FORUM

ROLE OF CYTOREDUCTIVE PROSTATECTOMY IN NON-ORGAN CONFINED PROSTATE CANCER

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Abstract

Prostate cancer is the most common cancer among Australian men. Despite the surrounding controversies, prostate specific antigen screening has resulted in diagnosis being made at a stage in which the cancer is still confined to the prostate in the majority of cases. However, there is still a small subset of men who are not diagnosed until after the cancer has metastasised. Historically, these cases have been managed with androgen deprivation therapy with no role for surgery. However, with data supporting cytoreductive surgery in other cancers such as kidney, breast and ovarian, there is increasing interest in the role of surgery as part of a multimodal approach to men with metastatic prostate cancer. Early data suggest that surgery in this situation is feasible and safe, with encouraging data suggesting an oncological benefit. Randomised trials are underway to establish who might benefit and which strategy should be incorporated. In the meantime, radical prostatectomy in the context of metastatic disease should be considered experimental.

Prostate cancer is the most common newly diagnosed cancer in Australia, accounting for 25% of all new cancers in men.1 The introduction of prostate-specific antigen (PSA) screening in the late 1980s is largely responsible for the upward trend in incidence, although this trend has reversed in recent years, likely due to negative messaging about PSA testing and the well-known consequences of over-diagnosis. This has also resulted in prostate cancer being commonly detected at a stage at which the cancer is still localised to the prostate. Surgery, radiation therapy and active surveillance may be considered at this stage of disease, with good outcomes overall.2,3 However, in approximately 7% of cases, the diagnosis is only made after the cancer has spread beyond the prostate and the role of surgery in this group of men is less clear.4

Current management for non-organ confined prostate cancer

Non-organ confined prostate cancer has a poor prognosis, with a five year survival rate of 28% compared with 100% in organ-confined disease.5 Presently, the treatment of choice in non-organ confined prostate cancer is androgen deprivation therapy (ADT).6 This has been demonstrated in a number of trials to improve overall survival by causing a PSA decline in approximately 90% of patients. However, the efficacy of cancer control tends to be short-lived. Even in the modern era using chemotherapy in addition to ADT, the median time to progression in men presenting with metastatic cancer is less than one year, with median survival less than four years.7

Furthermore, ADT is associated with a variety of adverse effects such as hot flushes, sexual dysfunction, osteoporosis, increased fracture risk, anaemia, decreased cognitive function, metabolic syndrome and increased cardiovascular morbidity, all of which have the potential to severely debilitate a man’s quality of life. Albeit a rare consequence, the ‘flare’ phenomenon that may occur at the initiation of treatment has the potential to be life-threatening in men with high-volume metastatic disease.8

Potential benefits of cytoreductive prostatectomy

The benefit of cytoreductive surgery has been clearly established when evaluating other sites of cancer such as the breasts, ovaries and kidneys.2,9 Regarding prostate cancer specifically, radical prostatectomy (RP) has been historically discouraged on the basis that surgery carries a risk of peri-operative and long-term morbidity and does not offer a definitive cure. Nonetheless, in recent years, the pendulum has begun to swing as a number of publications have supported cytoreductive prostatectomy being offered to men with metastatic disease, aided by the steady replacement of open surgery by minimally invasive techniques that can offer reduced peri-operative surgical risk.

Over the last 10 years especially, results from various studies have suggested an improvement in overall survival and disease specific survival in men with non-organ confined prostate cancer who have undergone surgery to...
have their primary tumour removed. Data from the Munich Cancer Registry demonstrated a significantly superior five-year overall survival rate of 55% in patients with metastatic disease undergoing RP, compared with 21% (p<0.01) in the group without surgery.\textsuperscript{10} A similar study based on the SEER database containing 8185 men also found superior overall survival rates in the group undergoing RP (67.4%) or brachytherapy (52.6%) compared with the no treatment (22.6%) group (p<0.001) (table and figure 1). The five-year disease-specific survival rates in the same study were analogous to the previous findings, with a significantly higher rate of 75.8% in the men who underwent surgery compared to 61.3% and 48.7% in those who underwent brachytherapy or neither local treatments respectively (p<0.001).\textsuperscript{11} These findings are promising for offering surgery to men with metastatic disease.

