



Review – Prostate Cancer

An Analysis of Radical Prostatectomy in Advanced Stage and High-Grade Prostate Cancer

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Abstract

Objectives: To clarify the role of radical prostatectomy (RP) in the treatment of locally advanced and high-grade prostate cancer.

Methods: Literature search of Medline publications on surgery for locally advanced and high-grade prostate cancer.

Results: In patients with locally advanced disease, the cancer-specific survival rate after RP at 5- and 10-yr follow-up was 85–100% and 57–91.6%, respectively. The overall survival rate at 5 and 10 yr was > 75% and 60%, respectively. In patients with high-grade prostate cancer (Gleason score \geq 8), the biochemical recurrence-free survival after RP at 5 and 10 yr of follow-up was 51% and 39%, respectively. Nomograms and modern imaging techniques are useful in predicting pathologic stage, presence of positive lymph nodes, or seminal vesicle involvement. These allow physicians to recognise those patients with locally advanced disease who are most likely to benefit from surgical treatment. Downgraded and organ- or specimen-confined high-grade tumours can have a good prognosis after surgery. The prostate-specific antigen value and the percent positive biopsy cores can be helpful in identifying men with high-grade prostate cancer most likely to benefit from RP.

Conclusions: It is likely that surgery has a role in the treatment of locally advanced and high-grade tumours. However, it is necessary and urgent to have randomised trials assessing survival and quality of life when RP is and is not included in the multimodality treatment.

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1. Introduction

Locally advanced prostate cancer is defined as cancer that has extended clinically beyond the

prostatic capsule, with invasion of the pericapsular tissue, apex, bladder neck, or seminal vesicles, but without lymph node involvement or distant metastases [1]. It is referred to as T3–T4 N0 M0 prostatic

cancer. High-grade prostate cancer, also referred to as poorly differentiated prostate cancer, involves tumours with Gleason scores from 8 to 10. In the literature we often find the term high-risk cancer. Based on preoperative parameters, Yossepowitch et al used eight definitions to identify high-risk clinically localised cancer patients and concluded that these patients do not have a uniformly poor prognosis after radical prostatectomy (RP). Many patients classified as being at high risk have pathologically organ-confined cancer and may be cured by RP alone [2]. Historically, patients with locally advanced disease and high-grade prostate cancer have not been viewed as good candidates for RP, due to the high incidence of positive pelvic lymph nodes and poor long-term survival rates [3,4]. The advent of prostate-specific antigen (PSA) screening and modern imaging modalities allow early detection of high-grade tumours. The use of these screening techniques has led to stage migration and decreased morbidity after RP, sparking renewed interest in the use of surgery in men with advanced prostate cancer. Nevertheless, the optimal therapy for patients with locally advanced and high-grade tumours remains to be clearly defined.

2. Surgery for locally advanced and high-grade prostate cancer

Until recently, surgical treatment has not been used in clinical T3–T4 disease and high-grade prostate cancer. Over-staging (pT2), over-grading, and understaging (pT4 or pN+) are common clinical errors. Nomograms can be useful in predicting the pathologic stage of the disease [5,6] and seminal vesicle invasion at RP [7]. In addition, nodal imaging with computed tomography (CT) scans, seminal vesicle invasion (SVI) imaging with magnetic resonance imaging (MRI), or directed specific-puncture biopsies of the nodes or seminal vesicles can be helpful in recognising patients who would not benefit from a surgical approach [8].

The European Association of Urology (EAU) guidelines on prostate cancer state that RP can be performed in patients with locally advanced prostate cancer (PSA < 20 ng/ml, \leq cT3a, and biopsy Gleason score \leq 8) [9]. However, patients with more advanced or poorly differentiated tumours could also potentially benefit from surgery. Surgical treatment in locally advanced T3 prostate cancer involves a radical extirpation, including an extended lymph node dissection, clean apical dissection, neurovascular bundle resection at the tumour-bearing side, complete resection of the seminal

vesicles, and resection of the bladder neck [10,11]. Increased overall surgical experience results in improved positive surgical margin rates over time (75% in 1987–1994, 42% in 1995–1999, and 10.4% in 2000–2004) [12].

