MANAGEMENT CHOICES IN PROSTATE CANCER

Nikolas Katelaris, MBBS

Submitted in fulfillment of the requirements of

Masters of Surgery

Department of Surgery

Austin Hospital

Faculty of Medicine, Dentistry and Health Sciences

University of Melbourne, Victoria

Australia

Word count 17 800

March 2018
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>DECLARATION</td>
<td>3</td>
</tr>
<tr>
<td>PUBLICATIONS</td>
<td>4</td>
</tr>
<tr>
<td>PRESENTATIONS</td>
<td>4</td>
</tr>
<tr>
<td>1 PROSTATE CANCER</td>
<td>5</td>
</tr>
<tr>
<td>1.1 Introduction</td>
<td>5</td>
</tr>
<tr>
<td>2 CURRENT ROLE OF mp-MRI IN THE MANAGEMENT OF PROSTATE CANCER</td>
<td>6</td>
</tr>
<tr>
<td>2.1 Introduction</td>
<td>6</td>
</tr>
<tr>
<td>2.2 Background: multiparametric MRI prostate</td>
<td>7</td>
</tr>
<tr>
<td>2.3 Systems for predicting prostate cancer risk on imaging</td>
<td>9</td>
</tr>
<tr>
<td>2.4 Comparison of pre-operative mp-MRI to radical prostatectomy histopathology</td>
<td>10</td>
</tr>
<tr>
<td>2.5 Histopathology from prostate biopsy</td>
<td>11</td>
</tr>
<tr>
<td>2.6 Comparison to Prostate-specific Membrane Antigen (PSMA) PET-CT</td>
<td>12</td>
</tr>
<tr>
<td>2.7 mp-MRI in active surveillance</td>
<td>13</td>
</tr>
<tr>
<td>2.8 Conclusions</td>
<td>14</td>
</tr>
<tr>
<td>3 CYTOREDUCTIVE SURGERY FOR METASTATIC DISEASE</td>
<td>15</td>
</tr>
<tr>
<td>3.1 Introduction</td>
<td>15</td>
</tr>
<tr>
<td>3.2 Evidence acquisition</td>
<td>15</td>
</tr>
<tr>
<td>3.3 Background</td>
<td>16</td>
</tr>
<tr>
<td>3.4 Techniques for local control in metastatic PC</td>
<td>17</td>
</tr>
<tr>
<td>3.5 Evidence for surgery in metastatic PC</td>
<td>18</td>
</tr>
<tr>
<td>3.6 Major trials in metastatic PC</td>
<td>23</td>
</tr>
<tr>
<td>3.7 Discussion</td>
<td>25</td>
</tr>
<tr>
<td>3.8 Conclusions</td>
<td>28</td>
</tr>
<tr>
<td>4 CYTOREDUCTIVE SURGERY FOR METASTATIC DISEASE</td>
<td>29</td>
</tr>
<tr>
<td>4.1 Introduction</td>
<td>29</td>
</tr>
<tr>
<td>4.2 Materials and methods</td>
<td>29</td>
</tr>
<tr>
<td>4.3 Results</td>
<td>29</td>
</tr>
<tr>
<td>4.4 Discussion</td>
<td>30</td>
</tr>
<tr>
<td>4.5 Conclusions</td>
<td>32</td>
</tr>
<tr>
<td>5 CONCLUSIONS AND FUTURE DIRECTIONS</td>
<td>33</td>
</tr>
<tr>
<td>6 TABLES AND FIGURES</td>
<td>34</td>
</tr>
<tr>
<td>7 REFERENCES</td>
<td>42</td>
</tr>
</tbody>
</table>
DECLARATION

This thesis contains no material, which has been accepted for any other degree in any university. To the best of my knowledge and belief, this thesis contains no material previously published or written by any other person, except where due reference is given in the text.

Signature:

N.Katelaris

...........................................

Nikolas Katelaris
PUBLICATIONS

1. Perera M, Katelaris N, Murphy DG, McGrath S, Lawrentschuk N. Prostate Imaging Reporting and Data System score of four or more: active surveillance no more. BJU Int. 2016


PRESENTATIONS

2015 Cytoreductive radical prostatectomy – a systematic review, Poster Presentation, VicTas Annual Surgical Meeting, Hobart

2018 An audit of antibiotic prophylaxis for endoscopic urology procedures at Bankstown - Lidcombe Hospital, Moderated Oral Poster Presentation, USANZ, Melbourne

2018 Cytoreductive surgery for men with metastatic prostate cancer, Moderated Oral Poster Presentation, USANZ, Melbourne
1 PROSTATE CANCER

1.1 Introduction

According to the Australian Institute of Health and Welfare, there will be almost 18000 new prostate cancer (PC) diagnoses in 2018. This is estimated to represent almost 25% of all new male cancer diagnoses. Whilst it is a very common cancer, the 5-year survival is over 95% (AIHW, 2017). There are a multitude of new technologies and imaging modalities that have a significant influence on management choices often before they have been validated in rigorous clinical trials. The challenge in PC is to select men for an appropriate treatment based on their risk profile, comorbidities and preference. The goal is to aggressively manage intermediate and high-risk disease whilst preventing morbidity associated with over treatment of low risk PC.

The use of new imaging modalities, particularly multiparametric MRI and PSMA PET scanning has been rapidly introduced into urological practice. The potential benefits of these technologies are significant as they have a broad utility encompassing diagnosis, detection of local recurrence following surgery and use for men on active surveillance. Despite these benefits, there are no accepted clinical standards governing their use. The current role of these imaging modalities is often determined by the discretion of the urologist and whether or not the patient has access to such technologies.

There is an evolving area within prostate cancer regarding the management of men with oligometastatic disease. Whilst the concept of cytoreduction is well established in other malignancies (breast, renal), men with oligometastatic prostate cancer have traditionally not been offered local treatment. Whether or not a significant survival benefit is also conferred is a controversial question that has not been adequately addressed in the medical literature. The management choices for these men are constantly evolving particularly with the increasing sophistication of systemic and radiation therapy. The benefits of local control with regards to preventing the complications of locally advanced PC are examined in the forthcoming.
CURRENT ROLE OF mp-MRI IN THE MANAGEMENT OF PROSTATE CANCER

2.1 Introduction

Prostate cancer screening using PSA testing remains controversial. According to the European Randomised Study of Screening for PC (ERSPC), PSA-based PC screening reduces PC specific mortality by 21% (Schroder, 2014) and yet the findings from this study are insufficient to justify population based screening. Over diagnosis by PSA screening of disease that is more appropriately managed with active surveillance is estimated at 50% (Schroder, 2014). Subsequent treatment of men with insignificant disease leads to unnecessary harm, which makes population screening unacceptable (Moyer, 2012), even to the vast majority of urologists. In order for any screening program to maximise benefit and minimise harm, men with clinically low-risk PC need to be identified and managed with active surveillance rather than being indiscriminately radically treated. Low risk PC as defined by the National Comprehensive Cancer Network (NCCN) is clinical stage T1-2a, Gleason score 6 of less and PSA < 10ng/mL (Gomez-Millan et al., 2015). Over detection of indolent disease is not the issue but rather over treatment, which carries economic burden and risks of urinary incontinence, erectile dysfunction and urethral stricture (Dall'Era et al., 2012; Wilt et al., 2012).

The lack of a validated population based screening protocol for such a ubiquitous disease underlies the dilemma of PC management. In many cases, only well informed men who meet certain criteria (age, comorbidities) and understand the issues surrounding screening undergo PSA testing, digital rectal exam and biopsy. Both transrectal and transperineal prostate biopsy are ‘blind’ techniques which randomly detect both high and low grade disease with a significant false negative rate (Pokorny et al., 2014). The detection is random or “non-targeted” because ultrasound does not reliably demonstrate prostate cancer tissue. A better strategy to prevent harm stemming from over diagnosis of indolent disease is required. The advent of active surveillance protocols based on individual risk stratification of patients has somewhat equilibrated the imbalance between diagnosis and treatment. The complicating factor has been that biopsy pathology (Gleason score) on which risk stratification is based underestimates PC aggressiveness by up to 30% (Schroder, 2014). This adds the confounding and arguably more serious issue of under treatment of high-risk disease.

The advent of multiparametric prostate MRI (mp-MRI prostate) and more recently targeted MRI – ultrasound fusion biopsy has provided a targeted and more accurate means of diagnosing PC in men with an elevated PSA level. In the best hands it has a specificity approaching 90% and a negative predictive value of around 85% (Raz, Haider, Trachtenberg, Leibovici, & Lawrentschuk, 2010; J.
Thompson, Lawrentschuk, Frydenberg, Thompson, & Stricker, 2013). Therefore, a negative mp-MRI justifies a non-biopsy approach at least in the first instance. Interval PSA monitoring is a sensible clinical strategy in this setting. The value of mp-MRI is in decreasing the unnecessary biopsy rate in men with elevated PSA. There is also emerging data to suggest that mp-MRI prostate may prove useful in determining which patients are managed with active surveillance (Panebianco et al., 2015). Pathological diagnosis is still necessary before stratifying patients into high and low risk categories. The authors see the role of mp-MRI as a means of clarifying an abnormal PSA result, not replacing PSA as the initial diagnostic test. The downside is that mp-MRI prostate is expensive and not readily available in all centres.

Yet questions remain: Can mp-MRI be calibrated to detect biologically significant disease? In the pre-diagnosis setting, mp-MRI may be useful for clarifying elevated PSA levels. In the setting of active surveillance it may lead to the detection of prostate cancer progression. With any new technology objective evaluation of its clinical applications is essential. How should we judge mp-MRI of the prostate and its ability to detect PC? This last question in particular is the focus of this review.

2.2 Background: multiparametric MRI prostate

Mp-MRI combines anatomical T2 weighted images (T2WI) with multiple functional parameters (see table 1) in order to more accurately assess and characterise PC. A high resolution T2 weighted image is usually combined with a minimum of two functional parameters in order to achieve the highest sensitivity and specificity (Barentsz et al., 2012). Diffusion weighted imaging (DWI) and MR spectroscopy (MRS) add specificity to lesion characterisation. Dynamic contrast enhancement (DCE) with gadolinium adds sensitivity for cancer detection (Barentsz et al., 2012).

