy should not be used in isolation in the management of dementia, but in conjunction with non-pharmacological management, including education and counselling of the patient and caregiver"; the guidelines further suggest that the decision to initiate pharmacotherapy should be made after a detailed consultation with the patient and family on the expected benefits, side-effects and associated costs of the treatment.[32] Lack of time, as well as lack of access to a multidisciplinary team may thus hinder GPs in initiating treatment with antidementia drugs even though they may be aware of the benefits of therapy.

As the older adult population increases in Singapore, the number of older adults with dementia is likely to increase proportionally and thus GPs, being at the forefront, will need to play an increasing role in both the diagnosis and management of dementia. Seow[33] suggested that the adoption of certain enablers—making a diagnosis over several visits, ensuring corroborative history by a caregiver who is familiar with the older adult, detailed physical examination, use of cognitive scales and early referral to a specialist for a definitive diagnosis—could help GPs in Singapore to overcome some of these barriers related to the diagnosis of the condition. Collaborative care has been proposed as a way to improve the quality of care of dementia among primary care patients and their caregivers.[34,35] A similar model of shared care between family physicians and specialists to manage persons with dementia within the primary care polyclinics has been explored in Singapore. These dementia shared care teams comprise a multidisciplinary team from the specialised hospitals (geriatricians, nurse clinicians, etc.) who co-run clinic sessions with family physicians[36] to provide assessment, treatment, and support for dementia patients. The programme should be evaluated, and if the results show increased early diagnosis, improvement in quality of care and increased patient and caregiver satisfaction, then the expansion of such teams must be considered.

Factor 3: Negative Perceptions of Dementia Care

The GPs in the sample endorsed some negative perceptions towards dementia care. For instance, 64% of the GPs strongly agreed or agreed that "managing dementia is usually more frustrating than rewarding" and 57.12% reported that "patients with dementia can be a drain on resources with little positive outcome". Endorsement of these negative perceptions was higher than that reported from other studies of GP.[16,18,37] These perceptions may be due to a multitude of reasons such as the inability of GPs to meet the demands of patients and their caregivers, especially in solo practices. In addition, family involvement in the care of the dementia patient may lead to conflicts in terms of treatment options and priorities, and the difficulties in providing a clear prognosis, especially if GPs feel that treatment is limited.[38] The majority of GPs disagreed with the statement that "there is little point in referring families to services as they do not want to use them". Thus, GPs in Singapore felt the need to refer families to services. Hence, it is important that they are aware of the community services available and that

the process of referral is made easy such that patients and their caregivers can be easily directed to relevant services.

Factor 4: Training

The vast majority of GPs in our study endorsed the need for training—in the form of both treatment guidelines as well as communication skills for establishing a better relationship with the PWDs and their caregivers. Our findings are similar to the findings of Kaduszkiewicz et al[39] who found that majority of the GPs (56%) expressed the opinion that "guidelines for the diagnosis and treatment of dementia would be of help" and half (50%) stated an interest in "participating in a training programme on how to deal and speak with demented patients and their relatives". Other studies have suggested that GPs do experience difficulty in explaining diagnosis of dementia to patients and carers,[40,41] fearing that informing the patients would inflict damage on them, or they were uncertain about the course of the disease.[42] Thus, training for GPs is essential and should be focused on both the provision of easy-to-read-and-use treatment guidelines as well as communication skills. Dementia training programmes delivered either as online training or using blended methods (i.e. a combination of web-based learning and traditional teaching) may be considered as a way to reach out to busy GPs. Various studies have demonstrated the effectiveness of educational interventions such as decision support software, practice-based workshops and academic detailing as effective tools to improve dementia diagnosis and management.[43-45] However, training alone may not be adequate to improve dementia diagnosis and management. Additional resources in the form of access to multidisciplinary teams and comanagement of patients with specialist hospitals are also needed to improve the care of dementia patients in community settings.[46]

Male GPs were less likely to perceive the benefits of early diagnosis and treatment of patients with dementia as compared to their female counterparts. Few studies have examined the gender differences in knowledge and attitudes towards dementia. Research from the United Kingdom (UK) showed that the attitudes towards dementia differed significantly between men and women. Women showed higher levels of concern and men had a generally more positive attitude towards dementia. Men were twice as likely as women to regard dementia as being part of normal ageing. On the other hand, women dreaded dementia more and reported direct negative experiences with dementia, and hence, were less convinced that their families could deal with them.[47] While the UK study was on the general population, it highlighted some of the reasons why there might be gender differences in the attitudes towards dementia. However, these need to be studied in further depth to see if they apply to GPs as well. Secondly, we found that GPs in a solo practice (i.e. those who practised without partners) perceived lower "benefits of early diagnosis and treatment of patients with dementia" than those who practised in a group. Group practices may be better positioned to deal with the complex healthcare needs of patients. It is also possible that group practices may have access to a multidisciplinary team. Studies have found that physicians in group practice have more resources, access to interdisciplinary care and technological advances, and are easily able to refer patients to their colleagues in the specialised field.[48] Thus, those in group practice may see more cases of dementia and/or are able to better manage the patients after diagnosis; hence, they may more often see the benefits of early diagnosis to patients and caregivers.

Our study found that GPs who had a MBBS and a Master's degree showed greater confidence in dealing with patients with dementia and their caregivers than those with only a MBBS. The Master of Medicine in Family Medicine prepares doctors by exposing them to intensive training, ranging from lectures to practical sessions on chronic disease management, geriatrics, mental health, etc.[49] With the additional knowledge and skills acquired during training, it is plausible that these GPs showed greater confidence in managing complex dementia care than those who had MBBS alone.

The study has some limitations. This study included private and non-government GPs in Singapore and hence, the generalisability of the result to other settings is limited. We were unable to determine if the sociodemographic profile of the GPs was representative of overall GPs in Singapore, although it was similar to that reported in previous studies conducted among GPs.[50,51] The response rate was just over 50%, thus, responses might not be strongly representative given the low response rate, and the resulting non-response bias may limit the generalisability of the results. However, our response rate of 52% in this mailing study involving GPs was higher than that reported in other similar studies[17,18] and the results are an important first step towards engaging GPs in dementia care. We were unable to determine how many dementia patients were seen on average by GPs over the past 6 months which could have been a significant factor affecting their attitudes and confidence in managing dementia patients. The study questionnaire was adapted from previous studies[17,18] and included inputs from local dementia experts and a GP (Alvin Lum) who was involved in the study. This increased the comprehensiveness of data collected. However, there is a need for qualitative studies among GPs, PWD and their caregivers to ensure that locally relevant concepts have not been ignored and to explore some of the concerns expressed in further detail to ensure that they are fully addressed resulting in better care for dementia patients.

The study demonstrated that GPs in Singapore held a generally positive attitude towards the need for early

dementia diagnosis but were not equally confident or comfortable about making the diagnosis themselves and communicating with and managing patients with dementia in the primary care setting. Dementia education and training programmes have shown improvements in early diagnosis and knowledge of the GPs.[43] Therefore, a critical first step for dementia care in Singapore should include an enhanced dementia education and training programme for GPs. They also need to form alliances with other healthcare professionals and learn to manage dementia patients as part of shared care teams. Lastly, they need to be familiar with the relevant community services, day care centres and long-term care facilities to incorporate them in the management of patients with dementia.

