Royal College of Surgeons
ADVANCING SURGICAL CARE

REVIEW

Ann R Coll Surg Engl 2017; **99:** 259–264
doi 10.1308/rcsann.2017.0031

Radical prostatectomy for locally advanced and metastatic prostate cancer

R Veeratterapillay[1], SS Goonewardene[2], J Barclay[1], R Persad[3], C Bach[1]

[1]Newcastle upon Tyne Hospitals NHS Foundation Trust, UK
[2]Guy's and St Thomas' NHS Foundation Trust, UK
[3]North Bristol NHS Trust, UK

ABSTRACT

The management of advanced prostate cancer remains challenging. Traditionally, radical prostatectomy was discouraged in patients with locally advanced or node positive disease owing to the increased complication rate and treatment related morbidity. However, technical advances and refinements in surgical techniques have enabled the outcomes for patients with high risk prostate cancer to be improved. More recently, the concept of cytoreductive prostatectomy has been described where surgery (often Combined with an extended lymph node dissection) is performed in the setting of metastatic disease. Indirect evidence suggests an advantage using the cytoreductive approach. Hypothetical explanations for this observed benefit include decreased tumour burden, immune modulation, improved response to secondary treatment and avoidance of secondary complications attributable to local tumour growth. Nevertheless, prospective trials are required to investigate this further.

KEYWORDS

Radical prostatectomy – Survival – Cytoreductive surgery

Accepted 9 January 2017

CORRESPONDENCE TO

Rajan Veeratterapillay, E: rajan.veeratterapillay@nuth.nhs.uk

Prostate cancer remains one of the most important cancers in men in Europe as it continues to be a leading cause of death.[1] It manifests as a spectrum of disease from indolent, slow growing, low grade tumours to high grade, aggressive neoplasms with metastasis. Given this heterogeneity, from a clinical perspective, the disease is often stratified into risk groups to guide management. Multiple algorithms are available for risk stratification but the classification based on D'Amico *et al* (based on prostate specific antigen [PSA], biopsy and digital rectal examination) is commonly used in clinical practice.[2] It is well recognised that patients in the high risk group (clinical stage ≥T2c, PSA 10–20ng/ml, biopsy Gleason score ≥8) are likely to develop biochemical recurrence after initial therapy and a multimodal approach for patients in this group is increasingly considered.[3]

Traditionally, patients with locally advanced disease were not offered radical prostatectomy (RP) as reports documented that extension of tumour into the rhabdosphincter, rectal wall and seminal vesicles were associated with poor oncological outcome, and were often accompanied by surgical complications that could be life threatening.[4] However, technical advances and refinements in surgical techniques have enabled the outcomes for patients with high risk prostate cancer to be improved in terms of both cancer control and the reduction of the morbidity associated with treatment.[5,6]

On the other hand, in the setting of metastatic disease, androgen deprivation therapy (ADT) has remained the mainstay of treatment. One concept that has received some attention recently and continues to be debated is that of cytoreductive prostatectomy, which involves surgical removal of the prostate in the setting of metastatic disease.[7] This notion is borrowed from therapeutic outcomes in other cancers where improved survival rates have been noted using a cytoreductive approach, for instance in metastatic renal cancer, where cytoreductive nephrectomy has been shown to carry a survival benefit.[8] With advances in surgical technique and staging, there has been some limited evidence suggesting a possible role for cytoreductive surgery in metastatic prostate cancer.[9]

In this paper, we explore the expanding role of surgery for locally advanced prostate cancer and examine the evidence for RP in the presence of metastatic disease. Studies on this topic are summarised in Table 1.[9–22]

Radical prostatectomy for T3/4 N0 M0 disease

Locally advanced prostate cancer is characterised by extracapsular extension including microscopic bladder neck involvement (pT3a), invasion of the seminal vesicles (pT3b) or invasion of other adjacent organs (T4).[23] Owing to various definitions of high risk disease and the range of

quality of published reports, it is difficult to compare outcomes across the literature. A retrospective study at a single institution identified 842 men who had RP for cT3 disease, and survival analysis showed that freedom from local or systemic disease at 5, 10 and 15 years was 85%, 73% and 67%, with the respective cancer specific survival (CSS) rates of 95%, 90% and 79%.[16] The authors also found that the mean time to adjuvant therapy after RP was not significantly different between men with cT3 and those with cT2 disease (4.0 vs 4.3 years).