T2WI demonstrates the zonal anatomy and capsule of the prostate. PC in the peripheral zone appears usually appears as a round or poorly defined low signal area (see figure 1). T2WI alone is sensitive but not specific for PC. In many cases it cannot reliably differentiate PC from prostatic intraepithelial neoplasia, haemorrhage or prostatitis. Transitional zone tumours are more challenging to detect due to the similar appearance of benign prostate hypertrophy and malignancy. The addition of at least two functional parameters significantly improves sensitivity and specificity (Barentsz et al., 2012). These parameters include a combination of DWI, DCE and MRS. DCE evaluates tumour angiogenesis (see figure 2). It is performed by administration of gadolinium-based contrast medium. It has been shown to be able to detect significant disease in up to 93% of cases (Barentsz et al., 2012). It has particular clinical utility in previously biopsy negative patients with rising PSA. It is a useful means of detecting recurrence following radical treatment (Roy et al., 2013).
PC restricts diffusion of water molecules due to hyper cellularity and destruction of normal glandular tissue. DWI allows an apparent diffusion coefficient or ADC map to be calculated enabling both qualitative and quantitative assessment of PC aggressiveness. Cancer shows a lower ADC value than normal tissue (Yacoub, Oto, & Miller, 2014). The “b value” with respect to diffusion-weighted sequences is a measure of variation in the strength of the magnetic field. At higher “b values” the sensitivity to water shift or diffusion is increased and anatomical information is filtered out. This enables areas of water restriction (tumour cells) to be more easily identified compared to the normal cells that allow water to diffuse more easily (Yacoub et al., 2014). This is because water movement is restricted in highly cellular tissues. The “b value” is a topic of growing research interest. Values range from 0 (which is essentially a T2 weighted image) to 2500 sec/mm². At this higher range, the anatomical features are not distinguishable and sensitivity to diffusion is at its peak. An area of suspicion will show up as a bright spot on a “b value” map, which corresponds to a darker region on an ADC map (see figure 3).

There is early data to suggest that the application of an ultra high “b value” may be beneficial in PC detection. Katahira et al. (n=201) demonstrated by comparison to whole mount pathology that the addition of DWI with a “b value” of 2000sec/mm² to T2WI has the potential to improve the detection of PC (Katahira et al., 2011). At this early stage it still important for clinicians to consider the overall risk of significant disease based on a system such as PIRADS (prostate imaging-reporting and data system, see below) which incorporates a range of parameters.

Notably several studies have demonstrated that ADC values correlate with Gleason scores. DWI and ADC can assist in risk stratifying patients based on tumour aggressiveness (Luczynska et al., 2014). Donati et al. demonstrated that ADC was independent predictor of tumour aggressiveness, which could significantly differentiate Gleason 6 from Gleason 7 and above disease (Donati et al., 2014). Boesen et al. demonstrated that measuring the ADC of normal tissue and of malignant tissue to develop a ratio lead to more precise correlation with Gleason score. Furthermore the authors claim that the ADC ratio improves accuracy in discriminating Gleason score ≤7 (3+4) from Gleason score ≥7 (4+3) tumors (Boesen, Chabanova, Logager, Balslev, & Thomsen, 2014). Whilst this technology has the potential to reliably differentiate significant disease from indolent disease, it cannot distinguish between individual Gleason scores.

MR spectroscopy can evaluate tumour metabolism by measuring concentration of choline, citrate and creatinine. Benign prostate tissue is rich in citrate. Malignancy is characterised by loss of the citrate peak and corresponding gain in the choline or creatinine peak. This technique is more technically demanding and time consuming and thus not as common as DWI and DCE(Yacoub et al., 2014).
Weinreb et al. (n=110) demonstrated that addition of MRS does not improve the diagnostic accuracy of mp-MRI (Weinreb et al., 2009). Most modern mp-MRI eliminates this phase.

2.3 Systems for predicting prostate cancer risk on imaging

A validated process of predicting final pathology from radiological parameters would further enhance risk stratification. A significant percentage of lesions detected by mp-MRI are benign (Bratan et al., 2013), therefore it is important that radiologists have a reliable method of assessing risk of malignancy in all visible lesions. There are a number of scoring schemes used by radiologists to predict risk of PC based on mp-MRI findings. The Likert-type scoring system is a subjective 5-point scale which radiologists use to assess risk of malignancy. Being a subjective tool, it relies significantly on the experience of the assessor (Rosenkrantz et al., 2013).

The PIRADS (prostate imaging-reporting and data system) is a structured radiological reporting scheme for mp-MRI prostate (see table 2), which is comparable to BIRADS for breast imaging. It has been validated for risk stratification in the setting of repeat biopsies (Portalez et al., 2012). It is based on three main parameters, namely the T2 signal, diffusion weighted imaging (DWI) and dynamic contrast enhancement (DCE) with gadolinium. A score is given which correlates with risk of malignancy on pathological assessment (see table 2). The images presented in figures 1 (T2WI), 2 (DCE) and 3 (DWI with corresponding ADC map) demonstrate images from the same patient. This patient was assigned a PIRADS score of 5 indicating that the lesion in the right peripheral zone was highly suspicious for malignancy. The prediction of a clinically significant prostate cancer for this lesion was based on several parameters including the ADC map (figure 3). This prediction was later confirmed by radical prostatectomy pathology. In addition to the PIRADS score, which aims to determine whether a lesion is significant, extra-prostatic involvement is usually scored on a 5-point scale (Portalez et al., 2012).

It can be difficult to assess the risk of a lesion, especially when the various functional parameters are discordant (Vache et al., 2014). Vache et al. compared several scoring systems used for mp-MRI prostate including the Likert and PIRADS schemes. The authors argue that experienced radiologists can delineate malignancy from benign change subjectively, even in the absence of a clearly defined ‘score’ based on the various parameters. Their data was ultimately in favour of a subjective Likert based system although Likert was familiar with radiologists in their centre compared with PIRADS.

Rosenkrantz et al demonstrated that both PIRADS and Likert performed well for tumour localisation with the caveat that the more subjective Likert system was preferred in the transition zone (Rosenkrantz et al., 2013) where interpretation is frequently complicated by the presence of benign hypertrophy. According to Junker et al, it may be necessary to amend the PIRADS scoring system for
DCE in the transition zone given its limitations in differentiating PC from benign disease in this region (Junker et al., 2014). It is important that consensus is reached regarding an objective scoring system in the transition zone in order that risk assessment continues to improve using this technology.

2.4 Comparison of pre-operative mp-MRI to radical prostatectomy histopathology

The “gold-standard” of evaluating mp-MRI is comparison of pre-operative radiological parameters with the histopathology following analysis of radical prostatectomy specimens. This important comparison has not been comprehensively studied to date yet is potentially the most valid means of evaluating mp-MRI. The limitations of data with mp-MRI include a lack of easy access due to cost and limited machines compounded by a correspondingly large scale, paradigm-shift to utilise this modality, which has been rolled out in an ad hoc fashion. Mp-MRI has been subsidised by Medicare for eligible patients from July of 2018 in Australia. The improved access to mp-MRI in the public system should lead to more robust studies. Despite the limitations of current data, there are credible studies with promising results.

In terms of comparing pre-operative mp-MRI to post-operative histopathology, Styles et al. from Melbourne demonstrated (n=38) that analysing T2WI and DWI in combination was the best strategy for detecting localised PC with a reported sensitivity of 85% for cancers with a volume >0.5cc (Styles et al., 2014). Kitamura et al. (n=54) examined cancer distribution in men who underwent mp-MRI prostate (T2, DWI, MRS), prostate biopsy followed by radical prostatectomy. The prostate was divided into 12 segments, each of which was examined for malignancy on the basis of T2WI, DWI and MRS. Notably DCE with gadolinium was not available. The mp-MRI and biopsy results were compared to the histopathology from radical prostatectomy specimens. They demonstrated T2 and DWI combined had a higher positive rate than any individual sequence when the biopsy result was negative. The authors also raised a practical issue of comparing histopathology with imaging due to distortion of the radical prostatectomy specimen after fixation (Kitamura et al., 2014).

The data relating to mp-MRI have not all been positive. In a study of men (n=106) who underwent mp-MRI for staging followed by radical prostatectomy, Billing et al. demonstrated that mp-MRI was not able to reliably predict extracapsular extension and seminal vesicle invasion. The authors concluded that mp-MRI has limited value in pre-operative staging because of the lack of reliable, predictive data relating to the extent of disease (Billing, Buchner, Stief, & Roosen, 2014). According to Min et al. (n=126), who retrospectively compared mp-MRI to radical prostatectomy pathology, mp-MRI had high specificity (87.5%) but not sensitivity (65%) for predicting extracapsular extension.

(Min et al., 2012). Notably, sensitivity improved from 46.4% to 65% with the addition of DWI. The authors concurred that there were a need for a new protocol to reliably predict extracapsular extension, however they were able to demonstrate that a combination of T1, T2WI, DCE and DWI resulted in accurate detection of PC. Tanaka et al. (n=67) achieved similar sensitivity (60%) and specificity (86%) for the detection of extracapsular extension as part of staging prior to robotic assisted radical prostatectomy. The authors believe that staging mp-MRI has the potential to guide surgical decision-making regarding preservation of the neurovascular bundle (Tanaka et al., 2013).

2.5 Histopathology from prostate biopsy

When radical prostatectomy is not indicated or not performed, comparison with histopathology from biopsy is an alternative when trying to evaluate the utility of mp-MRI prostate to detect biologically significant disease. An indeterminate or suspicious prostatic lesion according to mp-MRI can be targeted with biopsy. Comparison with the final histology (Gleason score and volume) gives a good indication as to the reliability of mp-MRI to detect significant disease.