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Intermediate Outcomes of Image-Guided Radiofrequency Ablation of Renal Tumours

Dear Editor,

Small renal tumours or T1a renal cell carcinoma (RCC) are increasingly being detected incidentally due to widespread imaging. Radical nephrectomy was historically the standard of care for renal tumours. However, it carries an increased risk of chronic kidney disease, and higher mortality and morbidity compared with nephron-sparing interventions (partial nephrectomy and image-guided ablative techniques).[1] Percutaneous ablative techniques have demonstrated rapid development over the past decade with radiofrequency ablation (RFA) being the most established and well studied modality. In this study, we present our experience with RFA of renal tumours within a South East Asian centre, and discuss the role of ablation in their clinical management.

Materials and Methods

This was a retrospective study of patients who underwent RFA of renal tumours at a single institution between June 2004 and June 2015. Patients were considered for RFA at our multidisciplinary meeting if they were non-surgical candidates due to advanced age, multiple comorbidities, solitary kidney, synchronous renal tumour, von-hippel-lindau disease or impaired renal function. Treatment options were offered to them during consult with the urologist. Those who desired to consider percutaneous RFA would subsequently be reviewed in an interventional radiology (IR) clinic.

Radiofrequency Ablation (RFA)

RFAs were performed at our hybrid computed tomography (CT) interventional suite with patients under conscious sedation. Initial limited CT was acquired for planning needle trajectory. Renal tumour was biopsied immediately prior to ablation except in 7 patients who were treated early in the series. Under ultrasound and/or CT fluoroscopy guidance, the renal tumour was targeted with internally cooled single electrode (Cool-tip, Covidien, Medtronic, Boulder, USA) of varying lengths (15-20 cm with active electrode lengths from 10-30 mm) depending on tumour size and patient's habitus. Single ablation cycle lasting 12 minutes was performed for each tumour with overlapping ablations applied to larger tumours (>3 cm) by repositioning of the electrode. During withdrawal of the RFA electrode, the track was ablated to reduce risk of haemorrhage and tumour seeding. Adjunctive techniques (hydrodissection or cold pyeloperfusion) were employed for renal masses in close proximity to surrounding organs to avoid heat-induced damage. After RFA, all patients were observed overnight and discharged the following day if clinically stable. Earlier in our practice, CECT was performed 1 day after RFA to evaluate for complications. This was subsequently replaced with an immediate post-ablation CT to document ablation zone and exclude complications.

Clinical and Radiological Follow-up

All patients had contrast-enhanced imaging (CT, ultrasound or magnetic resonance imaging) before and after RFA. Post-RFA imaging surveillance was at 1 and 6 months, and annually thereafter. On imaging, the degree of tumour beyond the renal contour classified their growth pattern as exophytic (≥75%), endophytic (≤25%) or mixed (25-75%). To standardise outcome measures, we used terminologies from the International Working Group on Image-Guided Tumour Ablation.[2] Technical success was defined as complete tumour ablation according to protocol, during or immediately after procedure. Primary technique efficacy was defined as tumour eradication with no residual enhancing component (≥20 HU) on the scan within 3 months after ablation. Local recurrence was defined as new enhancing component within the ablation zone after initial negative scan. Secondary technique efficacy was defined as successful repeat ablation of local tumour recurrence. Complications were prospectively recorded.

Follow-up review included clinical assessment and trending of serum creatinine level. Estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft-Gault equation, and eGFRs before and after RFA (at last follow-up) were compared. The overall (OS), cancer-specific (CSS) and recurrence-free survival (RFS) rates were also documented.

Data Analysis

Descriptive statistics were reported and P values <0.05 were considered statistically significant. Univariate analysis was performed using Fisher's Exact test to assess tumour size and location as predictors of technical success, as well as the change in GFR before and after RFA.

Results

A total of 22 patients (8 women, 14 men) with mean age of 71.8 years (standard deviation [SD] = 9.1, range 51-88) were treated. ASA (American Society of Anesthesiologists) scores of the patients were either 2 (n = 15) or 3 (n = 7). Patient profile and tumour characteristics are shown in Table 1. A total of 24 renal tumours (mean diameter, 2.6 cm) were ablated over 29 sessions. Nineteen tumours were completely ablated with a single RFA session whilst 5 tumours required 2 RFA sessions each. The mean diameter of tumours requiring 2 treatment sessions for complete ablation was 3.2 cm (SD = 1, range 2-4.8). Tumour growth pattern and size did not have significant effect on the likelihood of residual tumour ($P = 0.59$, $P = 0.27$). There were minor complications of perinephric haematomas in 6 patients, which were managed conservatively without the need for blood transfusion. There was no major procedure-related complication or mortality. The mean follow-up duration was 56.6 months (range 2-104 months). Outcomes of RFA are summarised in Table 2 and details of patients with residual or recurrent tumour are depicted in Table 3. There were a total of 6 mortalities during the follow-up period. Two developed metachronous RCC with eventual demise related to disease progression. The other 4 mortalities were not RCC-related. Regardless of the patient's baseline renal status (categorised into eGFR >60 and eGFR ≤60), there was no significant change in renal function after RFA respectively ($P = 0.29$ and $P = 0.79$).

Table 1. Patient Demographics and Tumour Characteristics

Previous RCC (%)	4 (18.2)
Radical nephrectomy	2
Partial nephrectomy	2
Indication for RFA	
Advanced age (>80 years)	3
Bilateral disease	2
Prior nephrectomy/single kidney	4
Treatment for existing cancer	3
Patient preference	8
Bleeding tendency	1
Poor renal function	1
No. of tumours ablated	24
Treated side	
Right	10
Left	14
Tumour location	
Upper pole	5
Mid pole	12
Lower pole	7
Tumour growth pattern	
Exophytic	13
Endophytic	4
Mixed	7
Tumour diameter, cm	2.6 (average)
>4 cm	2
2-4 cm	16
<2 cm	4
Renal mass biopsy (%)	17 (77.3)
RCC	16
Benign	1 (oncocytoma)
No biopsy	7

RCC: Renal cell carcinoma; RFA: Radiofrequency ablation

Discussion

RFA is an attractive treatment option for patients in our series who are elderly with multiple comorbidites, prior nephrectomy or bilateral RCCs. We achieved complete control in 91.7% of renal tumours at a mean follow-up of 56.6 months. Despite a small referral volume, technical success rate was comparably high at 95.8% with no major complication requiring treatment or prolonged hospitalisation. The comparatively lower primary efficacy rate at our centre (83.3%) compared to larger series[3-5] is reflective of an early series and we postulate several contributory factors: patient factors limiting positioning and cooperability; suboptimal tumour visualisation on non-contrast, intraprocedure ultrasound (US); and the learning curve of our operators.