Another study of over 2,000 men treated by RP identified 235 patients (10.3%) with unilateral cT3a disease by digital rectal examination.[14] Of those, 56% received adjuvant or salvage therapy. The ten-year overall survival (OS) and CSS rates were 77.0% and 91.6% respectively. Those findings suggested that in locally advanced prostate cancer, RP (with adjuvant or salvage treatment when needed) achieved high cancer control rates on long-term follow-up. In a 20-year follow-up study of 843 men who underwent RP for cT3 tumours between 1987 and 1997, Mitchell *et al* reported local recurrence free and CSS rates of 76% and 81% respectively.[10] Joniau *et al* studied 51 patients with cT3b–T4 disease undergoing RP.[11] The OS and CSS rates at ten years were 72.5% and 70.7% respectively, with an overall positive margin rate of 62.7%.

An analysis of the US National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database revealed that patients who underwent RP for cT4 prostate cancer had increased survival compared with patients who received radiotherapy alone or hormone therapy alone and had a survival comparable with that of patients who received radiotherapy plus hormone therapy.[15] Of the 1,093 patients with cT4 disease over a 7-year period, observed and relative survival rates were highest among patients who underwent RP. The increased use of RP for locally advanced disease was highlighted in a population-based study of over 3,000 patients aged ≥66 years with cT3 or cT4 non-metastatic prostate cancer diagnosed between 1998 and 2005.[12] The authors found that 48% received monotherapy (radiotherapy alone, ADT alone or RP alone) and interestingly, the proportion of patients who received RP increased over time, exceeding 10% in 2005.

In summary, those studies show that compared with traditional series, contemporary case series of RP in high risk prostate cancer have reported improved ten-year CSS and biochemical recurrence free survival. In addition, outcomes of multimodal RP for locally advanced disease appear equivalent to radiotherapy without the need for long-term adjuvant ADT.[13,24]

Radical prostatectomy for node positive disease

RP can improve progression free survival and OS in node positive prostate cancer although there is a lack of high level evidence. Consequently, the former practice of aborting surgery in the presence of positive nodes might no longer be supported by current evidence, especially in patients with a limited lymph node tumour burden.[25]

Initial data suggesting a prognostic benefit were reported in a retrospective series of 139 patients staged pN1–N3M0 at RP.[20] In 52 patients, it was decided intraoperatively to proceed with RP and in the remaining 87, the procedure was discontinued. The latter group experienced significantly higher progression rates and lower ten-year OS and CSS rates than the RP treated group.

Boorjian *et al* studied 507 men treated with RP who had positive lymph nodes.[18] Overall, 90% were treated with adjuvant hormonal therapy. At a median of 10.3 years following surgery, the 10-year CSS rate for patients with positive lymph nodes was 85.8%, with 56% of the men free from biochemical recurrence. Adjuvant hormonal therapy decreased the risk of biochemical and local recurrence but was not associated with CSS.

Further data from the Munich cancer registry (1988–2007) identified 1,413 patients with node positive prostate cancer.[17] In 456 of these cases, prostatectomy was abandoned but the other 957 patients underwent RP despite the node positive finding. The OS rate at ten years was 64% among patients who underwent RP but only 28% among those who did not. Multivariate analysis showed that RP was a strong independent predictor of survival (hazard ratio [HR]: 2.04, 95% confidence interval [CI]: 1.59–2.63, $p<0.0001$). These data highlight the survival benefit of RP even in node positive disease.