Transrectal or transperineal ultrasound guided prostate biopsy with a minimum of 12 cores has been the accepted method of confirming PC in men with an elevated PSA level. It is blind to the location of suspicion within the prostate. The false negative rate has been reported as high as 50%. Saturation biopsy (≥24 cores), aimed at improving detection rates may not detect more significant cancer and are associated with higher morbidity (Styles et al., 2014). This leads to repeated biopsies, especially in men for which the clinical suspicion is high. The key concern is the possibility of having undiagnosed significant disease. The detection rate of significant disease is improved with targeted biopsy with exciting implications for avoiding over diagnosis (Styles et al., 2014).

In an era where prostate biopsy is evolving too, some argue that transperineal biopsy with upwards of 24 cores is a better standard to which MRI should be held. Pepe et al (n=100) examined the role of mp-MRI in avoiding repeat transperineal saturation biopsies in men with persistently elevated PSA (4.1-10) with a free to total ratio less than 25% and normal digital rectal exam. They demonstrated that mp-MRI did not identify 22% of cancers, however, these were found to be histologically insignificant. At the same time, mp-MRI was shown to improve the diagnosis of significant disease in the anterior zone. The authors argue that 31 of the men would have been spared from repeat saturation biopsy (Pepe, Garufi, Priolo, & Pennisi, 2015) without a corresponding increased risk of aggressive disease.

The PROMIS study demonstrated that using mp-MRI as a triage test for men with elevated PSA levels may lead to avoidance of primary biopsy in up to 27% of men in addition to improving the detection of clinically significant PC (up to 18%) in men undergoing target biopsy following MRI compared
with biopsy alone. This data also indicated that mp-MRI in this setting reduced the diagnosis of clinically insignificant PC (Ahmed et al., 2017).

A pilot study (n=54) examined MRI – ultrasound fusion biopsy for prediction of final pathology. They compared biopsy pathology to final whole mount pathology. They performed both a mapping biopsy using a 12-point systematic grid and target biopsies of suspicious areas identified by mp-MRI prior to surgery. The results demonstrated that fusion technology allowed greater accuracy in predicting final pathology compared with conventional methods (Luczynska et al., 2014).

### 2.6 Comparison to Prostate-specific Membrane Antigen (PSMA) PET-CT

Mp-MRI has been demonstrated to be a useful triage tool for primary detection of prostate cancer for men with elevated PSA levels (Ahmed et al., 2017) in addition to a useful pre-operative tool for local staging (refer to table 1). The role of Ga68 PSMA PET-CT has not been examined to the same extent in this setting, however has been shown to be useful in pre-treatment staging of men with high-risk disease (Meyrick, Asokendran, Skelly, Lenzo, & Henderson, 2017). Comparative studies between imaging modalities are important and need to be done to address the paucity of reliable data though the current data suggest that the main utility of mp-MRI is for primary detection and that of PSMA PET scan is for detection of recurrent PC. Studies comparing PSMA PET-CT to mp-MRI would be useful in evaluating both modalities, particularly if PSMA PET-CT is to be extended to primary detection rather than just recurrent PC.

The current data suggest that PSMA PET-CT is particularly useful in the setting of detecting recurrent PC. PSMA PET-CT scans can detect PC in 82.8% of patients who were referred with biochemical recurrence (Afshar-Oromieh et al., 2014). Subsequent pathological analysis demonstrated accumulation of tracer in malignant lesions as identified on PSMA PET scan. The sensitivity of PC detection is improved at higher PSA levels (Afshar-Oromieh et al., 2014). Early detection of PC recurrence following radical local therapy is important as it has the potential to delay or even avoid the commencement of systemic therapies and their associated side effects – minimal metastatic disease may be amenable to treatment with targeted radiotherapy. More data is needed looking at such techniques.

PET CT using a choline-based protocol has traditionally been used for this purpose. However, there is poor choline uptake in PC cells and therefore this modality is associated with poor sensitivity and specificity particularly at low PSA levels and high Gleason score (Afshar-Oromieh et al., 2013). PSMA is garnering significant interest as it is over-expressed in PC compared with other PSMA expressing tumours (kidney, small bowel, salivary glands). Almost all adenocarcinomas of the prostate express
PSMA. A PSMA targeted radio ligand labelled with gallium 68 has a strong affinity to PC cells (Afshar-Oromieh et al., 2014).

2.7 Mp-MRI in active surveillance

Active surveillance is being utilised more frequently in the management of PC. The goal is to minimise the harm caused by overtreatment of low risk disease whilst providing a means of identifying men with disease progression who require definitive treatment. A significant number of men on active surveillance protocols have a suspicious lesion that is identifiable on MRI (Schoots et al., 2014). Mp-MRI may prove to be particularly useful in this setting because suspicious lesions can be targeted leading to preferential sampling of PC tissue. This means that PC progression can be detected more efficiently and accurately. There is growing evidence to support the role of repeat mp-MRI prostate with targeted biopsy to improve monitoring of men on active surveillance. In a retrospective analysis, Abdi et al. (n=603) demonstrated that mp-MRI prostate with the option of subsequent targeted biopsy improves the detection of PC progression for men active surveillance (Abdi et al., 2015). Walton-Diaz et al. (n=152) demonstrated that stable mp-MRI findings were associated with Gleason score stability on biopsy. Importantly, only 2.9 fusion biopsies were needed to detect 1 case of Gleason progression compared with 8.74 saturation biopsies (Walton Diaz et al., 2015). According to the authors, mp-MRI may be a promising means of reducing the number of biopsies for men on active surveillance. Once the urologist knows where the suspicious lesion is based on the mp-MRI, there are a number of techniques to target the lesion with biopsy. These include in-gantry MRI biopsy, cognitive fusion and MRI/ultrasound fusion biopsy. Theses techniques all have similar diagnostic yield (Yaxley, Yaxley, Thangasamy, Ballard, & Pokorny, 2017).

Siddiqui et al. (n=85) found that mp-MRI had the potential to reduce the number of repeat biopsies by up to 68% for men on active surveillance (Siddiqui et al., 2015). A tumour that is not detected on mp-MRI is more likely to be low risk (Culp, Schellhammer, & Williams, 2014) and according to Johnson et al., the risk of biologically significant disease in patients with negative mp-MRI is low enough to justify deferring definitive treatment without biopsy (Johnson, Choyke, Figg, & Turkbey). The findings in these studies are promising and certainly warrant evaluation in large prospective trials. The PRIAS (Prostate Cancer Research International: Active Surveillance) study, which is the largest prospective study evaluating active surveillance, has commenced recruiting eligible patients to have mp-MRI incorporated into the surveillance data. This will provide reliable information with regards to the feasibility of mp-MRI in the context of active surveillance (Bul et al., 2013).
2.8 Conclusions

The current literature indicates that mp-MRI prostate is a promising technology within PC management. Robust data to confirm many of these findings is still needed. Despite promising data indicating that Gleason score can be predicted without a tissue sample (particularly with DWI), such findings should be interpreted cautiously in the clinical setting. Particularly in the scenario of an elevated PSA test and negative mp-MRI prostate. The clinical confidence in this aspect of the technology is justifiably more guarded compared with the academic excitement.

Mp-MRI prostate should not be seen as a future replacement for tissue diagnosis but rather as a useful tool in PC diagnosis and management as well as a reliable means of assessing men in the context of active surveillance. Indeed the ability for targeted biopsy is a substantial and long-awaited step forward. It may prove difficult for mp-MRI to be incorporated into a population based screening model due to resource limitations; however, access to this technology has been improved with the new Medicare rebates. Like any new technology, it should be treated judiciously and used in combination with current clinical tools for risk stratification.

More likely than not, the “gold-standard” of evaluating mp-MRI is direct comparison of radiology to histopathology. The development of a more sophisticated, standardised model for correlating radiological parameters with histopathology in addition to higher volumes of good quality data is the logical next research pathway. Ultimately, the ability to reliably predict histological risk of significant PC will determine how we judge mp-MRI.
3 CYTOREDUCTIVE SURGERY FOR METASTATIC DISEASE

a) SYSTEMATIC REVIEW

3.1 Introduction
Men with metastatic prostate cancer (PC) have a survival rate of 30% at 5 years compared with those with organ-confined PC for whom the survival is approaching 100% (Howlader et al., 2010). The overall and cancer specific survival for patients who present with metastatic PC has not significantly improved over the past 20 years (Wu, Fish, Evans, Devere White, & Dall’Era, 2014). Local control for metastatic PC and in particular cytoreductive radical prostatectomy (RP) is an emerging area of research interest. Debulking of primary tumour in the setting of metastases is an established concept in oncological surgery for kidney (Thomas, Rini, & Campbell, 2009), ovarian (Bachmann et al., 2015) and colon cancer (Culliford et al., 2001). There is growing support for a similar approach for PC, however, there are virtually no substantive case matched or randomised controlled studies to support this concept. There is only retrospective evidence to support definitive local treatment for selected patients.

Important clinical questions remain unanswered; do the benefits outweigh the risks when considering RP for patients with metastatic PC? Will the retrospective data relating to cytoreductive surgery be confirmed in rigorous clinical trials? The potential benefit of local control needs to be balanced against the morbidity of surgery. There is consensus in the literature that good quality, prospective clinical data is lacking (Culp et al., 2014; Faiena, Singer, Pumill, & Kim, 2014; Gautam, 2014).