As the most established ablative technique, there are emerging results on the longer term oncological durability of RFA in T1a renal tumours.[6,7] Our results, though promising (3-year RFS 94.7%, overall CSS 90.9%), are shorter term and from a much smaller series. Notably, the sizes of

Table 2. Radiofrequency Ablation Outcomes of 24 Renal Tumours

Technical success (%)	23/24 (95.8)
Primary technique efficacy (%)	20/24 (83.3)
Secondary technique efficacy (%)	1/24 (4.2)
Complications (%)	6/29 (20.7)
Local recurrence (%)	2/24 (8.3)
Cancer-specific survival (%)	20/22 (90.9)
Overall survival (%)	16/22 (72.7)
Percentage of recurrence-free survival	
1 year	95.2
2 years	95.2
3 years	94.7

Table 3. Summary of Patients with Residual and/or Recurrent Disease

Age/Gender	Comorbidities	Tumour Characteristics	Indication for RFA	Residual/Recurrent Disease	Intervention	Follow-up
74/M	Gastric carcinoma s/p subtotal gastrectomy	Multifocal bilateral RCC: 1) Right upper pole, 2.1 cm, exophytic 2) Left mid pole, 1.6 cm, exophytic 3) Left lower pole, 3 cm, exophytic	Multifocal bilateral RCC	Residual disease in right upper pole and left lower pole tumours	Repeat ablation at 55 and 81 days, respectively	No local recurrence at 100, 66 and 38 months, respectively
72/F	Left radical nephrectomy for RCC	Right mid pole, 3.3 cm, abuts calyx (cooling with ureteric catheter)	Prior left radical nephrectomy for RCC	Residual disease	Repeat ablation at 40 days	Developed metachronous RCC at 37 months with metastatic progression to lungs and brain
72/F	Cardiovascular risk factors	Left mid pole, 2.8cm, mixed	Patient preference	Residual disease	Repeat ablation at 90 days	No local recurrence at 24 months
80/M	Moderate to severe stage CKD (eGFR 30)	Right upper pole, 4.8 cm, mixed	Advanced age, CKD	Technically challenging RFA, unable to target medial aspect of tumour	Repeat ablation at 19 days	Local recurrence at 28 months; not treated due to age. Slow tumour growth observed on active surveillance till 36 months
66/F	Factor VII deficiency, PRV	Left lower pole, 2.5 cm, exophytic (RFA with fresh frozen plasma cover)	Bleeding tendency	Recurrent disease at 39 months	Repeat ablation at 41 months	Died at 42 months due to PRV-related complication

CKD: Chronic kidney disease; F: Female; M: Male; PRV: Polycythemia rubra vera; RCC: Renal cell carcinoma; RFA: Radiofrequency ablation; s/p: Status post

tumours treated in our study were not limited to stage T1a. For larger renal masses (>3-4 cm), the oncologic efficacy of RFA is mixed with incomplete treatment rates >20% and local progression reported.[8,9]

We found no significant procedure-related complication or deterioration of renal function in our patients, consistent with the well documented safety and nephron preservation (≤25% reduction in GFR) of RFA.[5,10,11] On the contrary, laparoscopic partial nephrectomy is technically challenging with complications up to 33% even in skilled operators.[12,13] This steep learning curve should continue to drive the development and more extensive usage of image-guided tumour ablation. To date, our centre has started adopting newer ablative techniques such as multiple-electrode RFA. Cryoablation, which is also gaining popularity amongst urologists, has inherent advantages which may prove beneficial for T1b or central tumours. It allows real-time monitoring of the ablation zone, has lower susceptibility to perfusion-mediated thermodilution ("cold sink") and reduced risk of ureteral stricture.

Aside from ablation and partial nephrectomy, active surveillance is an option supported by the observation that most small RCCs are indolent. Although Larcher et al showed that tumour ablation was associated with significant protective effect on cancer-specific mortality compared to surveillance,[14] it can be argued that elderly patients may be more likely to die from other comorbidities than stage 1a RCC. Separately, in cases of patients with residual tumour after thermal ablation, active surveillance has been recently proposed as an acceptable alternative with delayed intervention in those with high tumour volume doubling time.[15]

Small patient numbers is a major limitation that may have prevented us from detecting any significant relationship between tumour factors and ablation efficacy (type II error). Future studies of a larger cohort will be useful to further aid our clinical decision-making.

Conclusion

We advocate due consideration for RFA of small renal tumours amongst elderly patients with significant comorbidities and/or poor renal function. Our experience

has reinforced the need to counsel patients on the intent of RFA (curative, palliative or debulking), its limitations in larger and central tumours and the attendant likelihood of requiring multiple ablation sessions to achieve complete tumour eradication.

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Excluding Severe Bacterial Infection in Neutrophilic Dermatoses with Systemic Manifestations: Negative Predictive Value of Procalcitonin

Dear Editor,

Extensive neutrophilic activation and infiltration occur in a number of dermatological conditions, resulting in typical features of pyrexia, neutrophilia, and raised erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). These conditions are namely generalised pustular psoriasis, acute generalised exanthematous pustulosis (AGEP) and Sweet syndrome, and they are termed as neutrophilic dermatoses with systemic manifestations. Their presentation is similar to that in patients with severe bacterial infections, such as severe pneumonia, peritonitis, meningitis, pyelonephritis and sepsis.

Early differentiation between neutrophilic dermatoses with systemic manifestations and severe bacterial infection is important due to the opposing treatment approaches. Whilst patients who have neutrophilic dermatoses with systemic manifestations require immunosuppressive therapy,[1,2] patients with severe bacterial infections require antibiotic therapy, and the use of immunosuppressive therapy should be avoided.

In the last decade, extensive research has been undertaken to study the diagnostic value of procalcitonin in bacterial infections.[3-6] The primary objective of this study is to evaluate the predictive value of procalcitonin for the presence of severe bacterial infections in patients who have neutrophilic dermatoses with systemic manifestations. If the procalcitonin levels in these patients are not elevated, clinicians can better decide if they can be commenced promptly on immunosuppressant for their underlying skin condition. The secondary objective is to evaluate if procalcitonin levels differ between generalised pustular psoriasis and AGEP, as it is clinically and histologically difficult to distinguish these 2 conditions.

Materials and Methods

Inpatients with a clinical diagnosis of generalised pustular psoriasis, AGEP or Sweet syndrome who were referred to the dermatology service in a tertiary hospital in Singapore, and who had their data recorded between May 2012 and April 2015, were evaluated retrospectively. Their diagnoses were made clinically and some patients had histopathological correlation. Severe bacterial infection was defined as either severe pneumonia resulting in shock or requiring mechanical ventilation, peritonitis, meningitis or bacteraemia. Bacteraemia was determined by a positive blood culture; cultures growing only coagulase-negative *staphylococci*—a typical contaminant during blood culture collection—were excluded. Patients with lower urinary tract infections or skin infections such as cellulitis were not classified as having a severe bacterial infection as physicians or dermatologists do not usually hesitate to commence immunosuppressant concurrently with antibiotic treatment in this group of patients and they do not usually constitute the clinical conundrum dermatologists face. Patients who did not have their procalcitonin levels measured during their hospitalisation were excluded from the study. Serum procalcitonin were measured using Roche Diagnostics' Roche Cobas e601, which utilises electrochemiluminescent immunoassay technology with a lower detection limit of 0.03 ug/L and a functional sensitivity of <0.06 ug/L. A procalcitonin level of >0.5 ug/L was considered as elevated[7] in keeping with previous investigations on the use of procalcitonin in sepsis.[3,7]

Our study was a retrospective review and most patients were referred to the dermatology department. As such, there were no stipulated guidelines for the physicians-in-charge on when to measure the patients' procalcitonin level and the frequency of its measurement. Procalcitonin was frequently measured based on the clinicians' individual practice and it was observed to be measured at different intervals over the course of the patients' hospitalisation, subjected to the primary physicians' choice. We then analysed the data based on the highest procalcitonin level measured during the patients' hospitalisation.