A systematic review to investigate whether local treatment of the prostate in advanced and/or lymph node metastatic disease improved the efficacy of ADT found that data from randomised trials highlighted a clinically important survival benefit (HR for OS: 0.69, 95% CI: 0.61–0.79) when local treatment (including RP) had been applied to the primary tumour.[26] It would therefore appear that the local therapy in T3 and/or node positive disease is an essential part of the optimal treatment. However, the chance to achieve long-term survival with RP alone for node positive stages is limited, and has been reported to vary between 10% and 14%.[19]

Increasing evidence suggests that RP and extended pelvic lymph node dissection (including the common iliac arteries) improve survival in node positive prostate cancer. A multimodal approach to therapy in this group could lead to long-term improved survival and even cure in selected patients.[25]

Cytoreductive prostatectomy

Indirect evidence supports the concept that removing the bulk of the tumour in metastatic disease impacts on the response to systemic therapy.[27] Culp *et al* evaluated the role of definitive local treatment (RP or brachytherapy [BT]) in patients with metastatic cancer of the prostate.[21] They conducted a retrospective analysis of a 7-year period (2004–2010) with 8,185 men from the SEER database. By comparing patients undergoing RP (n=245) or BT (n=129) with those not receiving surgery or radiation (NSR) (n=7,811), they found that men with metastatic disease who underwent RP or BT had significantly better disease

Table 1 Summary of studies on RP in cases of locally advanced, node positive and metastatic disease

Study	Number of patients	Median age (range)	Median follow-up duration	Median PSA (range)	Gleason score ≥7	Overall survival	Cancer specific survival	Freedom from biochemical recurrence	Other outcomes
Locally advanced disease									
Mitchell, 2012[10]	843	65 yrs (60–69 yrs)	170 mths	10.2ng/ml(4.7–23.7ng/ml)	58%	20 yrs – 36%	20 yrs – 81%	20 yrs – 41%	Margin status, seminal vesicle invasion and non-diploid chromatin were predictors of mortality.
Joniau, 2012[11]	51	64 yrs	108 mths	16.9ng/ml(7–37.2ng/ml)	Not available	5 yrs – 88.0%10 yrs – 70.7%	5 yrs – 91.9%10 yrs – 91.9%	5 yrs – 52.7%10 yrs – 45.8%	PSA and Gleason score were independent predictors of progression free survival.
Lowrance, 2012[12]	3,095	Not available	Not available	Not available	62%	Not available	Not available	10 yrs – 44%	Multimodal therapy produced better outcomes than monotherapy.
Spahn, 2010[13]	712	65 yrs (62–70 yrs)	77 mths	32ng/ml(24.6–50.8ng/ml)	50.9%	10 yrs – 3.6%15 yrs – 58%	10 yrs – 89.8%15 yrs – 84.5%	5 yrs – 64.8%10 yrs – 51.9%	Gleason score was strongest predictor of progression and mortality.
Hsu, 2007[14]	235	63 yrs (41–79 yrs)	70 mths	14.9ng/ml(1–127ng/ml)	40.5%	5 yrs – 95.5%10 yrs – 77.0%	5 yrs – 98.7%10 yrs – 91.6%	5 yrs – 59.5%10 yrs – 51.1%	Margin status and cancer volume were independent predictors of progression free survival.
Johnstone, 2006[15]	1,093	Not available	Not available	Not available	Not available	1 yr – 97.2% 5 yrs – 72.6%	1 yr – 98.4% 5 yrs – 82.5%	Not available	RP cohort had best survival rates.
Ward, 2005[16]	842	66 yrs (61–70 yrs)	124 mths	10.2ng/ml(4.7–23.7ng/ml)	54%	5 yrs – 85% 10 yrs – 75% 15 yrs – 67%	5 yrs – 95% 10 yrs – 90% 15 yrs – 79%	5 yrs – 58%10 yrs – 43%15 yrs – 38%	Preoperative PSA had little effect on outcome.