3.2 Evidence acquisition
This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines with pre-defined search terms and inclusion criteria. Studies that examined the local surgical treatment of the primary tumour for metastatic or nodal PC were included. A PubMed search was performed according to PRISMA guidelines in July 2015. The search strategy used combinations of the following terms; “metastatic” OR “oligometastatic” OR “nodal” OR “lymph node positive” OR “D1” AND “prostate cancer” OR “prostate carcinoma” AND “surgery” OR “radical prostatectomy” OR “local treatment” or “cytoreductive”. Additional records were added by reviewing the reference lists of salient articles. Literature search and review of reference lists identified 639 unique citations (see figure 4) of which 595 were excluded as they were not relevant to local surgical treatment of metastatic PC or were commentaries, abstracts or replies to editorials.
3.3 Background

Early evidence for local control in PC

Zincke et al. first described the concept of performing RP for men with regional lymph node involvement in 1982 (Zincke et al., 1982). In a study of 99 men with PC and regional lymph node involvement the authors were able to demonstrate a survival benefit for men who underwent RP and pelvic lymphadenectomy. The addition of simultaneous bilateral orchiectomy reduced the rate of progression. In the non-RP group of this study, survival was poor with the key prognostic indicator being the number of lymph nodes involved. The authors concluded that there was a therapeutic role for RP and pelvic lymphadenectomy for men with PC and limited nodal disease (Zincke et al., 1982). Notwithstanding this positive conclusion, this was not a controlled series comparing RP alone to RP and orchiectomy.

Subsequent to this study, Zincke's group published a large series of patients (n=3463) who underwent RP and pelvic lymphadenectomy for PC using progression free rate and cancer specific survival as the main outcomes. The results were promising with excellent local control being achieved through a combination of surgery and hormonal therapy in patients with PC and positive lymph nodes. The presence of multiple lymph node metastases was a poor prognostic indicator compared to men with single node involvement (Cheng et al., 2001). Historically, RP was abandoned if pelvic lymphadenopathy was noted intraoperatively due to the risk of surgical morbidity without the prospect of cure. This could explain why current data is almost exclusively retrospective.

The concept of cytoreductive surgery

Cytoreductive or ‘debulking’ surgery is a well-established concept in other solid organ malignancies. According to Bachmann et al., the degree or completeness of cytoreduction was an important prognostic factor for patients with advanced ovarian cancer needing colonic resection (Bachmann et al., 2015). Similar results have been demonstrated with colon cancer. Aggressive resection of peritoneal metastases from colon cancer in addition to intraperitoneal chemotherapy has been shown to be beneficial for selected patients. Culliford et al. demonstrated improved survival at 5 years with the combination of surgical cytoreduction and intraperitoneal chemotherapy (Culliford et al., 2001). With respect to genitourinary tumours, the combination of extirpative nephrectomy and chemotherapy has also been proven to be effective for the treatment of metastatic renal cell carcinoma (Thomas et al., 2009), although the results of further tyrosine kinase studies are awaited. The question of cytoreductive RP for metastatic PC still requires further evaluation both in terms of cancer specific survival and palliative benefits.

Understanding metastatic spread

The pattern of spread by organ specific tumours has been known for centuries, however, our
understanding of the process is poor. Previous thinking purported that intrinsic factors mediated autonomous transit of cells to distant sites. The primary tumour may have a more complex role in distant spread than previously thought (Kaplan, Rafii, & Lyden, 2006). The primary may produce an array of growth factors and it is their arrival at distant sites that alters the microenvironment, termed the pre-metastatic niche or ‘soil’ from which metastases form (Kaplan et al., 2006). Kaplan et al. describe up-regulation of growth factors, cytokines and infiltrates derived from bone marrow in the distant sites before the migration of tumour cells. This may dictate the pattern of metastatic spread. Improved understanding of the complex role of the primary tumour in metastatic spread may encourage a more aggressive treatment approach to the primary tumour.

On the other hand, growth factors and cytokines that are up regulated in post-operative wound healing may also promote tumour growth and angiogenesis (Ceelen, Pattyn, & Mareel, 2014). In a review article by Ceelen et al., the authors investigated the influence surgical resection of the primary tumour had on the tumour-host ecosystem in patients with residual or metastatic disease. On the basis of their findings, they hypothesised that resection of a primary can accelerate metastatic growth. There are randomised control trials underway to compare resection to observation in patients without local symptoms in breast and colon cancer. Further understanding of this area may have important consequences for the timing and mode of treatment in patients with synchronous metastatic disease (Ceelen et al., 2014). Similar randomised studies are necessary to address this question in the setting of metastatic PC.

3.4 Techniques for local control in metastatic PC

Surgery
There are number of techniques to achieve local control in PC (see table 3). Radical retro pubic prostatectomy is the most common surgical intervention for PC. Dr Patrick Walsh pioneered the addition of nerve sparing RP in 1982, which has lead to improvement in patient outcomes (Walsh, 2007). Over the past 10 years, minimally invasive robotic assisted radical prostatectomy (RARP) has continually increased in popularity although RARP and open RP seem to have comparable oncological outcomes in experienced hands. Whilst traditionally the morbidity of surgery has been a factor in advising against RP for men with advanced disease, the reduced peri-operative complications associated with minimally invasive approaches (Ficarra et al., 2009; Gandaglia et al., 2014; Trinh et al., 2012; Yu, Hevelone, Lipsitz, Kowalczyk, & Hu, 2012) has led to this option being revisited, particularly if a benefit in local control or survival can be demonstrated.

Radiation
Radiation is the alternative to surgery for definitive local treatment of PC. Several types radiation including external beam radiation therapy or brachytherapy can be utilised for treatment of localised
Conformal radiation therapy allows improved targeting of tumour through a computer generated 3 dimensional map of the tumour. Intensity modulated radiation therapy allows the radiation dose to be varied so that areas of tumour receive a higher dose whilst regions bordering important structures such the rectum and bladder are treated more conservatively in order to reduce toxicity (Gomez-Millan et al., 2015).

There have been significant advances in radiation therapy in recent years particularly with the advent of stereotactic radiosurgery and Cyberknife technology which allows far more accurate and effective treatment of both local PC (Freeman, Dickerson, & Perman, 2014) and oligometastatic disease (Napieralska, Miszczyk, Tukiendorf, & Stapor-Fudzinska, 2014). In a recent large Canadian trial, Nam et al. demonstrated that radiation was associated with higher incidence of non-genitourinary complications than RP in the context of localised disease. Men who underwent primary radiation therapy had a higher incidence of procedures and hospital admissions at 5 years compared with surgery (Wallis et al., 2015). Despite this, radiotherapy dose escalation with seed brachytherapy in combination with ADT resulted in improved systemic control for men with high grade PC (Gleason 9-10) compared to RP and ADT. There was however no difference in cancer specific or overall survival (Kishan et al., 2017).

The results of the PEACE-1 trial, which is a large multicenter study that will include a comparison between ADT + radiotherapy and ADT alone in men with metastatic PC alone are awaited. Similarly, the STAMPEDE trial will examine the role of radiotherapy directed against the primary tumour in slowing metastatic progression and thereby improving survival in men who present with metastatic PC (Parker et al., 2013).

### 3.5 Evidence for surgery in metastatic PC

Urologists are now more willing though still reticent to consider RP in the context of nodal or metastatic PC yet no robust study conclusively proving the merits of this approach has been published (Aoun, Peltier, & van Velthoven, 2014; Gratzke, Engel, & Stief, 2014a). In the absence of controlled trials, an aggressive approach to metastatic PC is difficult to justify, however, there is a growing body of retrospective evidence to support cytoreductive RP for carefully selected men (Fossati et al., 2015). Men with low metastatic burden who respond to neoadjuvant ADT and have disease that can be completely resected may be most suitable (Heidenreich, Pfister, & Porres, 2014b). In addition to oncologic benefits cytoreductive RP also enables more accurate pathological staging (Yossepowitch et al., 2007) and reduces the rate of local complications.

Despite the lack of high level evidence, meaningful conclusions regarding cytoreductive surgery for PC have still been drawn from retrospective studies over the past 20 years. A recent SEER based study
demonstrated that definitive local therapy (RP or brachytherapy) improved survival in men who presented with metastatic PC (Antwi & Everson, 2014). In 1995, Frohmuller et al. demonstrated that RP combined with ADT for men with stage D1 PC led to improved survival and quality of life compared with ADT alone (Frohmuller, Theiss, Manseck, & Wirth, 1995). Similarly, Thompson et al. performed a study in which patients were randomised into a group to receive orchiectomy and placebo or orchiectomy and flutamide. The data analysis included a secondary examination of the impact of previous RP or radiotherapy on survival. The results demonstrated that previous RP in men with metastatic PC was associated with a significant survival benefit compared with those who did not undergo previous RP (I. M. Thompson, Tangen, Basler, & Crawford, 2002).

Coen et al. reported that patients with biopsy proven local recurrence follow primary radiation therapy were at a significant disadvantage compared with men without recurrence. This indirectly demonstrates the importance of local treatment success. In men with successful local control, the incidence of metastatic PC decreased significantly over 5 years. Correspondingly, it progressively increased in the group who failed local therapy (Coen, Zietman, Thakral, & Shipley, 2002). A number of studies have demonstrated that patients with metastatic PC who previously underwent RP survived longer with a better response to systemic therapy (Faena et al., 2014).

Risk stratification has traditionally been oversimplified misleading clinicians towards a nihilistic mindset, often inappropriately selecting ADT as opposed to definitive local treatment (Yossepowitch et al., 2007). Yossepowitch et al. studied a large group of men treated with RP alone. They examined pathologic features and PSA levels to identify high risk patients based on previously described definitions. They discovered that patients stratified as high risk do not have a uniformly poor prognosis following RP. Furthermore, they found that many cases of PC deemed to be high risk were confined to the prostate following pathological examination. The lack of consistency when defining high risk disease complicates clinical decision making regarding recommending treatments to individual patients and enrolling patients into clinical trials (Yossepowitch et al., 2007).