Mann-Whitney U test was used to evaluate the statistical difference between procalcitonin levels in the various diseases. Receiver operating characteristic (ROC) analysis was done to evaluate serum procalcitonin while CRP test was used to diagnose severe bacterial infections among patients with neutrophilic dermatoses. The ROC curve illustrates the diagnostic ability of whether the patient has severe bacterial infections.

In conjunction with the ROC analysis, Youden index was used to determine the threshold value for which procalcitonin optimally differentiates patients with and without a concurrent severe bacterial infection. The maximum value

of the index was used to select the optimum cutoff point of the procalcitonin test, which was 1.3 ug/L. The study was approved by the institution's ethics review board.

Results

There were a total of 59 patients (26 males and 33 females) who were diagnosed with neutrophilic dermatoses with systemic manifestations but only 41 patients had their procalcitonin measured during hospitalisation. The mean age of our patients was 60.0 + 20.9 years and none of them were pregnant.

Thirty-six had generalised pustular psoriasis, 16 had AGEP and 7 had Sweet syndrome. There were 7 patients with severe bacterial infections—4 had bacteraemia, 2 had severe pneumonia and 1 had multiple intra-abdominal collections. Of the 7 patients who had severe bacterial infections, all of them had a procalcitonin value of >0.5 ug/L (mean, 16.40; range, 1.33 to 47.09) (Fig. 1). Four of these 7 patients died, 3 of whom had a procalcitonin level of >7 ug/L.

Fig. 1. This diagram shows the procalcitonin values in patients who have neutrophilic dermatoses with systemic manifestations according to the absence and presence of severe bacterial infection. The data is depicted as box-plot diagrams, with the box encompassing the range of values from the 25% percentile (lower bar) to the 75% percentile (upper bar). The horizontal line within the box represents the median and the vertical lines below the box signify the maximum and minimum values.

Thirty-four patients who had neutrophilic dermatoses with systemic manifestations did not have severe bacterial infections (Fig. 2). A procalcitonin cutoff level of >0.5 ug/L has 100% sensitivity and 67.6% specificity in predicting concurrent severe bacterial infections in patients who have neutrophilic dermatoses with systemic manifestations (Table 1).

ROC analysis of serum procalcitonin levels demonstrated a good value at 0.912 (P = 0.001; 95% CI, 0.822 to 0.100) (Fig. 3). This indicated that in almost 91.2% of all possible pairs of subjects—in which one was the case (had a severe bacterial infection) and the other a control (did not have a severe bacterial infection)—serum procalcitonin would assign a higher probability to the former. In contrast, the ROC for serum CRP was fair with a value of 0.660. This meant that CRP, as a marker to differentiate severe bacterial infections among patients who have neutrophilic dermatoses with systemic manifestations, only performed 16.0% better than chance.

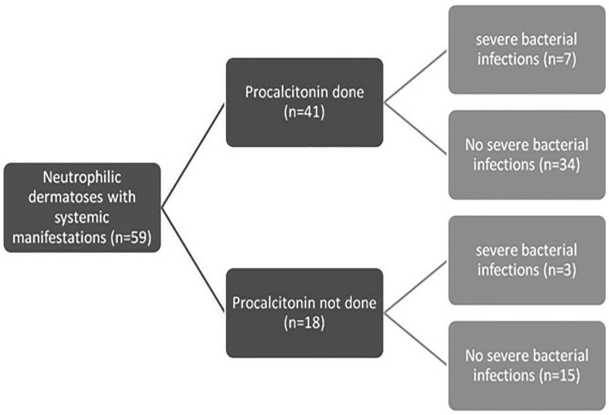

Fig. 2. Flowchart of patients with neutrophilic dermatoses with systemic manifestations.

Table 1. Sensitivity and Specificity of Using a Cutoff Value of 0.5 Ug/L and 1.3 Ug/L for Procalcitonin in Distinguishing Severe Bacterial Infections in Patients who Have Neutrophilic Dermatoses with Systemic Manifestation

Disease	Patients with Significant Bacterial Infection (Procalcitonin >0.5 ug/L) (n = 41)		Patients with Significant Bacterial Infection (Procalcitonin >1.3 ug/L) (n = 41)	
	Yes	No	Yes	No
Raised procalcitonin				
Yes	7	11	7	7
No	0	23	0	27
Sensitivity	1.00		1.00	
Specificity	0.676		0.794	
Negative predictive value	1.00		1.00	
Positive predictive value	0.389		0.500	

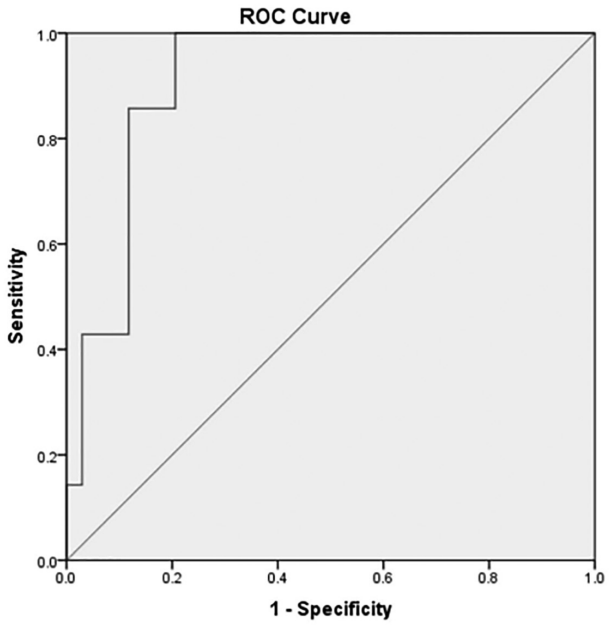

Fig. 3. Prediction of severe bacterial infection ROC curve, with area under curve for procalcitonin = 0.912.

With a Youden index of 0.794, a serum procalcitonin cutoff level of 1.3 ug/L gives 100% sensitivity and 79.4% specificity in predicting concurrent severe bacterial infections in patients who have neutrophilic dermatoses with systemic manifestations. This suggests that a higher cutoff value of serum procalcitonin performed better in identifying severe bacterial infections among patients with neutrophilic dermatoses with systemic manifestations.

Using the Mann-Whitney U test, there was no significant difference between procalcitonin in patients with generalised pustular psoriasis and AGEP.