Node positive disease									
Engel, 2010[17]	1,413 (938 had RP)	65 yrs	66 mths	41.9% were >20ng/ml	Not available	5 yrs – 84% 10 yrs – 64%	5 yrs – 95% 10 yrs – 84%	Not available	RP +/- RPLND improves mortality in node positive disease.
Boorjian, 2007[18]	507	66 yrs (47–79 yrs)	124 mths	42% were >20ng/ml	78.5%	Not available	10 yrs – 85.8%	10 yrs – 55.9%	Margin status, Gleason score and non-diploid chromatin were predictors of mortality.
Bader, 2003[19]	367	64 yrs (44–76 yrs)	45 mths	11.9ng/ml(0.4–172ng/ml)	42%	Not available	5 yrs – 74% (predicted)	3.9 yrs – 76%	Node positivity correlated with progression and mortality.
Frohmüller, 1995[20]	139	Not available	Not available	Not available	Not available	Group 1: 10 yrs – 29.7% Group 2: 10 yrs – 50.8%	Group 1: 10 yrs – 32.1% Group 2: 10 yrs – 70.7%	Not available	RP + ADT (group 2) led to better survival and quality of life than ADT alone (group 1)
Metastatic disease									
Heidenreich, 2015[9]	61(23 had R)	61 yrs (42–69 yrs)	34.5 mths	135.2ng/ml(3.5–150ng/ml)	100%	3 yrs – 91.6%	3 yrs – 95.6%	3 yrs – 78.3%	RP prevents obstructive complications of prostate cancer.
Culp, 2014[21]	8,185 (245 had RP)	62 yrs (58–67 yrs)	16 mths	20% were >20ng/ml	Not available	5 yrs – 67.4%	5 yrs – 75.8%	Not available	Treatment (RP or brachytherapy) improves survival outcomes compared with no intervention.
Thompson, 2002[22]	1,263 (148 had RP)	69 yrs (51–85 yrs)	Not available	46ng/ml(0–5,780ng/ml)	44%	Not available	Not available	Not available	Previous RP was associated with improved survival outcomes.

ADT = androgen deprivation therapy; PSA = prostate specific antigen; RP = radical prostatectomy; RPLND = retroperitoneal lymph node dissection

specific survival (DSS) and OS rates than the NSR group (5-year DSS: 75.8% vs 61.3% vs 48.7% respectively; 5-year OS: 67.4% vs 52.6% vs 22.5% respectively). While limitations of this study included its retrospective non-randomised design as well as a lack of information regarding adjuvant and salvage treatments, it does encourage us to re-examine the role of definitive primary treatment in the setting of metastatic prostate cancer.[28]

In a secondary analysis of the Southwest Oncology Group Study 8894, the authors found that patients who had undergone RP and subsequently developed metastatic disease had a significantly better survival (HR: 0.77, 95% CI: 0.53–0.89) than those who did not have the procedure.[22]

A feasibility study from 2015 investigated cytoreductive prostatectomy in patients with low volume metastasis. Heidenreich *et al* compared 23 patients with biopsy proven prostate cancer (minimal osseous metastases, absence of visceral or extensive lymph node metastases and PSA decrease to <1.0ng/ml after neoadjuvant ADT) who underwent RP with a group of 38 men with metastatic prostate cancer who were treated with ADT without local therapy.[9] The authors found that the median time to castration resistant prostate cancer was 40 months in the RP group and 29 months in the ADT group. Patients in the RP group also experienced significantly better clinical progression free survival (38.6 vs 26.5 months) and higher CSS rate (95.6% vs 84.2%) but OS was similar.

One of the concerns from oncologists regarding RP in the context of metastatic disease has been the lack of evidence of benefit so far. The fundamental oncological principle in treating metastatic prostate cancer patients systemically rather than locally is that malignant tumour cells have already entered the systemic circulation and established metastatic sites. As a result, local therapy to the prostate has potential for harm without a clearly defined benefit.

With limited evidence, robust prospective trials are required to further evaluate the place of cytoreductive prostatectomy. While hypothetical explanations for this observed benefit can be many (decreased tumour burden, immune modulation, improved response to secondary treatment, avoidance of secondary complications attributable to local tumour growth),[7,9,28] it still remains to be seen whether these findings can be replicated in prospective trials.