Extended lymph node dissection (LND) is mainly advised in locally advanced disease and high-grade prostate cancer, due to a higher risk of node-positive disease. In older surgical series of cT3 disease, the node-positive rate is between 27% and 41% [4,13,14]. Two series had a much lower rate of pN+ cases, with only 8.5% and 11%, respectively, probably due to more accurate and dedicated CT scanning of the pelvis and methods of patient selection [12,15]. CT scanning and fine-needle aspiration cytology increase the preoperative diagnostic accuracy of lymph node invasion [8]. CT-guided biopsies or, when available, sentinel-guided laparoscopic lymphadenectomy can improve the preoperative lymph node assessment [16]. Moreover, the percentage of positive biopsy cores can improve the ability to predict lymph node invasion in patients undergoing RP and extended pelvic lymph node dissection [17]. The most common postoperative complications are urinary incontinence and sexual dysfunction, which occur immediately after RP and tend to improve over time. In early stages of the disease, the incidence of these complications can be reduced by nerve-sparing surgery. In men with T3 disease, however, non-nerve-sparing RP must be carried out [18]. Increased overall surgical experience leads to decreased operative morbidity and better functional results [14,19].

3. Locally advanced prostate cancer

3.1. Studies with RP monotherapy

RP monotherapy may be an acceptable treatment option for cT3 disease. This is true not only in overstaged patients (pT2), but also in true unilateral pT3a, especially if the tumour is specimen-confined (RO). In cT3 disease, the cancer-specific survival (CSS) rate after RP at 5- and 10-yr follow-up is 85–100% and 57–72%, respectively. The overall survival rate (OS) at 5 and 10 yr of follow-up is > 75% and 60%, respectively [4,20,21].

A retrospective multi-institutional analysis of RP monotherapy, looking at 345 patients with cT3 disease, found an actuarial 10-yr CSS rate of only 57%. For patients with well-differentiated, moderately differentiated, and poorly differentiated tumours, CSS rates at 10 yr were 73%, 67%, and 29%, respectively. These results suggest a clear role for RP in treatment of patients with low- to

intermediate-grade tumours. However, in poorly differentiated tumours, RP alone appears unlikely to result in long-term survival [4]. In a single-center series of 83 surgically treated cT3 patients, Van den Ouden et al reported that RP monotherapy produces acceptable results in men with well- or moderately differentiated tumours. In this study, the 5- and 10-yr OS rates were 75% and 60%, respectively, and the 5- and 10-yr CSS rates were 85% and 72%, respectively [20,22].

A study from Van Poppel et al demonstrated that RP monotherapy is an effective treatment in men with T3 disease, particularly in patients with a serum PSA value < 10 ng/ml and uninvolved lymph nodes and seminal vesicles. Clinical T3a patients with PSA values < 10 ng/ml had a 5-yr biochemical recurrence-free survival rate exceeding 60% [15]. Martinez de la Riva et al evaluated 83 surgically treated cT3a patients at a mean follow-up of 68.7 mo and reported OS and CSS rates of 97.6% and 100%, respectively. The authors used very strict selection criteria: limited cT3a on digital rectal examination combined with < T3a on transrectal ultrasonography [21].

These results support the use of RP monotherapy as a possible treatment for selected locally advanced prostate cancer. The possible occurrence of complications is not seen as a valid reason for not performing RP in cT3 disease because only two serious events were observed in a recently reported surgical feasibility study [19].

3.2. Multimodality treatment

In a substantial number of patients, RP monotherapy will not result in a definitive cure; therefore, early adjuvant or late salvage radiation (RT) or hormone treatment (HT) should be considered. In addition, neoadjuvant HT is a possible treatment method, although its role in clinical T3 prostate cancer remains controversial [12,23–26].

In a study by Ward et al, 78% of patients eventually needed adjuvant or salvage RT or HT compared to 56% of patients in a recent study from Hsu et al. These studies reveal excellent 5-, 10-, and 15-yr OS and CSS rates, comparable to those obtained in cT2 patients. In addition, the Ward and Hsu studies had similar survival rates, with 5-yr CSS rates of 95% and 98.7%, respectively, and 10-yr CSS rates of 90% and 91.6%, respectively [14,27]. Ward et al also reported a 15-yr CSS rate of 79%.