Discussion

Procalcitonin is a 116-amino acid precursor of calcitonin. In healthy subjects, the thyroid C cells are the only tissue which transcribe and translate the procalcitonin gene. Only a small amount of procalcitonin is released into the general circulation such that in healthy individuals, procalcitonin concentration is <0.05ug/L. In the presence of bacterial infection, however, procalcitonin production is activated in all parenchymal tissues and concentrations rapidly increase.[8] Procalcitonin production caused by these tissues is stimulated by 2 mechanisms—directly by bacterial endotoxins and lipopolysaccharides, and indirectly by inflammatory mediators, namely tumour necrosis factor-alpha (TNF-alpha), interleukin-6 and interleukin-1. During infections associated with marked TNF-alpha release, such as Gram-negative infections and malaria, marked procalcitonin elevation is seen.[9] Because procalcitonin level is attenuated by interferon-gamma (a cytokine released in response to viral infections), procalcitonin is a more specific marker of bacterial infections. It is mainly degraded by proteolysis, and to a lesser extent, excretion through the kidneys.[10]

It is important to differentiate patients who have a flare of solely neutrophilic dermatoses with systemic manifestations from those who have concurrent severe bacterial infections. In sepsis, the traditional gold standard has been blood culture, but this method lacks sensitivity as causative microorganisms is detected only in 30% to 50% of patients with suspected bloodstream infection.[11]

It was previously found that a procalcitonin level of <0.5 ng/L had a high negative predictive value for the exclusion of sepsis while high levels (>2 ng/L) indicated severe sepsis or septic shock in patients admitted to the general medicine team or medical intensive care unit.[12] In our study, a procalcitonin cutoff of 1.3 ug/L conferred an excellent sensitivity and negative predictive value for concurrent severe bacterial infections in patients who had neutrophilic dermatoses with systemic manifestations. In all 27 patients who had a procalcitonin value of <1.3 ug/L, none of them were diagnosed with a severe bacterial infection. This, to our knowledge, is the first study investigating the utility of procalcitonin in predicting concurrent severe bacterial infections in patients who had neutrophilic dermatoses with systemic manifestations.

The results of our study indicated that procalcitonin could be useful in ruling out a concurrent severe bacterial infection in patients who had neutrophilic dermatoses with systemic manifestations. Out of 23 patients with non-elevated procalcitonin level, 22 received systemic antibiotics. In such cases, the focus and approach of management would be on reducing uncontrolled activation of the innate immunity rather than to treat infection, in which more aggressive anti-inflammatory agents can be confidently used rather than stronger antibiotics. In addition, procalcitonin is a relatively quicker and minimally invasive test compared to other tests such as blood culture and radiography that can be used as a tool for ruling out infections. Procalcitonin results could be confirmed in less than a day and a negative result could mean that immunosuppressive therapy would be started much faster rather than having to wait for more traditional tests such as blood cultures to be reported.

In our data, out of 7 patients who were diagnosed with Sweet syndrome, only 5 had their serum procalcitonin levels measured. In these 5 patients, only 1 patient had concomitant myelodysplastic syndrome and myelofibrosis. None of the patients with Sweet syndrome in our study had associated ulcerative colitis, Crohn's disease, rheumatoid arthritis or lupus erythematosus. In our literature review,

serum procalcitonin has been found in previous studies to be a promising marker in haematological malignancy, inflammatory bowel disease and autoimmune diseases to aid in the differentiation between bacterial infections and inflammatory flares.[13-16] In these studies, serum procalcitonin was measured using instruments from different manufacturers with different lower detection limits. Thus, comparison of quantitative serum procalcitonin levels between studies may be difficult. Serum procalcitonin levels are not significantly different between pregnant women and healthy controls.[17]

There are several limitations of our study. Firstly, our study sample size was small, which would limit the generalisability of the ROC analysis to the general population. Secondly, the number of patients who had a concurrent diagnosis of severe bacterial infection was markedly lesser than the number of patients who did not have a severe bacterial infection. Thirdly, in our study, we only included patients with generalised pustular psoriasis, AGEP and Sweet syndrome as they shared a similarity of systemic neutrophilic activation with the main manifestation in the skin. However, these 3 conditions have different pathogenetic mechanisms of neutrophilic activation and are not a uniform entity. We believe larger future prospective studies will be useful to validate our findings and study the outcomes of early implementation of immunosuppressive therapy guided by procalcitonin levels or trends.[18]

Conclusion

The study results indicate that in patients with neutrophilic dermatoses with systemic manifestations with a procalcitonin value of <1.3 ug/L, it is very unlikely that their clinical manifestations of systemic inflammation are due to a severe bacterial infection. In such instances, immunosuppressant therapies, which are typically withheld for fear of causing fulminant sepsis, can be reasonably instituted early to treat their diseases.

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Clinical versus Echocardiographic Parameters in Assessing Cardiac Resynchronisation Therapy Response in a Multiethnic Asian Population

Dear Editor,

Systolic heart failure is the most common cardiac cause for admission to Singapore hospitals, accounting for approximately 25% of such hospital stays.[1] Age-adjusted heart failure admission rates rose 40% over 7 years from 1991 to 1998.[2]

Studies have shown that cardiac resynchronisation therapy (CRT) not only reduced recurrent hospitalisation rate in selected symptomatic patients with systolic heart failure,[3,4] but more importantly, resulted in up to 35% of relative risk reduction in mortality.[3,5]

However, the correlation between improvements in clinical response based on the New York Heart Association (NYHA) system of heart failure versus echocardiographic parameters remained uncertain. Bleeker et al[6] observed a discrepancy between clinical response and echocardiographic response: only 51% of CRT patients with improvement in NYHA class showed reductions of >15% in left ventricular end systolic volume (LVESV). Most of the studies, however, involved predominantly non-Asian population.

The objective of this study was to evaluate the correlation between clinical response rates versus echocardiographic end points in CRT patients in our institution.

Materials and Methods

We conducted a retrospective study in our centre from 2009 to 2014 by recruiting all CRT patients with follow-up of at least 6 months. All had transthoracic echocardiography and documentation of NYHA status pre- and post-CRT implantation.

Based on previous studies,[6,7] CRT responders were defined as either "clinical improvement of ≥1 NYHA class (clinical responder)" or "improvement in echocardiography parameters (echocardiographic responder)". Echocardiographic responders were defined as either "an absolute improvement in left ventricular ejection fraction (LVEF) >5% (measured by Simpson's Biplane method)", and/or "a reduction in LVESV of >15% on transthoracic echocardiography (non-contrast method in evaluating LVEF and LV volumes) using either General Electric or Philips echo machines, at least 6 months following CRT device implantation".

Data was expressed as mean ± standard deviation for continuous variables and as frequency and percentages for discrete variables. Continuous variables were compared using independent sample t-tests. Categorical variables were compared using chi-squared tests. Statistical agreement among NYHA class and echocardiographic parameters were performed using Cohen κ-coefficient. The κ-coefficient ranges from -1 (perfect disagreement) to +1 (perfect agreement) whereas κ-coefficient of 0 indicates that the amount of agreement was exactly expected by chance. For all tests, a P value of <0.05 was considered statistically significant.

This study was reviewed and approved by the hospital institutional review board.

Results

A total of 32 patients received CRT during the study period. However, only 24 patients were included in the study as 4 patients had follow-up duration of less than 12 months and the remaining did not have post-CRT transthoracic echocardiography evaluation. The baseline characteristics of the study population are shown in Table 1. Majority were male (79.2%) and Chinese (62.5%). Ischaemic cardiomyopathy (66.7%) was the most common cause of cardiomyopathy. Mean follow-up duration was 26.9 ± 16.9 months.

Prior to CRT implantation, 45.8% were in NYHA class III and IV while 45.8% of subjects had left bundle branch block morphology. QRS duration was 156 ± 16 milliseconds. Mean duration of transthoracic echocardiography performed post-CRT device implantation was 16 months.

Overall, compared with pre-CRT, there was significant improvement in NYHA class (P = 0.008), LVEF (pre-CRT: 24.6 ± 7.9%; post-CRT: 35.5 ± 11.2%; P = 0.001) and LVESV (pre-CRT: 114.1 ± 50.1 mL; post-CRT: 83.6 ± 43.4 mL; P = 0.017) post-CRT (Table 2). Responder rate was highest for NYHA class (83.3%), followed by LVEF (62.5%) and lowest for LVESV at 54.2%.