| Table 1: Five-year overall survival rates for men with non-organ confined prostate cancer. |
|-------------------------------------|-------------------------------------|-------------------------------------|
| **No local treatment** | **Radiotherapy/brachytherapy** | **Radical prostatectomy** |
| **n Total** | **n 5-year OS** | **n 5-year OS** | **n 5-year OS** | **Comments** |
| Culp et al\textsuperscript{11} | 8185 | 7811 | 22.5 | 245 | 52.6 | 129 | 67.4 | Overall survival and disease specific survival was higher in patients undergoing local therapy of the prostate compared to those undergoing no local treatment. The lack of information regarding ADT is a major limitation given the impact of ADT on prostate cancer progression and survival. No significant difference in cancer-specific mortality was found when comparing BT and radical prostatectomy groups. |
| Gratzke et al\textsuperscript{10} | 1538 | 635 | 24.0 | 389 | 20.5 | 74 | 55.0 | Significant difference in five-year overall survival (55% vs 21%) in men undergoing radical prostatectomy compared to those who did not. |
| Engel et al\textsuperscript{12} | 938 | 250 | 60.1 | N/A | N/A | 688 | 84.0 | Men who had their radical prostatectomy aborted had a higher number of positive lymph nodes and had inferior 10-year overall and relative survival rates. Not undergoing RP was determined to be an independent predictor of decreased survival [hazard ratio: 2.04]. |

**Figure 1**: Five-year overall survival rates for men with non-organ confined prostate cancer.

**Five-year overall survival**

<table>
<thead>
<tr>
<th>Survival rate</th>
<th>No Local Treatment</th>
<th>Radiotherapy/Brachytherapy</th>
<th>Radical Prostatectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culp et al (11)</td>
<td>50.0</td>
<td>40.0</td>
<td>80.0</td>
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<td>Gratzke et al (10)</td>
<td>60.0</td>
<td>50.0</td>
<td>85.0</td>
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<tr>
<td>Engel et al (12)</td>
<td>70.0</td>
<td>60.0</td>
<td>90.0</td>
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Although the concept of cytoreductive radical prostatectomy is relatively new and has only been explored directly in a small number of studies, there exist other publications that indirectly support this idea. Engel et al reported a greater overall survival of 84% and 64% at five and 10-years respectively in men with prostate cancer who underwent a prostatectomy, despite intraoperative detection of positive lymph nodes. In contrast, those who had their surgery abandoned due to positive nodes displayed rates of 60% and 28% respectively. In multivariate analysis, RP was an independent predictor of survival in this study [hazard ratio 2.04, 95% confidence interval 1.59 to 2.63, p<0.0001].

Furthermore, Suardi et al examined men with nodal recurrent prostate cancer on 11C-choline PET/CT, who then underwent salvage lymph node dissection, and reports that 40% of the cohort remained clinical recurrence-free after a median follow-up of 81.1 months. A lack of a control group makes interpretation of this result difficult, but suggests a role of removing tissue where cancer is detectable. Additionally, despite not having a surgical intervention arm, the importance of local treatment to the primary tumour is further highlighted by the reduction in both cancer-specific and overall mortality of 12% and 9.8% respectively in patients who have been managed with both radiotherapy and ADT compared with ADT alone.

Cytoreductive surgery has also been shown to improve the effectiveness of adjuvant treatment. This potential advantage was first reported in studies of metastatic renal cell carcinoma that had a better response to systemic therapy in patients who underwent a nephrectomy than those who did not. In the SWOG 8894 randomised study, Thompson et al saw the same effect in prostatic carcinoma where that had a better response to systemic therapy in patients who underwent a nephrectomy than those who did not. In the SWOG 8894 randomised study, Thompson et al saw the same effect in prostatic carcinoma where men who underwent RP prior to ADT experienced a statistically significant decrease in risk of death compared to those who had no prostatectomy [hazard ratio 0.77, 95% confidence interval 0.53 to 0.89]. Importantly, the time to castration-resistant prostate cancer was delayed among the group that had undergone prior surgery compared to the men who had not, with a median time of 40 and 29 months respectively. Likewise, newer agents, such as sipuleucel-T, were also more efficacious in patients who have had their prostate removed.