In a recent study by Gontero et al, RP appears to be a valid treatment with acceptable morbidity in patients with locally advanced prostate cancer of any T \geq 3, N0-1. The 7-yr OS and CSS rates were 77% and 90%, respectively; 89.5% of the patients received

immediate adjuvant treatment after RP [28]. This is also the opinion of Lange in a recent editorial. However, he expressed the need for a randomised study testing the efficacy of RT and RP as initial therapy for locally advanced prostate cancer [29].

In the meantime, RP series revealed survival rates that surpass those for RT alone and comparable to those of 3 yr of androgen-deprivation therapy combined with external RT (Bolla series; 5-yr OS 78%) [30].

Two randomised studies compared postoperative RT with RP alone for locally advanced prostate cancer. Bolla et al reported an improved biochemical progression-free survival (BPFS) in patients treated with adjuvant postoperative RT (74% vs. 52.6%, $p < 0.0001$) within a follow-up period of 5 yr. Thompson et al showed that adjuvant postoperative RT significantly reduced the risk of PSA relapse (median PSA relapse-free survival, 10.3 yr for RT vs. 3.1 yr for observation, $p < 0.001$) and disease recurrence (median recurrence-free survival, 13.8 yr for RT vs. 9.9 yr for observation, $p = 0.001$). No significant differences in CSS and OS have been observed yet [31,32].

Our belief that RP has a place in the treatment of locally advanced prostate cancer is supported by a few studies recently conducted in the United States [33–38]. A recent US study showed that patients who underwent RP ($n = 72$) for cT4 disease had a better survival than those who received HT alone or RT alone and comparable survival to that of men who received RT plus HT [39].

4. High-grade prostate cancer

4.1. Studies with radical prostatectomy monotherapy

A Gleason score ≤ 7 in a RP specimen, when the biopsy specimen was scored from 8 to 10, is defined as pathologic downgrading. A recent study reported that the incidence of downgrading was 45% and that downgraded patients had an increased BPFS probability (56% vs. 27%). Moreover, patients with a biopsy Gleason score of 8 and a clinical stage of T1c were more likely to be downgraded and, thus, had a better BPFS probability. Of these patients, 64% were free of biochemical or clinical recurrence [40]. In a study from Manoharan et al, the incidence of downgrading was reported as 31%, with patients having a lower biochemical recurrence rate (32% vs. 41%) [41]. Grossfeld et al assessed the surgical outcome of 114 men with high-grade prostate cancer and noted downgrading in 38% of the patients [42]. In a

study from Bastian et al, 34% of men in the patient cohort were downgraded and had a 5- and 10-yr estimated BPFs of 62% and 38%, respectively. In the Shared Equal Access Research Cancer Hospital (SEARCH) database, 55% of men were downgraded and had a 5- and 10-yr estimated BPFs of 34% and 34%, respectively [43].

These results suggest that one third of patients with a biopsy Gleason score ≥ 8 may in fact have a specimen Gleason score ≤ 7 with better prognostic characteristics. Therefore, refusing RP, which is an excellent treatment for those patients, would be incorrect [41]. A number of reports have addressed the success rates of RP monotherapy in high-grade cancer. Donohue et al examined the outcome of RP monotherapy in 238 patients with high-grade prostate cancer and found a 5- and 10-yr BPFs of 51% and 39%, respectively, in agreement with rates reported in other series [40,44–46]. Mian et al assessed the outcome of patients with a specimen Gleason score ≥ 8 treated with RP alone. The reported 5- and 7-yr BPFs of 71% and 55%, respectively, are better than the rates reported by Donohue and other studies. In addition, the rate of lymph node metastasis was only 6% compared to 20% in the Donohue study [47]. In a study analysing 79 high-grade patients treated with RP at a mean follow-up of 55 mo, the overall biochemical failure rate was 38% (41% if Gleason score was ≥ 8 , and 32% if it was ≤ 7). Manoharan et al concluded that RP is a reasonable treatment option for patients with a biopsy Gleason score ≥ 8 and clinical stage T1–2, especially if their PSA level is ≤ 20 ng/ml [41].