Despite 66.7% of patients showing improvement in both NYHA class (clinical responder) and echocardiography parameters (either improvement in LVESV and/or LVEF), there was poor κ-coefficient agreement between

Table 1. Baseline Characteristics

Characteristic	Value
Age at implant (years), mean ± SD	60 ± 8
Male (%)	79.2
Ethnicity (%)	
Chinese	62.5
Malay	25.0
Indian	8.3
Others	4.2
Comorbidities (%)	
Diabetes	54.2
Hypertension	50.0
Atrial fibrillation	25.0
Cardiomyopathy (%)	
ICMP	66.7
NICMP	33.3
QRS complex	
Left bundle branch block	45.8
Right bundle branch block	20.8
Complete heart block	33.4
QRS duration (millisecond) prior CRT, (mean ± SD)	156 ± 16
Medications, %	
Beta-blocker	95.8
ACE inhibitor/ARB	70.8
Diuretics	87.5
Potassium-sparing diuretics	58.3
Statin	83.3
Aspirin	62.5

ACE: Angiotensin-converting-enzyme; ARB: Angiotensin II receptor blockers; CRT: Cardiac resynchronisation therapy; ICMP: Ischaemic cardiomyopathy; NICMP: Non-ischaemic cardiomyopathy; SD: Standard deviation

Table 2. NYHA Class, LVEF and LVESV Before and After CRT Implantation

	Before CRT	After CRT	*P* Value
NYHA (%)			
Class I	12.5	58.3	
Class II	41.7	29.2	
Class III	45.8	12.5	
Class IV	0	0	0.008
LVEF (%)	24.6 ± 7.9	35.5 ± 11.2	0.001
LVESV (mL)	114.1 ± 50.1	83.6 ± 43.4	0.017

NYHA: New York Heart Association; CRT: Cardiac resynchronisation therapy; LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end-systolic volume

Table 3. Agreement between Clinical Responder and Reduction in LVESV >15%

	Clinical Responder	Clinical Non-Responder
LVESV reduced >15%	12 (50.0%)	1 (4.2%)
LVESV reduced ≤15%	8 (33.3%)	3 (12.5%)

LVESV: Left ventricular end-systolic volume

Table 4. Agreement between Clinical Responder and Improvement in LVEF >5%

	Clinical Responder	Clinical Non-Responder
LVEF improved >5%	14 (58.3%)	1 (4.2%)
LVEF improved ≤5%	6 (25.0%)	3 (12.5%)

LVEF: Left ventricular ejection fraction

NYHA and LVESV, κ = 0.21 ± 0.16 (Table 3) as well as NYHA class and LVEF, k = 0.30 ± 0.19 (Table 4). About 25% showed either a positive clinical response or echocardiographic response while the remaining 8.3% were non-responders (no improvement in NYHA class as well as both echocardiography parameters) (Fig. 1). The disagreement was mainly caused by patients who showed improvement in clinical response without improvement in LVESV, 33.3% (Table 3) or LVEF, 25% (Table 4). The κ-coefficient between LVEF versus LVESV post-CRT was poor as well, κ = -0.32 ± 0.20.

Patients with non-ischaemic cardiomyopathy had significantly higher echocardiographic response rate, 87.5% (based on LVESV reduction of >15%) compared to patients with ischaemic cardiomyopathy (ICMP), 37.5% (*P* = 0.02).

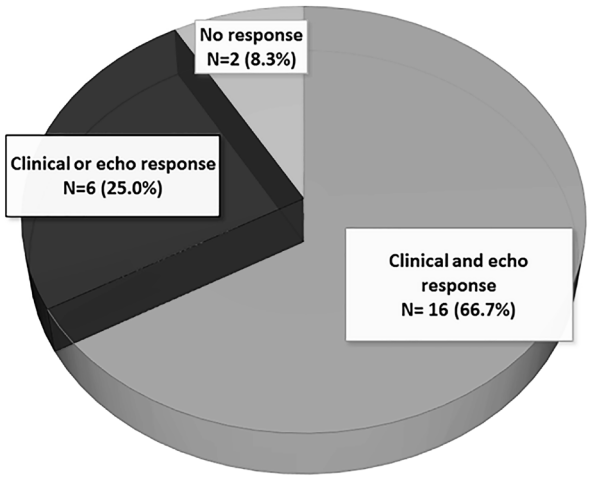

Fig. 1. Pie chart showing the clinical versus echocardiographic parameters (LVEF and/or LVESV) to assess response to CRT. CRT: Cardiac resynchronisation therapy, LVEF: Left ventricular ejection fraction, LVESV: Left ventricular end-systolic volume

Discussion

Previous studies[7-11] have reported different rates of response to CRT when different definitions of response (up to 17 response parameters) were used. The parameters (NYHA class, LVEF and LVESV) that were used in this retrospective study were the most widely accepted parameters.[7] This study showed that in a multiethnic Asian population, up to 83.3% of patients responded to CRT using NYHA class assessment (clinical responder). However, the responder rate based on echocardiographic parameters (LVEF responder rate: 62.5%; LVESV responder rate: 54.2%) were lower when compared to NYHA class. These findings were consistent with previous studies.[6,8,11,12]

Even though up to 66.7% of patients showed improvement in both NYHA class (clinical responder) and echocardiography parameters (either improvement in LVESV and/or LVEF), the κ-coefficient agreements were poor between NYHA class and LVESV ($\kappa = 0.21 \pm 0.16$ [Table 3]), as well as NYHA class and LVEF ($k = 0.30 \pm 0.19$ [Table 4]). The disagreement was mainly caused by patients who showed clinical responses without either improvement in LVEF (25.0%) or LVESV (33.3%). This observation may be explained by the presence of multifactorial effects including an improvement in efficiency as well as oxygen utilisation which may not be fully reflected in echocardiographic measurements of cardiac function. The κ-coefficient between LVEF versus LVESV was poor as well ($\kappa = -0.32 \pm 0.20$), although it appears consistent that half to two-thirds of cohort are echocardiographic responders by either echocardiographic parameters. This suggests that these 2 echocardiographic parameters may be assessing different aspects of cardiac function and may also represent different stages of left ventricular remodelling. These echo parameters could also be confounded by measurement and interobserver variability. LVESV may be a more sensitive and reproducible marker of response than LVEF which may have greater measurement variability. Furthermore, the mechanism of clinical improvement may not be entirely mediated by improvement in LVEF and/or LVESV. Perhaps more standardised and specific parameters, such as peak oxygen consumption at exercise (Vo_2max), should be used in assessing response to CRT that could accurately predict outcomes.

The main limitation of our study was a retrospective single centre study with a small number of subjects. As this was a retrospective study, the interobserver agreement was not evaluated for LVEF and LVESV measurements. Furthermore, studies[13] have shown that the 2-dimensional echocardiographic evaluation of LVEF and LV volumes was found to be more accurate when adding an intravenous contrast agent. Besides, although NYHA class improvement and the selected echo parameters are established methods of determining CRT response, they could potentially overestimate the true response rate as neither subjects nor doctors were blinded to the presence of the CRT. Our study population was relatively heterogeneous; in particular, we included patients with atrial fibrillation, right bundle branch block as well as complete heart block. Our study follow-up was relatively short (mean follow-up duration was 26.9 ± 16.9 months) as CRT has been shown to have persistent, increasing benefits with a longer mean follow-up of 56 months.[14,15]

Conclusion

Our local data showed CRT-responder rate of 66.7% (improvement in both clinical and echocardiographic parameters) as well as discordance between clinical versus echocardiographic response. These findings were similar to previous established publications mainly involving Caucasian population.