High-risk PC comprises up to 35% of newly diagnosed cases. It is associated with high rates of metastasis and death. PSA level, Gleason score and stage are standard criteria for determine high-risk disease (Hernandez, Nielsen, Han, & Partin, 2007; Sundi et al., 2014). High-risk PC has been historically managed with ADT or radiation. RP has become more frequent in this context for selected patients. As a primary treatment option RP can provide a definitive stage and grade, prevent local complications thus reducing the need for palliative intervention and possibly reduce metastatic progression. Patients may still need adjuvant radiation or ADT, however, RP as a primary treatment option confers multiple benefits (Soares & Eden, 2015).
Establishing a clinical role for cytoreductive RP hinges on a risk-benefit analysis to determine whether the benefits of surgery outweigh the potential risks. Heidenreich et al. addressed the question of feasibility in a recent article published in the Journal of Urology. The authors performed a feasibility and case control study. They included men with minimal osseous metastases (3 or less on bone scan), no visceral disease or extensive lymph node metastases and PSA <1.0ng/mL following neoadjuvant ADT. They compared this group to a control group (matched for age, initial PSA, Gleason score, clinical stage and extent of metastases) who received ADT without any local therapy. Heidenreich et al. established that cytoreductive is feasible and safe in this setting (Heidenreich, Pfister, & Porres, 2014a). The authors proved that there was no difference in surgical outcomes including post-operative continence recovery for cytoreductive RP compared to RP for high risk PC.

In addition to determining feasibility and safety, it is important to also consider the direct benefits of cytoreductive RP. In the study by Heidenreich et al., men who underwent cytoreductive RP did not have genitourinary complications due to local progression (Heidenreich et al., 2014a). These complications include lower urinary obstruction, gross haematuria, clot retention and anaemia. They result in significant increase in palliative procedures. According to the data presented by Heidenreich et al., cytoreductive RP may improve cancer specific survival based on individual PSA response to neoadjuvant ADT. A prospective randomised trial is underway comparing ADT + RP to ADT alone in the setting of distant disease (Heidenreich et al., 2014a).

A significant benefit of RP in the setting of high risk or metastatic PC is the reduction or avoidance of local complications including persistent gross haematuria, bladder neck obstruction, ureteric obstruction and pelvic pain (Heidenreich & Schrader, 2010). These complications have a significant effect on quality of life and are not preventable by systemic therapy. For selected men with metastatic PC, RP can provide excellent local palliation with acceptable morbidity (Steinberg, Epstein, Piantadosi, & Walsh, 1990). Local complication rates have been demonstrated to be higher in patients with nodal disease who were treated with ADT only compared to those who had undergone RP (Stewart & Boorjian, 2014). Local complications often require palliative intervention including transurethral resection of prostate (TURP) or colostomy in rare cases.

Preventing local complications associated with PC invasion is an important consideration before determining a suitable treatment. RP combined with ADT has been shown to provide improved local control in men with nodal disease (Wiegand, Hernandez, Pisters, & Spiess, 2011). A retrospective analysis by Won et al. (2011) demonstrated that treatment of primary PC with RP improves local palliation in men who eventually develop castrate resistant PC. Further, RP was associated with the lowest local complication rate (at the stage of metastatic disease) compared to external beam radiation therapy (Won, Gurney, Marx, De Souza, & Patel, 2013).
ADT has been integral in the management of locally advanced and metastatic PC for many years. The timing and duration of optimal ADT remains controversial. A systematic review by Verhagen et al. concluded that the combination of local and systemic therapy confers a significant survival benefit (Verhagen, Schroder, Collette, & Bangma, 2010). The key question is whether or not the adverse effects of local control and the side effects of ADT are offset by the reported benefits of combination treatment. Careful selection of patients with the goal of maximising survival and quality of life should be the clinical focus. Patients with a life expectancy of 3-5 years in addition to other factors are likely to benefit most from combination local and systemic therapy (Verhagen et al., 2010). A significant number of men who undergo ADT without local treatment will suffer from complications from local invasion of PC. RP in this setting may confer a survival benefit and result in a more durable and favourable response to systemic therapy (Swanson, Thompson, Basler, & Crawford, 2006) in addition to reducing the number of palliative procedures necessary to address local complications (Verhagen et al., 2010).

In an interesting retrospective study by Qin et al., the authors investigated the influence of transurethral resection of the prostate (TURP) for bladder outlet obstruction as a cytoreductive procedure for men with metastatic PC in the setting of complete androgen blockade. They compared the TURP group to a group of men who only received ADT. The two groups were matched on age, baseline PSA and Gleason score. They were able to conclude that TURP resulted in a more prolonged response to hormone therapy with an early trend towards improvement in disease specific survival (Qin et al., 2012). Whilst only a preliminary study this could have significant implications should the survival trend be confirmed (Qin et al., 2012), however, this may only be applicable to men with primary transitional zone tumours.

Lymph node positive PC
Urologists have been historically reluctant to perform RP in patients with nodal disease. Improved understanding of the role of the primary tumour in node positive PC has lead to RP with pelvic lymph node dissection and radiation becoming a viable strategy as part of a multimodal approach for men with node positive PC. Increasing evidence suggests that RP and extended pelvic lymph node dissection improve survival in men with low nodal tumour burden (Gakis et al., 2014; Grimm et al., 2002; Muck et al., 2015; Rusthoven et al., 2014; Schumacher, Burkhard, Thalmann, Fleischmann, & Studer, 2008; Zwergel et al., 2004).

The evidence suggests that combination therapy with surgery and hormone deprivation for selected patients resulted in the best outcome with respect to survival and disease progression Steuber et al. evaluated patients with clinically localised PC and regional lymph node metastasis. They compared
the outcomes for men who underwent RP and those who underwent LN dissection and discontinued RP. Both groups received hormonal therapy. Cancer specific survival at 10 years was 76% for men treated with RP and adjuvant ADT compared to 46% among patients who were given ADT as a monotherapy. The authors controlled for nodal burden. These findings support the role of RP as an important component of a multimodal approach to PC with nodal involvement (Steuber et al., 2011). Zincke et al. demonstrated that the addition of bilateral adjuvant orchiectomy to RP and pelvic lymph node dissection conferred a significant survival benefit compared to RP and pelvic lymph node dissection alone. Only the number of nodes involved and whether or not bilateral orchiectomy was performed determined the survival and disease progression rates (Zincke & Utz, 1984).

RP may offer improved long-term survival for men with lymph node positive PC. Gleason score, positive or negative margins and number of nodes involved predict disease progression and survival. Men with Gleason score <8 and low nodal metastatic burden represent a favourable group for RP. A substantial group of men with limited nodal disease benefit from improved survival after RP and extended lymph node dissection alone (Boorjian et al., 2007; Daneshmand et al., 2004; Frazier, Robertson, & Paulson, 1994; Touijer, Mazzola, Sjoberg, Scardino, & Eastham, 2014). The reasons why RP may be beneficial despite the presence of lymph node metastases are unclear. The primary PC may continue to seed malignant cells into the circulation and thus removal of the primary reduces this seeding (Studer, Collette, & Sylvester, 2010). There is growing evidence to suggest that the involvement of the primary tumour in facilitating spread is far more complex than simply seeding cells into the bloodstream.

PC with the presence of nodal disease in often considered to be a systemic disease state. Engel et al. identified patients (n=1413) with nodal disease using the Munich Registry (between 1988 and 2007). RP was abandoned in 456 men and 957 underwent RP despite the finding of positive lymph nodes. The authors demonstrated an overall survival of 64% for patients who underwent RP compared with 28% when RP was abandoned. They concluded that abandonment of RP in nodal disease was not justified (Engel et al., 2010). Stewart et al. performed a case controlled study to evaluate treatment options in the management of D1 PC. They compared men who underwent RP and pelvic lymph node dissection (PLND) to PLND alone. Their data suggested that RP may extend survival compared to conservative treatment (Cadeddu, Partin, Epstein, & Walsh, 1997). Gratzke et al. (2014) concluded that there was evidence from cohort studies to support aggressive cytoreductive surgery in men with metastatic PC, however, due to a lack of level 1 evidence they are only in support of this treatment strategy in the context of a clinical trial. There are currently RCTs underway in the USA and Europe comparing best systemic therapy to definitive treatment of the prostate + best systemic therapy (Gratzke, Engel, & Stief, 2014b).
In a retrospective study conducted at the Mayo Clinic in 1999, Ghavamian et al. demonstrated a survival benefit for men with lymph node positive PC treated with prostatectomy, pelvic lymph node dissection and early adjuvant orchiectomy compared with men who were treated with ADT only. The 2 groups were case matched for age, T stage, number of positive nodes and pre-operative PSA level. The 10 year and PC specific survival was 66% and 79% respectively in the RP arm compared with 28% and 39% in the ADT arm (Ghavamian, Bergstralh, Blute, Slezak, & Zincke, 1999). The evidence for local control is promising but remains unconfirmed in this context. RP may be beneficial to men with locally advanced PC, even in the presence of low volume metastatic regional lymph node disease (Studer et al., 2010). Bivalacqua et al. compared extended to limited pelvic lymph node dissection. They proposed that extended dissection may confer oncological benefit whilst improving the accuracy of staging for men with positive lymph nodes noted at time of RP (Bivalacqua et al., 2013).

### 3.6 Major trials in metastatic PC

**STAMPEDE trial**

The clinical imperative to improve outcome for men with high risk localised, nodal or metastatic PC currently being managed with long term ADT prompted the STAMPEDE (Systemic Therapy for Advanced or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) trial in the United Kingdom. STAMPEDE recruits men with locally advanced or metastatic PC who are commencing long term ADT. It is a randomised controlled trial, which has been conducted using a multi-arm, multi-stage approach. This enables the comparison of multiple distinct treatment regimes to a single control arm. The multi-stage design allows for initial conformation of feasibility and safety to late stage assessment of survival. It is an efficient means of assessing multiple therapies. The study evaluates three systemic therapies (docetaxel, zoledronic acid and celecoxib) used alone or in combination at the initiation of hormone manipulation for high-risk PC (James et al., 2009).