Surgical removal of the primary tumour also decreases patient morbidity and subsequently improves quality of life. Studies of patients with non-organ confined prostate cancer have reported that men who do not have local treatment of their primary cancer tend to develop complications of their urinary tract. Heidenreich et al observed that 28.9% of men who did not receive any local treatment required surgical or percutaneous intervention for local progression of their cancer. Nearly a quarter of this group had a transurethral resection of the prostate for subvesical obstruction and 5.2% required a nephrostomy for hydronephrosis. Surgical management of the primary tumour was most effective in decreasing the rates of local complications, even compared to external beam radiotherapy. Although complications can be treated through various interventions, it is important to consider that these treatments themselves are not risk-free and may negatively impact patient morbidity.

**Pathophysiological basis for cytoreductive surgery**

The pathophysiological mechanisms behind the conferred benefit of cytoreductive surgery are not fully understood, but different theories have been floated. Kaplan et al proposes that bone marrow-derived haematopoietic progenitor cells play a crucial role in priming the microenvironment of a future metastatic site so that it is more receptive to cancerous cells. Post-colonisation by a cancer cell, growth and cell proliferation is stimulated by endocrine molecules released from the primary tumour site. Hence, it is inferred that by removing the primary tumour progression at a metastatic site would be stunted due to the cells being devoid of the factors necessary for progression.

In a different ‘self seeding’ hypothesis, it is suggested that circulating tumour cells have the ability to colonise their primary tumour. This can consequently accelerate tumour growth, angiogenesis and stromal recruitment through seed-derived factors causing tumour progression. If this concept were applied, cytoreductive RP would prevent self-seeding and lead to improved survival.

**Safety of surgery**

Only one relatively small feasibility study has evaluated surgical outcomes of RP in men with metastatic disease, because surgery has not been historically offered as a potential management option in this group. The feasibility study allocated 23 men with biopsy proven prostate cancer with minimal osseous metastases, absence of visceral or extensive metastases and PSA nadir below 1.0ng/mL after neoadjuvant ADT into the intervention group, and 38 men with metastatic prostate cancer who were treated with ADT only into the control arm. This cohort reported a mean surgical time of 127 minutes, blood loss of 355mL, catheterisation time of 5.6 days and hospital stay of 7.8 days. Complications were somewhat higher, as 13% of patients developed lymphoceles that required treatment and 8.6% developed deep vein thromboses. Continence rates of 91.3% were reported using a safety pad definition. This study is however, limited by its retrospective nature, small sample and short follow-up. Thus while the initial results of cytoreductive RP show potential, at present we are mainly restricted to drawing parallels to outcomes of RP in high-risk patients, generally pT3 or greater, in trying to evaluate the safety of surgery aimed at debulking tumour volume in those with metastatic prostate cancer.
Perioperative measures of prostatectomy in clinically advanced disease were comparable to men with organ-confined disease. A review by Yuh et al, examining robotic RP in high-risk patients, reports mean estimated blood loss as 189mL, 168 minutes operative time and complication rates ranging from 3 - 30%. This compares satisfactorily with Novara et al in their review of outcomes in patients of all diseases that reported figures 166mL, 152 minutes and 3 - 26% for identical parameters. Gontero et al in a single-surgeon experience, found no significant difference in surgical morbidity between patients of different risk categories, but there was a higher rate of blood transfusions, operative time and lymphoceles in the high-risk patients. The increased incidence of lymphoceles is explained by the high rate of lymph node dissection to more accurately stage the cancer and remove potentially cancerous tissue in patients classified as high-risk, as recommended by the current European Association of Urology guidelines. The rate of lymphoceles in extended lymph node dissections is approximately 3% as reported in a systematic review. Oncological outcomes for men with high-risk disease undergoing RP are acceptable when contrasted to those men with a lower-grade of prostate cancer. Yee et al reported an overall positive margins rate of 7.4% with subset analysis according to pathological grade, showing positive margins of 3.1% in pT2, 15.9% in pT3 and 55.6% in pT4 disease. Importantly, the abovementioned feasibility study compares favourably with positive margins of 14.3%. The potential to nerve spare is observed by Casey et al, who demonstrated that there was no significant difference in positive margin rates regardless of the extent of nerve-sparing completed in the procedure. This consequently has a positive impact on the man’s functional ability.