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A Massive Pleural Effusion: What Lies Beneath?

A 21-year-old male of Chinese ethnicity attended the institution's radiology department for an outpatient chest radiograph for right lower chest reduced air entry. Concurrently, he had an outpatient computed tomography (CT) intravenous pyelography (IVP) for right renal colic and microscopic haematuria for investigation.

What do the radiograph (Fig. 1) and CT (Fig. 2) images show?

A. A pleural effusion
B. Empyema necessitans
C. Pleural mesothelioma
D. Pleural rhabdomyosarcoma
E. Pleural liposarcoma

Findings and Diagnosis

The chest radiograph (Fig. 1) showed a large right-sided pleural effusion, extending superiorly to the periphery of the right upper zone. Partial opacification of the right middle zone adjacent to the pleural effusion was deemed likely related to compressive atelectasis. The heart was mildly shifted to the left. There was also a subtle widening of the interval between the right ninth and tenth ribs posterolaterally (dashed black line) when compared with that on the left side (dashed white line). The left lung was unremarkable.

On CT (Fig. 2), a large right pleural effusion was again demonstrated. However, there was also a large, heterogeneously enhancing, lobulated soft tissue mass (Fig. 2, indicated by *) which was broad-based against, and appears to arise from, the posterolateral parietal pleura of the lower right hemithorax. No internal fat attenuation was noted. There was an extension of the enhancing soft tissue posterolaterally between the right ninth and tenth ribs (Fig. 2, indicated by the arrowheads), with invasion of the intercostal and overlying latissimus dorsi skeletal muscles. No bony destruction of the right ninth and tenth ribs was seen. Other small enhancing pleural nodules were demonstrated in the anterior aspect of the lower right hemithorax.

On further questioning, the patient had non-mechanical right upper back pain for over a year's duration. The pain was pleuritic in nature and initially mild, but progressively worsened. This was associated with weight loss. He had also been pyrexial for the past month, and recently had a productive cough for 5 days. Clinical examination of the patient revealed an elevated body temperature of 38.1°C, with stony dull percussion over the right lower zone. He

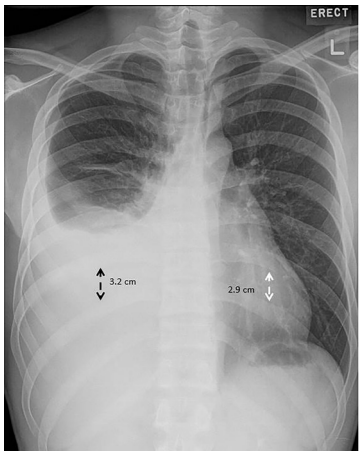

Fig. 1. Chest radiograph showing a right pleural effusion, with subtle widening of the distance between the right 9th and 10th ribs compared to the left. The distances were measured on a radiology imaging workstation.

Fig. 2. CT study showing a large, heterogeneously enhancing, lobulated soft tissue mass (indicated by *), extending through the intercostal space into the latissimus dorsi muscle (indicated by arrowheads).

Answer: D

also had an elevated serum C-reactive protein level (175.4 mg/L [<3.0]), but otherwise his blood results were largely unremarkable.

A pleural tap was performed, which was slightly turbid and orange in colour on gross inspection, with no frank pus or haemorrhage. The pleural aspirate had abundant lymphocytes on cytology. The patient was started empirically on rocephine and doxycycline for the presumptive diagnosis of an empyema. A CT study of the thorax was performed—this again showed the heterogeneously enhancing pleural-based mass with large right pleural effusion, which was deemed suspicious for a primary pleural-based neoplasm, or an atypical infection.

The patient subsequently underwent an ultrasound-guided core needle biopsy of the pleural-based mass. Histologic examination of the mass revealed a tumour composed of spindle cells arranged in fascicles, infiltrating into the skeletal muscle. The spindle cells appeared pleomorphic with a high nuclear-cytoplasmic ratio and mitotic figures were present. The tumour cells showed diffuse cytoplasmic staining for WT1, and also stained positive for desmin, CD56 and myogenin, which are muscle-specific proteins. The overall pathology findings were thus in keeping with a spindle cell rhabomyosarcoma.

To complete the staging procedure, a positron emission tomography-computed tomography (PET-CT) study was performed (Fig. 3). It showed increased metabolic activity of the known primary pleural-based mass, as well as the smaller pleural nodules—the latter suspicious for pleural metastases. There were also metabolically active lymph nodes in the mediastinum and right supraclavicular regions, suspicious for nodal metastases.

Discussion

Rhabdomyosarcoma is the commonest childhood malignancy of mesenchymal origin.[1] Although usually related to skeletal muscle, it can arise from any site, possibly via pluripotent cells differentiating into neurogenic or myogenic elements. Most cases arise in the head and neck region, followed by the genitourinary system and extremities. Thoracic manifestation of primary rhabdomyosarcoma is rare; to date, there have been only 9 reported cases of pleural rhabdomyosarcoma in the literature.[1,2]

This case is unusual as the patient attended for an unrelated condition, and the diagnosis was made almost serendipitously. The large pleural effusion, although somewhat unusual for a young adult male, could have been readily attributed to a chest infection, given the patient's history of fever and raised inflammatory markers. However, there was also a very subtle widening of the posterior right ninth intercostal space when compared to the left (Fig. 1).

On CT, the solid components are much more readily appreciable; this was thus not a mere bland pleural effusion. Two main groups of differentials were offered, in the form of a primary malignancy or atypical infection. Another common cause of abnormal pleural soft tissue is pleural metastases (Fig. 4), although this was deemed less likely in this clinical setting given the patient's relatively young age and absence of risk factors.

Of primary tumours, possible differentials would include pleural mesothelioma (Fig. 5), liposarcoma (Fig. 6) or a rhabdomyosarcoma. For example, mesothelioma may manifest as an effusion with enhancing nodular solid components which can be severe enough to encase the lung in a "rind-like" fashion.[3] It can also be locally aggressive, invading the chest wall, mediastinum and diaphragm. Calcified pleural plaques are present in 20% of cases. However, this diagnosis is unlikely for someone in this age group, particularly in the absence of occupational risk factors.

A liposarcoma may occur in this region, but was effectively excluded on CT given the absence of a fatty component in the mass.[4]

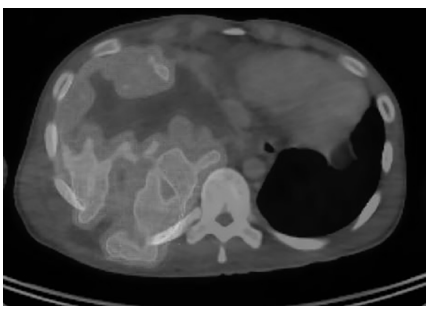

Fig. 3. PET-CT study showing increased metabolic activity in the dominant solid component in the posterior aspect in keeping with a tumour, as well as pleural metastases anteriorly. PET-CT: positron emission tomography-computed tomography

Fig. 4. On this CT study, there are several irregularly-outlined soft tissue nodules arising from the right pleura (indicated by arrowheads). The multiplicity of the lesions, in conjunction with known renal cell carcinoma (not shown), is compatible with pleural metastases. There is also a large right pleural effusion, with midline shift of the mediastinal structures to the left.