James et al. analysed the data (n=917) from the men in the control arm of the STAMPEDE trial. Survival was affected by performance status, age, grade and distribution of metastases (bone-only or bone and soft tissue). Survival was disappointing in men presenting was advanced disease who are started on ADT as a monotherapy. This holds true despite active treatments being available at failure of ADT. Men with metastatic PC often spend the majority of their remaining life with castrate resistant disease (James et al., 2014). The analysis of node positive men (N1M0) enrolled in the STAMPEDE study demonstrates improved outcomes in the men randomised to receive prostate radiotherapy which strengthens the argument for treatment of the primary disease in men with node positive PC at presentation (James et al., 2016).
SEER trial

There is a paucity of data regarding the impact on survival of definitive local treatment in men with metastatic disease. Several studies have attempted to address this question. The Surveillance, Epidemiology and End Results (SEER) is a population based cancer database that combines clinical information from cancer registries linked to Medicare in selected states across the United States. Studies with regards to PC have aimed to identify any causal link between definitive treatment (RP or radiation) and cause specific survival. It has been increasingly used as a data pool for research into oncological management and outcomes in recent years. Culp et al. identified men (n=8185) with stage M1a-c (American Joint Committee on Cancer (AJCC) stage) PC at diagnosis using SEER and then divided them based on the definitive treatment they received (either RP, brachytherapy or no surgery or radiation)(Culp et al., 2014).

Main outcomes were overall survival, disease specific survival and cause specific survival. The authors concluded that definitive treatment of metastatic PC with either RP or radiation confers a survival benefit. Increased cause specific survival in patients undergoing local therapy included T4 stage, high-grade disease, PSA > 20ng/ml, age over 70 years and pelvic lymphadenopathy (Culp et al., 2014). The data from SEER is derived from registries linked to Medicare and accordingly there is a lack of important detail regarding factors that are known to affect survival of men with metastatic PC. The most notable of these is treatment with systemic therapy. There were significant limitations in the data presented by Culp et al. The retrospective design using the SEER database means that important confounding factors were not known such as comorbidities and burden of metastatic disease.

In another SEER based analysis, Satkunasivam et al. compared RP, intensity modulated radiation therapy and conformal radiation therapy to no local therapy for men with metastatic PC. They demonstrated a PC specific survival benefit for RP and intensity modulated radiation for patients with metastatic PC. Studies based on the SEER database share similar limitations. The authors concluded that their findings warrant prospective evaluation (Satkunasivam et al., 2015). In another SEER study, Shao et al. demonstrated that following the development of metastases men who previously underwent RP had a longer PC specific survival than men who received primary radiation therapy (Shao et al., 2014). This type of indirect evidence is indicative of the benefits of RP in this context but without confirmation in future trials it is insufficient to guide current practice.

Patients who received local therapy in the SEER study by Culp et al. could be a highly selected group. A retrospective analysis, particularly from a registry, has disadvantages. The reasons for selecting a treatment were not documented in the SEER database. Further, the groups were not matched. The PSA levels were >30ng/dl in more than 60% of the patients in the no local treatment group but only
13% in the RP group has similar PSA levels. The stage and grade of disease was poorly recorded in the non-surgical group whilst it was well documented in the local therapy group introducing a significant selection bias (Panda, 2014).

**CHAARTED trial**

There have been significant improvements in systemic therapy including hormonal and chemotherapy, however, ADT remains the standard of care for men with metastatic disease. The CHAARTED trial (Chemohormonal therapy versus Androgen Ablation Randomised Trial for Extensive Disease) demonstrated the benefit of docetaxel in combination with ADT compared to ADT as a mono therapy, giving clinicians another option in this patient group. Men presenting with metastatic PC are almost always treated with ADT +/- docetaxel without addressing the primary tumour with either RP or radiation. Indeed, the current standard of care is systemic therapy usually without any consideration of surgery. The logic is that the metastases are the salient component of disease progression. It has however been demonstrated that self-seeding from the primary tumour is mediated through circulating tumour cells. Furthermore, that self-seeding can accelerate malignant growth and angiogenesis (Kim et al., 2009).

### 3.7 Discussion

The potential benefits of cytoreductive surgery include delaying or avoiding the initiation of ADT and improved cancer specific survival – there is an increasing body of retrospective evidence that supports the latter (Engel et al., 2010; Ghavamian et al., 1999; Heidenreich et al., 2014a; Steuber et al., 2011), though definitive data is lacking. Metastatic PC exists on a spectrum and should not be treated as a single entity. PC ranges from organ-confined disease to nodal involvement to widespread metastases. Data needs to be organised to address the differences between types of metastatic disease. The impact of the number of lymph nodes on prognosis has been demonstrated in several papers [38-41]. Whilst still limited, the evidence for treating the primary is more convincing for men with nodal involvement than with bony metastases.

There are significant biases affecting surgical studies (Engel et al., 2010; Faiena et al., 2014; Steuber et al., 2011) that demonstrate oncolgical benefit for metastatic PC and therefore the findings should be carefully evaluated. Some of the demonstrated benefit can be attributed to selection bias – men undergoing surgery are more likely to be fitter have a lower burden of metastatic disease. Similarly, with newer imaging techniques such as PSMA PET scan, men who were previously classified as having localised diseased are being classified as having metastatic disease due to the higher sensitivity of PSMA PET scan compared with traditional imaging techniques. With the increasing sophistication of diagnostic techniques, metastases are being identified which would have previously been silent and unidentified. Stage migration, previously described in the New England Journal of
**Medicine as the “Will Rogers” phenomenon** (Feinstein, Sosin, & Wells, 1985) may also contribute to a more favourable outcome in surgical patients. Because the prognosis of those men who migrated (to the metastatic group), although worse than for members of the localised PC group is still more favourable than for the men who were initially classified as having metastatic disease. In this scenario, oncological outcomes actually improve in both groups. Stage migration is particularly significant for uncontrolled, non-randomised data of which the literature is mostly comprised.

There is a paucity of data regarding local surgery for men with oligometastatic disease compared with metastatic nodal disease. Feasibility studies that demonstrate the safety and low morbidity of RP for men with metastatic PC are a positive initial step (Gontero et al., 2007; Heidenreich et al., 2014a; Sooriakumaran et al., 2015), however, controlled trials looking specifically at this patient group with respect to oncological outcomes are still needed to answer key clinical questions. A recent case series (n=6) from Melbourne, Australia also demonstrated that surgery can be safely performed in men with low volume bony disease with minimal morbidity (N. Katelaris, Murphy, D, Lawrentschuk, N, Katelaris, A, Moon, D, 2015). Ideally a randomised study should be performed comparing surgery + ADT to ADT alone, however, this type of study design presents several challenges including difficulty in obtaining consent for randomisation due to a desire to be the active or surgery group. Prospective studies are underway to determine which group of patients is most likely to benefit from the inclusion of local therapy in the setting of metastatic disease (Bayne et al., 2015).

The proven benefits of cytoreductive RP include preventing local complications thereby improving quality of life and allowing for accurate pathological staging. Improving quality of life may be sufficient to justify aggressive treatment for carefully selected men. Locally advanced PC is a highly morbid condition. The complications of uncontrolled pelvic malignancy include recurrent bladder neck obstruction requiring TURP, gross haematuria that can be difficult to control, rectal compression, ureteric obstruction and intractable pelvic pain. Therefore, cytoreductive surgery should be considered even if cure is not achievable (Wiegand et al., 2011). RP in the presence of oligometastatic disease should be considered in the context of definitive palliation and also for its potential to improve cancer specific survival (Frohmuller et al., 1995).

Surgery has several benefits compared to other means of achieving local control in the context of metastatic disease (see table 3). Definitive local treatment is the first step to improving survival or potentially curing men with oligometastatic disease. The options for this include radical surgery or radical radiation therapy. Surgery has several advantages over radiation therapy for men with metastatic PC. The advantages include arguably better local control particularly for high-grade disease and the option of salvage radiation for multi-modal local therapy with options available for
treatment of permanent side effects such as urinary incontinence should they occur.

It should be noted that the risk of urinary incontinence for men with high risk PC that undergo RARP is higher than for intermediate or low risk patients. A systematic review reported variable urinary continence at 1 year using a “no-pad” definition for men with high-risk disease, mostly using the D’Amico classification. The range was between 51-95% (Yuh et al., 2014). Yee et al reported the pad free continence rate at 1 year at 84% for high risk patients (Yee, Narula, Amin, Skarecky, & Ahlering, 2009).

Shao et al. demonstrated that in men who developed metastases following primary treatment with RP or radiation those who received RP had a longer cancer specific survival (Shao et al., 2014). Whilst this reflects indirect evidence, it may have implications for selecting a treatment modality. With effective treatment of the primary cancer and the oligometastatic disease with stereotactic radiation, it may be that ADT can be avoided or at least significantly delayed thereby reducing the morbidity associated with it.

In order to definitively treat PC with oligometastatic disease, it is necessary to control the primary with RP and the oligometastatic disease with stereotactic radiation therapy. The advent of the PSMA PET scan may have an important role in the management of men with oligometastatic disease. Currently, PSMA PET scanning is primarily being used to detect PC recurrence in the context of a rising PSA (Afshar-Oromieh et al., 2014). However, its ability to identify lymph node and osseous metastases means that it has the potential to facilitate treatment of metastases with stereotactic radiosurgery, which in turn may improve cancer specific survival in men with metastatic PC. Men with oligometastatic disease in whom the primary tumour is effectively treated may die from their distant disease. By identifying the site of distant disease, PSMA PET scanning enables treatment of the distant disease with stereotactic radiation, possibly improving survival.