The TRoMbone (Testing Radical prostatectomy in men with prostate cancer and oligoMetastases to the bone) trial was set up as a multicentre study to test the feasibility of randomising men with oligometastatic prostate cancer (1–3 skeletal lesions, no visceral lesions) to either treatment-as-usual (ADT) or treatment-as-usual plus RP (including extended pelvic lymphadenectomy).[29] The primary outcome measure is feasibility to randomise, measured at six months. The trial started in early 2016 and is due to finish in April 2017.

Another trial investigating the impact of RP as primary treatment in patients with prostate cancer with limited bone metastases is also currently recruiting.[30] This study includes patients with newly diagnosed prostate cancer, and at least one and at most five bone metastases in imaging tests at diagnosis with no evidence of visceral metastasis. Patients are randomised either to ADT plus RP with extended lymphadenectomy or to ADT alone. The primary outcome measure is CSS at five years. The study started in May 2015 and is expected to run until April 2025.

A further multicentre, randomised phase 2 trial is underway in North America.[31] This study is investigating best systemic therapy versus best systemic therapy plus definitive local therapy (radiation or surgery) of the primary tumour in metastatic prostate cancer. These three trials will be informative in identifying the role of surgery in the context of metastatic prostate cancer but as they are still in the early stages, it may be years before the level 1 evidence emerges.

Conclusions

There is accumulating evidence for the benefit of RP for locally advanced disease as first line therapy in selected cases or as part of a multimodal approach. Indirect evidence supports the concept of cytoreductive prostatectomy although this needs to be investigated in prospective trials.

References

1. Heidenreich A, Bellmunt J, Bolla M *et al*. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. *Eur Urol* 2011; **59**: 61–71.
2. D'Amico AV, Moul J, Carroll PR *et al*. Cancer-specific mortality after surgery or radiation for patients with clinically localized prostate cancer managed during the prostate-specific antigen era. *J Clin Oncol* 2003; **21**: 2,163–2,172.
3. Rider JR, Sandin F, Andrén O *et al*. Long-term outcomes among noncuratively treated men according to prostate cancer risk category in a nationwide, population-based study. *Eur Urol* 2013; **63**: 88–96.
4. Stenzl A, Merseburger AS. Radical prostatectomy in advanced-stage and -grade disease: cure, cytoreduction, or cosmetics? *Eur Urol* 2008; **53**: 234–236.
5. Jacobs EF, Boris R, Masterson TA. Advances in robotic-assisted radical prostatectomy over time. *Prostate Cancer* 2013; 902686.
6. Turpen R, Atalah H, Su LM. Technical advances in robot-assisted laparoscopic radical prostatectomy. *Ther Adv Urol* 2009; **1**: 251–258.
7. Faiena I, Singer EA, Pumill C, Kim IY. Cytoreductive prostatectomy: evidence in support of a new surgical paradigm. *Int J Oncol* 2014; **45**: 2,193–2,198.
8. Margulis V, Matin SF, Wood CG. Cytoreductive nephrectomy in metastatic renal cell carcinoma. *Curr Opin Urol* 2008; **18**: 474–480.
9. Heidenreich A, Pfister D, Porres D. Cytoreductive radical prostatectomy in patients with prostate cancer and low volume skeletal metastases: results of a feasibility and case-control study. *J Urol* 2015; **193**: 832–838.
10. Mitchell CR, Boorjian SA, Umbreit EC *et al*. 20-Year survival after radical prostatectomy as initial treatment for cT3 prostate cancer. *BJU Int* 2012; **110**: 1709–1713.
11. Joniau S, Hsu CY, Gontero P *et al*. Radical prostatectomy in very high-risk localized prostate cancer: long-term outcomes and outcome predictors. *Scand J Urol Nephrol* 2012; **46**: 164–171.
12. Lowrance WT, Elkin EB, Yee DS *et al*. Locally advanced prostate cancer: a population-based study of treatment patterns. *BJU Int* 2012; **109**: 1,309–1,314.
13. Spahn M, Joniau S, Gontero P *et al*. Outcome predictors of radical prostatectomy in patients with prostate-specific antigen greater than 20 ng/ml: a European multi-institutional study of 712 patients. *Eur Urol* 2010; **58**: 1–7.
14. Hsu CY, Joniau S, Oyen R *et al*. Outcome of surgery for clinical unilateral T3a prostate cancer: a single-institution experience. *Eur Urol* 2007; **51**: 121–128.
15. Johnstone PA, Ward KC, Goodman M *et al*. Radical prostatectomy for clinical T4 prostate cancer. *Cancer* 2006; **106**: 2,603–2,609.