Serni et al evaluated the outcome of 116 patients with Gleason scores ≥ 8 who underwent RP. The 3- and 5-yr progression-free survival rates for all patients were 84.6% and 78.1%, respectively. The 5-yr BPFs for those with Gleason scores of 8 and 9 were 72.1% and 38.2%, respectively ($p \leq 0.05$) [48].

Bastian et al reviewed the data of men with Gleason scores of 8–10 treated with RP at the Johns Hopkins Hospital ($n = 220$; 3.8% of the total cohort) and those within the SEARCH database ($n = 149$, 7.7% of the total cohort). The authors reported 5- and 10-yr estimated BPFs rates of 40% and 27%, respectively, for the Johns Hopkins cohort, and 32% and 28%, respectively, for those within the SEARCH database [43]. In conclusion, patients undergoing RP with biopsy Gleason scores of 8–10 do not necessarily have a poor prognosis.

Although most high-grade tumours extend outside the prostate, those that are confined to the prostate at histopathologic examination have a good prognosis after RP [49].

PSA screening enables detection of high-grade tumours with smaller volume at an earlier stage, thus improving the organ- and specimen-confined disease rates [47]. Two separate studies reported the incidence of organ-confined disease at 26% and 31% [44,47]. Mian et al showed that patients with organ- and specimen-confined disease had a higher 5-yr disease-free survival rate than those with non-specimen-confined disease (82%, 84%, and 50%, respectively). A favourable disease-free survival could be expected in patients treated with RP alone, especially if the cancer is confined to the prostate or surgical specimen [47]. Bastian et al found higher 5- and 10-yr estimated BPFs among men with organ-confined disease and negative surgical margins (79% and 50% vs. 40% and 27% for the entire cohort, respectively) [43].

Serni et al reported that the incidence of organ-confined node-negative disease is 11.2%. At a mean follow-up of 46 mo, all patients with organ-confined disease were free of biochemical recurrence. These results emphasise the importance of early diagnosis and indicate that intracapsular tumours are less likely to metastasise, even with a high Gleason score. The incidence of pT3, specimen-confined, node-negative disease (29.3%) was greater than has been reported in other series [45,46,48,50]. Serni et al reported that the 5-yr BPFs rates for pT3a specimen-confined, pT3a non-specimen-confined, and pT3b disease were 68.2%, 53.3%, and 10.5%, respectively. These results show that high-grade tumours that have invaded the capsule can also be cured by surgery. The finding of negative margins improves the BPFs, although the presence of histologically confirmed SVI indicates a poor prognosis. Using the anterograde technique minimises the incidence of positive surgical margins in high-risk patients and increases the pT3a specimen-confined detection rate [48].

Grossfeld et al noted a 5-yr disease-free survival rate of 47% in high-grade patients with PSA ≤ 10 ng/ml versus 19% in those with PSA > 10 ng/ml. Patients with high-grade disease might therefore be appropriate candidates for RP if the PSA value is ≤ 10 ng/ml and the % PBCs $< 66\%$ [42].

A more recent study by Hurwitz et al assessed the surgical outcome of 168 men with high-grade prostate cancer. Patients with PSA < 10 ng/ml and % PBCs $< 50\%$ had a 5-yr BPFs probability of 67% versus 23% for all other patients [51]. Both studies suggest that the PSA value and the % PBCs can be helpful in selecting men with high-grade prostate cancer most likely to benefit from RP.

Interobserver variations in pathologic staging are well documented and need consideration.

4.2. Comparison among conservative treatment, RP, and RT

Recently, Tewari et al compared the use of conservative treatment ($n = 197$), RP ($n = 119$), and RT ($n = 137$) in high-grade prostate cancer. The study was conducted as a single institutional, retrospective cohort study including 453 patients with biopsy Gleason scores ≥ 8 . Using propensity-scoring analysis, the median OS rate for conservative treatment was 5.2 yr, for RT it was 6.7 yr, and for RP it was 9.7 yr. Median CSS was 7.8 yr for conservative treatment and > 14 yr for both RT and RP. The risk of cancer-specific death after RP was 68% lower than after conservative treatment and 49% lower than after RT ($p < 0.001$ and $p < 0.053$, respectively) [52].