Particularly with the emergence of ultra sensitive PSMA PET scanning, it is increasingly important that the role of cytoreductive RP is thoroughly investigated. The rapid introduction of PSMA PET scanning into clinical practice means there are a growing number of men who are being classified as having M1 disease because it is more sensitive than traditional imaging techniques. Indeed, it may prove deleterious to deny these men aggressive local treatment based on ultra sensitive PSMA findings. Whilst PSMA PET scanning still needs to be validated through rigorous trials, it may well be used as a primary pre-operative staging modality (Eiber et al., 2015; N. C. Katelaris et al, 2015) superseding CT and nuclear medicine bone scans.
3.8 Conclusions
Aggressive management of men with oligometastatic PC may be associated with an improvement in cancer specific survival in addition to the significant advantages associated with reducing local complications. Particularly with the emergence of minimally invasive robotic surgery, low morbidity RP combined with the increasing sophistication of imaging (PSMA PET scan) and radiation therapy provides a safe, feasible means of treating men with metastatic PC with the potential for improved cancer specific survival (Safir, Lian, Alemozaffar, & Master, 2015). It is clear from the literature that we need a prospective, multicenter registry to study long-term outcomes and validate the findings of retrospective studies. The hypothesis regarding the benefits of local control in metastatic PC needs to be robustly investigated.
4 CYTOREDUCITIVE SURGERY FOR METASTATIC DISEASE

b) CLINICAL RESEARCH

4.1 Introduction
Aggressive cytoreductive surgery for men with metastatic prostate cancer (PC) is not yet a part of mainstream urology and is considered by some to be experimental (Gratzke et al., 2014b), however, there is growing evidence to support radical prostatectomy (RP) for selected men with oligometastatic disease. The potential benefits include prevention of local complications and improved cancer specific survival (Heidenreich et al., 2014a; Swanson et al., 2006). A combined treatment approach incorporating RP and stereotactic radiation can delay the initiation of hormone therapy or possibly avoid it altogether. This treatment approach is still in the exploratory phase and there is a need for further data from ongoing studies to assess the outcomes for men undergoing radical surgery in the presence of oligometastatic prostate cancer.

4.2 Materials and methods
A retrospective review of clinical notes was performed to identify men with metastatic prostate cancer who underwent radical surgery between 2012 and 2014 for a group of urologists at a single institution in Melbourne. Men included in the data set had metastatic PC and were offered cytoreductive surgery after careful discussion with the treating urologist. Outcome was measured by surgical complications and post-operative continence recovery. Six cases were identified - five men who underwent robot assisted radical prostatectomy (RARP) and one pelvic exenteration for metastatic PC with symptoms of locally advanced disease. Their presenting features are outlined in Table 4. The surgical and oncological outcomes are summarised in Table 5. Each patient was evaluated with regard to preoperative prostate-specific antigen, grade, stage, adjuvant therapy, and surgical outcomes.

4.3 Results
Patients 1-3 presented with solitary bony metastases and Gleason 9 malignancy on biopsy. Patient 6 presented with two sites of osseous metastases in addition to a single lymph node metastasis and Gleason 8 disease on biopsy. These patients were otherwise fit and well and expressed a strong preference for local treatment, accepting that: this was not mainstream management; oncologic outcomes could not be easily predicted; and that they could subsequently receive stereotactic radiation to the bony lesions – patients 2 and 4 proceeding under the auspice of a clinical trial involving the treatment of men with oligometastatic disease.

Patients 4 and 5 had been diagnosed years earlier and denied local treatment due to the presence of
metastatic disease at presentation. Patient 4 underwent RARP after his PSA had remained stable for 5 years on androgen deprivation therapy (ADT). Patient 5 had undergone radiation to a solitary rib metastasis at presentation 9 years earlier following which ADT was commenced. He was referred with castrate resistant disease and significant local progression causing recurrent urosepsis, haematuria, ureteric obstruction and obstructive voiding, but no sign of metastatic progression on restaging. Given the profound symptomatology related to the locally invasive pelvic malignancy he elected for cystoprostatectomy/anterior resection.

Patients 1-4 and 6 had an uncomplicated recovery from RARP with a median hospital stay of 2 days (1-3). All regained continence within 3 months and remain pad free at follow-up. Patient 5 required temporary colonic diversion for a rectal anastomotic leak and subsequently recovered well. All patients proceeded to additional treatment to sites of metastatic disease with a variable PSA response, however at follow-up, three of the six men have required recommencement of ADT for biochemical progression. Notably, in the three men on ADT pre-operatively the PSA remains lower after aggressive treatment of local and metastatic disease, and at follow-up none of the men have local symptoms from malignancy or the surgery. A surgical approach has demonstrated benefit without deleterious effect in these cases.

4.4 Discussion
Locally advanced PC is a highly morbid condition. The complications of uncontrolled pelvic malignancy include recurrent bladder neck obstruction requiring TURP, gross haematuria that can be difficult to control, rectal compression requiring stoma, ureteric obstruction and pelvic nerve infiltration causing intractable pain. Therefore, palliative surgery should be considered even if cure is not achievable due to the presence of metastatic disease (Wiegand et al., 2011). RP in the presence of oligometastatic disease should be considered in the context of definitive palliation and also for its potential to improve cancer specific survival (Frohmuller et al., 1995). The presented data is retrospective, small and uncontrolled, however, it demonstrates that surgery can be safely performed in this patient group with minimal morbidity. Ideally a randomised study should be performed comparing surgery + ADT to ADT alone, however, this type of study design presents several challenges including difficulty in obtaining consent for randomisation due to a desire to be in the surgery group.

Aggressive local control with RP is only justified if the surgical morbidity is very low. Our experience with RARP for selected men with metastatic PC is that of a low morbidity procedure (see table 5) despite the high-risk patient group. This supports the findings presented by Heidenreich et al. particularly with regards to the excellent post-operative continence (Heidenreich et al., 2014a). The
minor post-operative morbidity was similar to that of RP for men with localised disease. All cases presented were performed at high volume units with experienced operators. In these circumstances, we believe the risk-benefit analysis is in favour of RP rather than ADT alone. The proven palliative benefit of RP for selected men with metastatic PC (Heidenreich et al., 2014a; Stewart & Boorjian, 2014) was also demonstrated in that no palliative procedures were required following definitive local treatment. There was no mortality for the 5 patients presented notwithstanding a short follow up period.

A survival benefit for men undergoing RP for metastatic disease is yet to be proven despite the increasing body of evidence that supports it (Engel et al., 2010; Ghavamian et al., 1999; Heidenreich et al., 2014a; Steuber et al., 2011). It seems reasonable to offer RP to selected, well-informed men with metastatic PC. The use of stereotactic radiation for the treatment of oligometastatic disease means that men in this group may have the chance for cure. The use of Cyberknife stereotactic radiosurgery has been demonstrated to be useful in men with low volume bony metastases (Napieralska et al., 2014) and the use of stereotactic radiation for oligometastatic disease following primary surgical treatment of PC is currently under investigation (POPSTAR trial) in Melbourne. A multimodal approach including primary surgery, radiation and ADT seems to provide the most comprehensive treatment strategy.

To definitively treat PC with oligometastatic disease, it is necessary to control the primary with RP and the oligometastatic disease with stereotactic radiation therapy. The advent of the prostate-specific membrane antigen (PSMA) positron emission tomography (PET) scan may have an important role in the management of men with oligometastatic disease. Currently, PSMA PET scanning is primarily being used to detect PC recurrence in the context of a rising PSA (Afshar-Oromieh et al., 2014; Afshar-Oromieh et al., 2013). However, its ability to identify lymph node and osseous metastases means that it has the potential to facilitate treatment of metastases with stereotactic radiosurgery, which in turn may improve cancer specific survival in men with metastatic PC. Men with oligometastatic disease in whom the primary tumour is effectively treated may die from their distant disease. By identifying the site of distant disease, PSMA PET scanning may enable treatment of the distant disease with stereotactic radiation, possibly improving survival.

Although PSMA PET scanning still needs to be validated through rigorous trials, it may well be used as a primary pre-operative staging modality (Eiber et al., 2015; N. C. Katelaris et al., 2015) superseding CT and nuclear medicine bone scans. The rapid introduction of PSMA PET scanning into clinical practice means there are a growing number of men who are being classified as having M1 disease because it is more sensitive than traditional imaging techniques. It is therefore particularly important in the PSMA era for further studies investigating the role of aggressive local treatment in
men with oligometastatic PC. Indeed, it may prove deleterious to deny men with M1 disease aggressive local treatment based on ultra sensitive PSMA findings.

Aggressive treatment of men with oligometastatic disease includes definitive treatment of the primary. The options for this include radical surgery or radical radiation therapy. Surgery has several advantages over radiation therapy for men with metastatic PC. The advantages include arguably better local control particularly for high-grade disease and the option of salvage radiation for multimodal local therapy with options available for treatment of permanent side effects such as urinary incontinence should they occur. With effective treatment of the primary cancer and the oligometastatic disease with stereotactic radiation, it may be that ADT can be avoided or at least significantly delayed thereby reducing the associated morbidity.

4.5 Conclusions

Minimally invasive RARP combined with the increasing sophistication of imaging (PSMA PET scanning) and radiation therapy provides a safe, feasible means of treating carefully selected men with metastatic PC, with the potential for cure or improved cancer specific survival in addition to preventing local complications. This data supports previous findings that RP in the setting of low-volume metastatic PC is a feasible procedure without increase in morbidity. Further data is needed in order to substantiate these findings.
5 CONCLUSIONS AND FUTURE DIRECTIONS

Management choices in PC are continuously evolving. In an ideal scenario the diagnosis and management of PC would be guided by rigorous randomised trials, however, this is often not feasible. Establishing good quality randomised trials can be problematic, particularly within the field of cytoreductive surgery, as there is often a desire for men to be the ‘active’ or treatment group that offers aggressive local control. Particularly in this setting it is important to consider the available evidence, as this approach may be suitable for carefully selected and appropriately counselled men even if a survival benefit has not been clearly demonstrated.

