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Original Article

# Cytoreductive surgery for men with metastatic prostate cancer

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ABSTRACT

**Background:** Cytoreductive surgery for metastatic prostate cancer is an emerging area of interest with a potential upside that includes local control, delayed initiation of hormone therapy, and possibly improved cancer specific survival. In order for radical prostatectomy to be an effective treatment option for men in this group, the benefits must outweigh the surgical morbidity. The aim of this study was to present a case series and assess the literature feasibility of cytoreductive surgery for men with metastatic prostate cancer.

**Methods:** A retrospective review of clinical notes was performed to identify men with metastatic prostate cancer who underwent cytoreductive surgery between 2012 and 2014 for a group of urologists at a single institution in Melbourne. Each patient was evaluated with regard to preoperative prostate-specific antigen, grade, stage, adjuvant therapy, and surgical outcomes.

**Results:** Six cases were identified. This included 1 pelvic exenteration and 5 robot-assisted radical prostatectomies. The men who underwent RARP had uncomplicated recoveries, regained continence within 3 months and remained pad-free at follow up. All patients proceeded to additional treatment of sites of metastatic disease with a variable PSA response, however, 3 of 6 men required recommencement of ADT for biochemical progression at follow up.

**Conclusions:** This data supports recent findings demonstrating that radical prostatectomy for metastatic prostate cancer is feasible. Further studies are needed to explore the role of cytoreductive surgery with regards to the potential oncological benefit.



## 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 [1], 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 [2,3]. 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.

## 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

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**Table 1**
Summary of Patients–presenting Features.

| Patient | Age (yr) | Initial PSA (ng/mL) | Gleason score | Clinical stage | Sites of metastasis | Time from diagnosis to surgery | Pre-operative ADT | Local symptoms | Cytoreductive surgery |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 77 | 7.8 | 4+5 | T2b | 7th rib | 4 wk | – | – | RARP |
| 2 | 65 | 30.0 | 4+5 | T2b | Right inferior pubic ramus | 11 mo | LHRH agonist | Obstructive voiding symptoms | RARP |
| 3 | 69 | 27.0 | 5+4 | T3b | L3 vertebra | 4 wk | – | – | RARP |
| 4 | 49 | 62.0 | 4+4 | T2b | T11 vertebra | 5 y | LHRH agonist | – | RARP |
| 5 | 68 | 81.0 | 4+3 | T4 | 4th rib, T7 vertebral body | 9 y | LHRH agonist + bicalutamide | Haematuria, bladder outlet & ureteric obstruction | Pelvic exenteration |
| 6 | 55 | 45.0 | 4+4 | Not known | Symphysis pubis, right inferior pubic ramus, & left internal iliac node | 5 mo | LHRH agonist | – | RARP |

ADT, androgen-deprivation therapy; LHRH, luteinizing hormone-releasing hormone; PSA, prostate-specific antigen; RARP, robot-assisted radical prostatectomy.

metastatic PC with symptoms of locally advanced disease. Their presenting features are outlined in Table 1. The surgical and oncological outcomes are summarised in Table 2. Each patient was evaluated with regard to preoperative prostate-specific antigen, grade, stage, adjuvant therapy, and surgical outcomes.

## 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

**Table 2**
Surgical and Oncologic Outcomes.

| Patient | Cytoreductive surgery | Surgical complications | Final Gleason score | Pathological stage | Surgical margin status | Postoperative PSA (ng/mL) | Postoperative ADT | Postoperative radiation | Follow-up (mo) | Follow-up continence | Follow-up PSA (ng/mL) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | RARP + pelvic lymphadenectomy | – | 4+5 | pT3bN1 | Negative | 1.23 | – | Stereotactic radiation to 7th rib | 8 | Pad-free | 0.36 |
| 2 | RARP | – | 4+5 | pT3bNx | Negative | 0.77 | LHRH agonist + bicalutamide | Stereotactic radiation to pubic ramus (POPSTAR trial) | 21 | Pad-free | 0.44 |
| 3 | RARP+ pelvic lymphadenectomy | – | 5+4 | pT3bN0 | Focal positive margins at base, apex | 19.9 | LHRH agonist + bicalutamide | Stereotactic radiation to L3 vertebra | 21 | Pad-free | 4.7 |
| 4 | RARP + pelvic lymphadenectomy | – | 4+5 | pT3bN0 | Positive | < 0.1 | LHRH agonist | Adjuvant radiotherapy, subsequent stereotactic radiation to right iliac lesion (POPSTAR trial) | 36 | Pad-free | 0.1 |
| 5 | Pelvic exenteration | Colorectal anastomotic leak managed with defunctioning stoma | 4+3 | pT4N0 | N/A | 0.3 | Nil | Stereotactic radiation to new metastatic lesions 7 mo. Post-op (pelvic lymph node, ilium, rib) | 10 | Ileal conduit | 5.1 |
| 6 | RARP | Nil | 4+4 | pT2c | Negative | < 0.01 | LHRH agonist (ceased 2 mo. post- RARP) | Stereotactic radiation to three metastatic sites | 17 | Pad-free | 0.07 |

ADT, androgen-deprivation therapy; LHRH, luteinizing hormone-releasing hormone; N/A, not applicable; PSA, prostate-specific antigen; RARP, robot-assisted radical prostatectomy.

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. Discussion

Locally advanced PC is a highly morbid condition. The complications of uncontrolled pelvic malignancy include recurrent bladder neck obstruction requiring transurethral resection of the prostate, 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 a cure is not achievable due to the presence of metastatic disease.[4] 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.[5] The presented data is retrospective, small and uncontrolled, it demonstrates that surgery can be safely performed in this patient group with minimal morbidity. Ideally, a randomized 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 randomization 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 1), despite the high-risk patient group. This supports the findings presented by Heidenreich et al,[2] particularly with regard to the excellent postoperative continence. The minor postoperative morbidity was similar to that of RP for men with localized disease. All cases presented were performed at high volume units with experienced operators. In these circumstances, we believe the risk-benefit analysis is in favor of RP rather than ADT alone. The proven palliative benefit of RP for selected men with metastatic PC[2,6] was also demonstrated in that no palliative procedures were required following definitive local treatment. There was no mortality for the five patients presented, notwithstanding a short follow-up period.

A survival benefit for men undergoing RP for metastatic disease has yet to be proven, despite the increasing body of evidence that supports it.[2,7–9] 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 to be cured. The use of Cyberknife stereotactic radiosurgery has been demonstrated to be useful in men with low-volume bony metastases,[10] 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.[11,12] 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 tumor 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 rates.

Although PSMA PET scanning still needs to be validated through rigorous trials, it may well be used as a primary pre-operative staging modality[13,14] 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.

## 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 supported 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.

## Conflicts of interest

All authors have no conflicts of interest to declare.

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