16. Ward JF, Slezak JM, Blute ML *et al*. Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome. *BJU Int* 2005; **95**: 751–756.
17. Engel J, Bastian PJ, Baur H *et al*. Survival benefit of radical prostatectomy in lymph node-positive patients with prostate cancer. *Eur Urol* 2010; **57**: 754–761.
18. Boorjian SA, Thompson RH, Siddiqui S *et al*. Long-term outcome after radical prostatectomy for patients with lymph node positive prostate cancer in the prostate specific antigen era. *J Urol* 2007; **178**: 864–870.
19. Bader P, Burkhard FC, Markwalder R, Studer UE. Disease progression and survival of patients with positive lymph nodes after radical prostatectomy. Is there a chance of cure? *J Urol* 2003; **169**: 849–854.
20. Frohmüller HG, Theiss M, Manseck A, Wirth MP. Survival and quality of life of patients with stage D1 (T1–3 pN1–2 M0) prostate cancer. Radical prostatectomy plus androgen deprivation versus androgen deprivation alone. *Eur Urol* 1995; **27**: 202–206.
21. Culp SH, Schellhammer PF, Williams MB. Might men diagnosed with metastatic prostate cancer benefit from definitive treatment of the primary tumor? A SEER-based study. *Eur Urol* 2014; **65**: 1,058–1,066.
22. Thompson IM, Tangen C, Basler J, Crawford ED. Impact of previous local treatment for prostate cancer on subsequent metastatic disease. *J Urol* 2002; **168**: 1,008–1,012.
23. Edge S, Byrd DR, Compton CC *et al*. *AJCC Cancer Staging Manual*. 7th edn. New York: Springer; 2010.
24. Bach C, Pisipati S, Daneshwar D *et al*. The status of surgery in the management of high-risk prostate cancer. *Nat Rev Urol* 2014; **11**: 342–351.
25. Gakis G, Boorjian SA, Briganti A *et al*. The role of radical prostatectomy and lymph node dissection in lymph node-positive prostate cancer: a systematic review of the literature. *Eur Urol* 2014; **66**: 191–199.
26. Verhagen PC, SchrÃ¶der FH, Collette L, Bangma CH. Does local treatment of the prostate in advanced and/or lymph node metastatic disease improve efficacy of androgen-deprivation therapy? A systematic review. *Eur Urol* 2010; **58**: 261–269.
27. Swanson G, Thompson I, Basler J, Crawford ED. Metastatic prostate cancer – does treatment of the primary tumor matter? *J Urol* 2006; **176**: 1,292–1,298.
28. Gautam G. Is it truly outrageous to consider radical prostatectomy for men with metastatic prostate cancer? *Indian J Urol* 2014; **30**: 366–367.
29. Testing Radical prostatectomy in men with oligoMetastatic prostate cancer that has spread to the bone. http://www.isrctn.com/ISRCTN15704862 (cited January 2017).
30. Impact of Radical Prostatectomy as Primary Treatment in Patients with Prostate Cancer with Limited Bone Metastases (g-RAMPP). http://clinicaltrials.gov/ct2/show/NCT02454543 (cited January 2017).
31. Best Systemic Therapy or Best Systemic Therapy (BST) Plus Definitive Treatment (Radiation or Surgery). http://clinicaltrials.gov/show/NCT01751438 (cited January 2017).