In some cases, once a technology has been validated its use in clinical practice may have become reduced or obsolete. In each individual circumstance, treatment must be tailored to reflect the patient’s PC risk profile, their comorbidities and preferences. Patient selection remains the key criteria in determining the best management choice. The process of planning appropriate investigations or treatments should begin even before an initial screening test is ordered. Even if technologies are rolled out in an ad hoc fashion, the process of risk stratification and patient selection should be maintained. In such a way, exciting new technologies can be incorporated into PC management without compromising patient care.
### 6 TABLES AND FIGURES

#### Table 1 MR Sequences and their implications for prostate cancer imaging (adapted from Raz et al.[Raz et al., 2010](#))

<table>
<thead>
<tr>
<th>MR Sequence</th>
<th>Specifics</th>
<th>Implications for prostate cancer imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-weighted</td>
<td>Gradient echo sequence with short echo time and short repetition time. Can be used with contrast agents.</td>
<td>Detects hemorrhage secondary to prostate biopsy as hyperintense regions. Used to detect bone metastases and enlarged lymph nodes. A fast pulse sequenced version is used for dynamic contrast-enhanced imaging (see below).</td>
</tr>
<tr>
<td>T2-weighted</td>
<td>Fast spin echo sequence with long echo time and long repetition time. Tissues with higher free water content are brighter. Fat tissue is also bright.</td>
<td>Differentiates zonal anatomy. Cancers are low in signal. Glandular peripheral zone cancers appear as round or ill-defined low-intensity foci. Central gland cancers have similar signal characteristics to the normal and hypertrophic central gland and can be identified by poorly defined borders and lenticular shape. Extracapsular extension can be directly observed. Prostatitis, hemorrhage, atrophy, benign prostatic hyperplasia, and changes after treatment (e.g. radiation induced arteritis) can be mistaken for cancer.</td>
</tr>
<tr>
<td>MRS</td>
<td>The MR signal produces a spectrum of resonances that correspond to different molecular arrangements of the isotope being excited. MRS reflects tumour metabolism.</td>
<td>In cancer tissue the production of citrate is reduced, whereas choline is increased, leading to an increased choline to citrate ratio. 3 Tesla MRI allows for better spectral separation and overall signal when used in combination with MRS.</td>
</tr>
<tr>
<td>DWI-MRI</td>
<td>Water molecules naturally move randomly according to Brownian motion. In tissues with high cellularity (cancer in particular) diffusion is restricted, which results in an increase in MRI signal with this sequence. The degree of sensitivity to water diffusion is reflected in the “b value”. The higher the “b value” the more sensitive the tissue to restricted diffusion. Apparent diffusion coefficient maps can be calculated from the MRI images.</td>
<td>Prostate cancer exhibits restricted diffusion (dark on ADC maps, high signal on source MRI images).</td>
</tr>
<tr>
<td>DCE-MRI</td>
<td>T1-weighted sequence. Low molecular weight contrast agent diffuses from vascular space to extracellular space and then leaks slowly back into the vascular space. The rate of forward leakage, the rate of backward leakage, and the fractional volume of the extracellular space are calculated using pharmacokinetic modelling.</td>
<td>Tumours show early enhancement and early washout of the contrast agent, which enables detection. The higher the tumour grade, the higher these parameters tend to be.</td>
</tr>
</tbody>
</table>

Abbreviations: DCE-MRI, dynamic contrast enhanced MRI; DWI-MRI, diffusion weighted imaging MRI; MRS, magnetic resonance spectroscopy
Figure 1 T2 weighted image demonstrating an area of low signal intensity in the right peripheral zone consistent with PC.
Figure 2 demonstrates a DCE image (top) and post-contrast washout curve (bottom) of a right peripheral zone lesion.
Figure 3 demonstrates a diffusion weighted image (b value=2500) (left) and the corresponding ADC map (right) demonstrating Gleason 4+3 PC in the right peripheral zone.
Table 2 Summary of PIRADS classification: a radiological risk stratification system for PC

<table>
<thead>
<tr>
<th>PIRADS Classification</th>
<th>Risk of PC</th>
<th>Multiparametric score with T2, DWI, DCE and (including MRS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Most probably benign</td>
<td>3,4 (4,5)</td>
</tr>
<tr>
<td>II</td>
<td>Probably benign</td>
<td>5,6 (6-8)</td>
</tr>
<tr>
<td>III</td>
<td>Indeterminate</td>
<td>7-9 (9-12)</td>
</tr>
<tr>
<td>IV</td>
<td>Probably malignant</td>
<td>10-12 (13-16)</td>
</tr>
<tr>
<td>V</td>
<td>Highly suspicious of malignancy</td>
<td>13-15 (17-20)</td>
</tr>
</tbody>
</table>
Records identified through database searching
(n = 626)

Additional records identified through other sources
(n = 13)

Records after duplicates removed
(n = 639)

Records screened
(n = 639)

Records excluded
(n = 595)

Full-text articles assessed for eligibility
(n = 44)

Full-text articles excluded, with reasons
(n = 0)

Studies included in qualitative synthesis
(n = 44)
Table 3 Comparison of treatment modalities for metastatic PC

<table>
<thead>
<tr>
<th>Modality</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>Improved local control compared to radiation, improves accuracy of staging, option of salvage radiotherapy if PC recurs, possibility for cure as part of a multimodal approach with stereotactic radiation for osseous metastases, option of minimally invasive robotic approach, low surgical morbidity</td>
<td>Risk of urinary incontinence (although treatment options are available if this occurs)</td>
</tr>
<tr>
<td>Radiation</td>
<td>Less invasive than surgery, can achieve local control of PC in men not fit to undergo surgery</td>
<td>Bladder and bowel toxicity, limited options for local recurrence following radiotherapy</td>
</tr>
<tr>
<td>Chemohormonal therapy</td>
<td>Least invasive approach, can control advanced disease for several years</td>
<td>Metabolic complications (e.g. osteoporosis), does not prevent local complications, only effective in controlling disease for 3-5 years</td>
</tr>
</tbody>
</table>
### Table 4 Summary of patients – presenting features

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Initial PSA (ng/mL)</th>
<th>Gleason Score</th>
<th>Clinical stage</th>
<th>Sites of metastasis</th>
<th>Time from diagnosis to surgery</th>
<th>Pre-operative ADT</th>
<th>Local symptoms</th>
<th>Cytoreductive surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>77</td>
<td>7.0</td>
<td>4+5</td>
<td>T2b</td>
<td>7th rib</td>
<td>4 weeks</td>
<td>Nil</td>
<td>Nil</td>
<td>RARP</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>30.0</td>
<td>4+5</td>
<td>T2b</td>
<td>Right inferior pubic ramus</td>
<td>11 mth</td>
<td>LHRH agonist</td>
<td>Obstructive voiding symptoms</td>
<td>RARP</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>27.0</td>
<td>5+4</td>
<td>T3b</td>
<td>L3 vertebra</td>
<td>4 weeks</td>
<td>Nil</td>
<td>Nil</td>
<td>RARP</td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>62.0</td>
<td>4+4</td>
<td>T2b</td>
<td>T11 vertebra</td>
<td>5 years</td>
<td>LHRH agonist</td>
<td>Nil</td>
<td>RARP</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>81.0</td>
<td>4+3</td>
<td>T4</td>
<td>4th rib, T7 vertebral body</td>
<td>9 years</td>
<td>LHRH agonist + bicalutamide</td>
<td>Haematuria, bladder outlet and ureteric obstruction</td>
<td>Pelvic exenteration</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>45.0</td>
<td>4+4</td>
<td>Not known</td>
<td>Symphysis pubis, right inferior pubic ramus and left internal iliac node</td>
<td>5 months</td>
<td>LHRH agonist</td>
<td>Nil</td>
<td>RARP</td>
</tr>
</tbody>
</table>

### Table 5 Surgical and oncologic outcomes

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cytoreductive surgery</th>
<th>Surgical complications</th>
<th>Final Gleason score</th>
<th>Pathological stage</th>
<th>Surgical margin status</th>
<th>Time from diagnosis to surgery</th>
<th>Pre-operative ADT</th>
<th>Post-operative radiation</th>
<th>Follow-up (mth)</th>
<th>Follow-up continence</th>
<th>Follow up PSA (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RARP + pelvic lymphadenectomy</td>
<td>Nil</td>
<td>4+5</td>
<td>pT3bN1</td>
<td>Negative</td>
<td>4 weeks</td>
<td>Nil</td>
<td>Stereotactic radiation to 7th rib</td>
<td>8</td>
<td>Pad-free</td>
<td>0.36</td>
</tr>
<tr>
<td>2</td>
<td>RARP</td>
<td>Nil</td>
<td>4+5</td>
<td>pT3bNx</td>
<td>Negative</td>
<td>0.77</td>
<td>LHRH agonist + bicalutamide</td>
<td>Stereotactic radiation to pubic ramus (POPSTAR trial)</td>
<td>21</td>
<td>Pad-free</td>
<td>0.44</td>
</tr>
<tr>
<td>3</td>
<td>RARP + pelvic lymphadenectomy</td>
<td>Nil</td>
<td>5+4</td>
<td>pT3bN0</td>
<td>Focal positive margins at base, apex</td>
<td>19.9</td>
<td>LHRH agonist + bicalutamide</td>
<td>Stereotactic radiation to L3 vertebra</td>
<td>21</td>
<td>Pad-free</td>
<td>4.7</td>
</tr>
<tr>
<td>4</td>
<td>RARP + pelvic lymphadenectomy</td>
<td>Nil</td>
<td>4+5</td>
<td>pT3bN0</td>
<td>Positive</td>
<td>&lt;0.1</td>
<td>LHRH agonist</td>
<td>Adjuvant radiotherapy, subsequent stereotactic radiation to right iliac lesion (POPSTAR trial)</td>
<td>36</td>
<td>Pad-free</td>
<td>0.1</td>
</tr>
<tr>
<td>5</td>
<td>Pelvic exenteration</td>
<td>Colorectal anastomotic leak - managed with defunctioning stoma</td>
<td>4+3</td>
<td>pT4N0</td>
<td>N/a</td>
<td>0.3</td>
<td>Nil</td>
<td>Stereotactic radiation to new metastatic lesions 7 mths post-op (pelvic lymph node, ilium, rib)</td>
<td>10</td>
<td>Beal conduit</td>
<td>5.1</td>
</tr>
<tr>
<td>6</td>
<td>RARP</td>
<td>Nil</td>
<td>4+4</td>
<td>pT2c</td>
<td>Negative</td>
<td>&lt;0.01</td>
<td>LHRH agonist (ceased 2 months post RARP)</td>
<td>Stereotactic radiation to 3 metastatic sites</td>
<td>17</td>
<td>Pad free</td>
<td>0.07</td>
</tr>
</tbody>
</table>
REFERENCES


42