Fig. 5. Axial CT image with a thin rind of enhancing soft tissue along the posterior right pleura (indicated by arrowheads). Note the slightly irregular outline, versus the smooth outline in empyema. No calcification is present on this example. There is also a large hydropneumothorax in this patient after percutaneous biopsy.

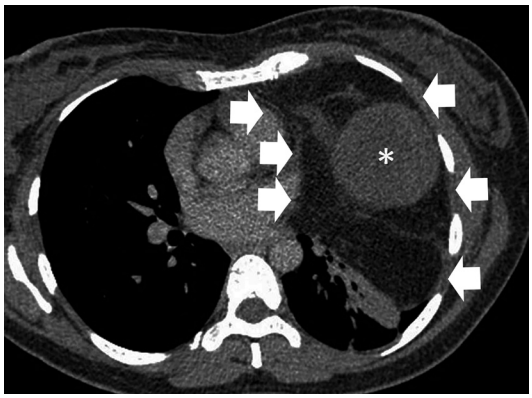

Fig. 6. Contrast-enhanced CT study showing a large left pleural-based mass (indicated by arrowheads) with mild deviation of the heart to the right. The mass is predominantly of fatty attenuation; the hypodense areas are of similar density to the subcutaneous fat. However, there is a large rounded soft tissue focus within (indicated by *), which represents a focus of dedifferentiation, proven on histology.

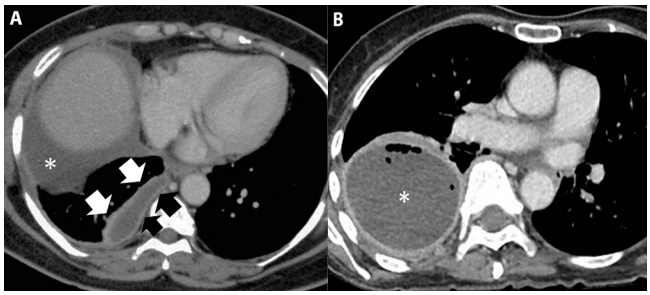

Fig. 7. A: CT thorax study, with fluid interspaced between the visceral and parietal pleurae (white and black arrowheads respectively), giving signs of "split pleura". Both pleurae are smoothly thickened and mildly enhancing, due to the inflammatory/infective change. In contrast, note the more bland pleural effusion anteriorly (indicated by *) which lacks the associated finding of a thickened enhancing pleura. B: In this study, this fluid collection (indicated by *) is more rounded in configuration, with thick enhancing walls and a concavity of the visceral pleura. Small gas locules within this loculated empyema are secondary to recent aspiration, which yielded frank pus. Apparent midline shift is due to the underlying spinal scoliosis.

Infections resulting in empyema will usually have a pleural effusion and smoothly thickened enhancing pleura (Figs. 7a and 7b). Although uncommon, when a pleural infection extends out of the thorax into or beyond the chest wall, it is known as empyema necessitans. This is usually secondary to atypical infections, of which the 2 most common are tuberculosis and actinomycosis. Actinomycosis produces proteolytic enzymes, which can create fistulae without regard for tissue planes.[5] Soft tissue thickening which mimics nodular pleural thickening (Fig. 8), as well as bony destruction, can be observed.

Ultimately, the patient required tissue sampling to differentiate between a primary malignancy or atypical infection. In our case, this was performed under image guidance using ultrasound (Figs. 9a and 9b). Generally speaking, image-guided intervention may be performed using fluoroscopy, ultrasound, CT or magnetic resonance imaging, depending on which modality the lesion being

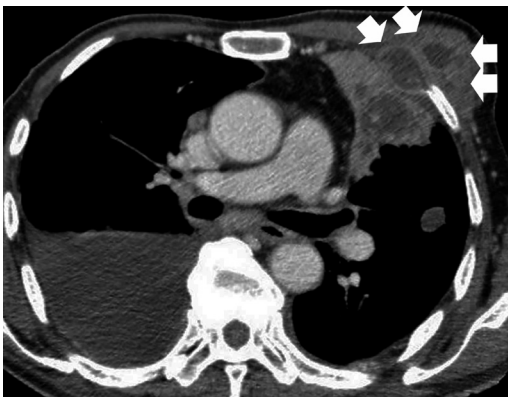

Fig. 8. CT thorax axial image, with a large solid cystic mass along the anterior left pleura extending through the chest wall into the left pectoralis muscles and subcutaneous space (indicated by arrowheads). Note the aggressive, invasive appearance. This was subsequently proven on biopsy to be due to empyema necessitans from pulmonary mycobacterial tuberculosis. A bland right pleural effusion is also present.

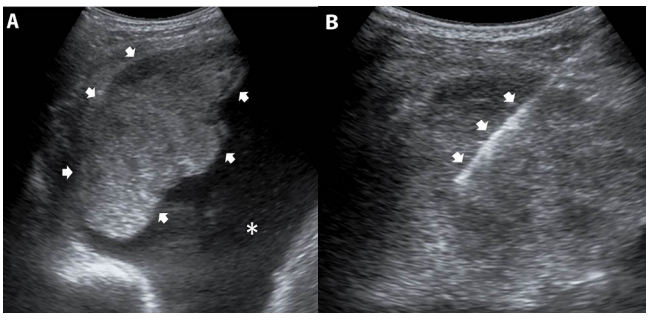

Fig. 9. A: The solid lesion is clearly shown on the ultrasound study (indicated by arrowheads), outlined by the pleural effusion (indicated by *). B: Confirmation of the biopsy needle (indicated by arrowheads) within the centre of the solid mass is shown on ultrasound during the image-guided intervention.

studied is best visualised upon. In this case, either ultrasound or CT would be viable options. However, ultrasound was opted for as it has several advantages over CT such as the absence of ionising radiation (to both the patient and the interventionist), real-time dynamic imaging and lower cost.[6] A formal, preprocedure ultrasound study would have been useful to evaluate the pleural-based lesion of interest, such as in confirming the presence of a solid mass showing vascularity, or identifying cystic spaces representing abscesses within the mass which were potentially drainable, although this was not performed in our case.

Generic, potential complications of imaging-guided percutaneous intervention are haemorrhage, infection and postprocedure pain. More specific potential complications of the ultrasound-guided biopsy performed in our case would include a pneumothorax, haemothorax or inadvertent injury to the subcostal neurovascular bundle.

Conclusion

This young adult male had a chest radiograph which showed a large right pleural effusion. On CT, there were soft tissue components which extended through the intercostal space. Differentials of a soft tissue sarcoma or an atypical infection (empyema necessitans) were entertained. Ultimately, a diagnosis of spindle cell rhabomyosarcoma was made on histology. The learning point here is that a seemingly simple pleural effusion on radiograph may harbour a sinister underlying lesion, and cross-sectional imaging via CT should be performed, in particular, if there were any worrisome clinical features; this patient, for example, had non-mechanical back pain for over a year.

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