It is important to consider whether RP in metastatic prostate cancer is feasible in terms of acceptable functional outcomes of continence and potency. A recent systematic review found continence rates ranging from 78% to 95% using a 0-1 safety pad definition in patients undergoing robotic RP. Yee et al reported rates as high as 84% at 12 months using a strict no-pad definition. The aforementioned systematic review also reported potency rates that ranged from 52% to 60%. Additionally, defining high-risk as PSA ≥ 15 ng/mL, ≥T2b (disease palpable at least bilaterally on digital rectal examination) or Gleason 8-10, Loeb et al reported continence and potency rates of 92% and 62% respectively within 10 years. These figures are comparable to patients with lower-risk disease. Therefore, as is the case with patients with low-risk disease, post-operative continence appears to be markedly less of an issue than potency.

In a comparison of different modes of RP in high-risk patients, there was no significant difference in rates of complications, positive surgical margins or additional therapy between the open and robotic-assisted RP groups. The number of blood transfusions and the length of stay was however, significantly lower in the robotic surgery subset. Thus, it is suggested that while both means of surgery are safe for high-risk patients, robotic-assisted prostatectomy may hold a slight benefit.

**Patient selection**

Although the aforementioned trials demonstrate that removing the primary tumour is beneficial to the patient, it is important to note that these results are most applicable in only a subgroup of men with certain characteristics. Age ≥70 years, PSA ≥20 ng/mL, high-grade disease and pelvic lymphadenopathy were all determined by Culp et al to act as independent factors that increased cancer-specific mortality. Five-year overall survival and disease-specific survival were greatest in men with one or fewer factors - 77.3% [95% CI, 67.4-84.5] and 89.9% respectively. Patients with two factors showed rates of 53.1% [95% CI, 38.9-65.4] and 68.5%, but these were still superior to those who had neither surgery nor radiotherapy. The subset of men with three or more of the above factors who had their primary cancer treated, showed no significant difference to those who did not. In concordance with other literature, further analysis revealed that patients over 70 years of age, or those with a PSA above 20 ng/mL, were less likely to benefit from local therapy.

Furthermore, it is those patients with a relatively low burden of metastatic disease who are most likely to benefit from this approach. Oligometastatic disease usually refers to patients with five or less sites of recurrent metastatic disease following prior treatment of the primary prostate cancer. There is considerable interest in targeting oligometastatic disease in these cases using ablative techniques such as stereotactic radiotherapy, or extirpative approaches such as salvage pelvic lymph node dissection. However, the definition of oligometastatic disease is contingent of the sensitivity of the imaging used to identify metastases. Conventional imaging such as CT and bone scanning have poor sensitivity and the use of more advanced imaging, such as 68Ga-PSMA PET scanning, will improve selection of patients with truly low volume metastatic disease.

**Ongoing trials**

There are a number of prospective studies currently recruiting which will address the role of radical prostatectomy in men presenting with metastatic disease. These include a randomised study of ADT plus surgery, versus ADT plus radiotherapy, or radiotherapy alone, being run from MD Anderson Cancer Centre (clinicaltrials.gov NCT01751438). Also, a similar study in Ghent is randomising men presenting with metastatic disease to ADT alone versus ADT plus radical prostatectomy (clinicaltrials.gov NCT02138721).
Conclusion

In the context of the recent publications described here, there is increasing interest in the role of RP in select patients with metastatic disease at presentation. These initial results are promising, showing both an improved survival and the potential to delay the time to castration-resistant disease. The surgery itself appears feasible with peri-operative, functional and oncological outcomes being satisfactory compared to other RP data. However, there has only been one study evaluating the safety of cytoreductive RP and as such, most of the parallels have been drawn from men with locally advanced disease. Consequently, further prospective data is required in order establish the role of RP in non-organ confined prostate cancer in selected patients, as part of a multimodal approach.

References