4.3. Multimodality treatment

To achieve complete elimination of local disease and to improve outcomes, multimodality treatment is often recommended for high-grade prostate cancer. Lau et al reported that treatment with adjuvant HT in patients with high-grade cancer appears to improve the 10-yr progression-free survival rate after RP but does not significantly reduce death from prostate cancer within 10 yr [44]. Postoperative RT in the treatment of high-grade prostate cancer may improve outcomes, but its role remains controversial. In men with high-grade prostate cancer, Do et al reported a 5-yr BPFs of 65% in patients treated with RP and postoperative RT compared with 30% after RP alone, and 25% after RT alone. The clinical progression-free survival was also improved with the addition of postoperative RT compared with RP and RT alone (80%, 60%, and 35%) [53]. Other reports have indicated that adjuvant RT is associated with a lower risk of biochemical recurrence, although there is no significant improvement in CSS rates at 10-yr follow-up [44,45]. Loeb et al reviewed the data of 288 men who underwent RP, 254 of whom were high-risk patients (cT2b, a Gleason score of 8–10, PSA > 15 ng/ml). For the high-risk patients, the 10-yr progression-free survival, CSS rate, and OS rate were 37%, 88%, and 75%, respectively. Patients received adjuvant or salvage treatment when needed [36].

Bastian et al recommend multimodality therapy for high-grade tumours. This often consists of RT plus HT; however, newer possibilities exist, such as a combination of RP plus neoadjuvant or adjuvant (chemo)-HT or RP with adjuvant RT [43]. A recent paper reviews the use of a combination of external-beam RT and systemic agent with RP for high-risk prostate cancer patients [54].

5. Conclusion

It is very likely that RP is an effective form of treatment for locally advanced and high-grade tumours. The best candidates for RP are patients who were clinically over-staged or over-graded by the puncture biopsy and whose tumours were subsequently found to be locally confined, to have limited extracapsular extension, or to be moderately differentiated. However, this does not mean that more advanced stages or grades are necessarily a contraindication for surgery. In younger patients, even advanced tumours and Gleason scores ≤ 8 are best managed initially by surgery. The increased use of nomograms and modern imaging techniques is helpful in recognising patients with locally advanced disease or high-grade disease most likely to benefit from surgical treatment.

Urologists must use the pathologic results, which indicate the need for additional postoperative treatment, to improve the final outcome. Further studies will be required to clarify whether neoadjuvant (chemo)-HT, adjuvant/salvage (chemo)-HT, and adjuvant/salvage RT can improve the results of RP.

5.1. Locally advanced prostate cancer

RP monotherapy provides tumour control in selected patients with cT3 disease, with 5- and 10-yr CSS rates of $> 85\%$ and 57% , respectively. The OS rates at 5 and 10 yr are $> 75\%$ and 60% , respectively.

In well-selected patients, RP, combined with adjuvant or salvage treatment when needed, may result in better outcomes than RT alone, similar to the combination of RT plus HT therapy. These findings should be confirmed in randomised, prospective studies.

5.2. High-grade prostate cancer

In a recent study, patients with high-grade prostate cancer who underwent RP monotherapy had 5- and 10-yr BPFs rates of 51% and 39% , respectively. This is in agreement with rates reported in other series. Studies show that up to one third of patients with high-grade prostate cancer are subsequently down-graded and have a better BPFs probability after RP. Disease-free survival after RP can also be expected if the cancer is confined to the prostate or surgical specimen. PSA value and the % PBCs can be useful in selecting men with high-grade prostate cancer most likely to benefit from RP. Patients with high-grade prostate cancer are likely to be good candidates for multimodality treatment, often consisting of RP

with adjuvant or salvage RT and HT, although newer treatment combinations are being tested.

Conflicts of interest

The authors have nothing to disclose.

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