REVIEW

Locally advanced and high risk prostate cancer: The best indication for initial radical prostatectomy?

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1. Introduction

For many years urologists have proposed radical prostatectomy (RP) as the gold standard for localised prostate cancer in often low risk and intermediate risk prostate cancer patients. Today, surgery for these patients is often considered overtreatment. Since the issue of high risk prostate cancer, that was often undertreated (with androgen deprivation therapy or combined radiotherapy), oncologic urologists have more and more focused on high risk prostate cancer. Locally advanced prostate cancer has extended clinically beyond the prostatic capsule, with invasion of the pericapsular tissue, bladder neck, or seminal vesicles, but without lymph node involvement or distant metastases. It is referred to as T3–T4 N0 M0 prostatic cancer. High-grade prostate cancer, also called poorly differentiated prostate cancer, has Gleason scores from 8 to 10.

Based on preoperative parameters (clinical stage, initial PSA and Gleason Score), Yossepowitch et al. [1] defined eight different categories amongst high risk prostate cancer (HRPC) patients and concluded that these HRPC patients do...
not have a uniformly poor prognosis after RP. Joniau et al. [2] analysing a multi-institutional database have shown that there are three distinct categories with different cancer specific survival rates considering three prognostic parameters: initial PSA, clinical stage, and Gleason score. Many patients classified as being at high risk have pathologically organ-confined cancer and may be cured by RP alone [1]. 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 unclear.

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. Overstaging (pT2), over-grading, and under-staging (pT4 or pN+) are common clinical errors. Nomograms have been developed to predict the pathologic stage of the disease and seminal vesicle invasion at RP [5, 6]. In addition, nodal imaging with computed tomography (CT) scans, seminal vesicle invasion (SVI) imaging with magnetic resonance imaging (MRI), or directed needle core biopsies of the nodes or seminal vesicles can be helpful in recognising patients who for some time were deemed not to benefit from a surgical approach [7].

The European Association of Urology (EAU) guidelines on prostate cancer state that RP can best be proposed to patients with locally advanced prostate cancer when the PSA is <20 ng/mL, with a clinical stage ≤T3a, and a biopsy Gleason score ≤8). However, patients with more advanced or poorly differentiated tumours are also considered to potentially benefit from surgery [8]. Surgical treatment in locally advanced T3 prostate cancer involves a radical prostate 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 most often resection of the bladder neck [9, 10]. Increased overall surgical experience results in improved surgical margins over time (75% in 1987–1994, 42% in 1995–1999, and 10.4% in 2000–2004) [11].

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% [12]. Other series had a much lower rate of pN+ cases (11%), respectively, probably due to more accurate and dedicated CT scanning of the pelvis and methods of patient selection [13]. The percentage of positive biopsy cores can help to predict lymph node invasion in patients undergoing RP and extended pelvic LND [14]. 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 at least at the tumour bearing side. Increased overall surgical experience leads to decreased operative morbidity and better functional results [15].

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 over-staged patients (pT2), but also in true unilateral pT3a, especially if the tumour is specimen-confined (R0). In cT3 disease, the cancer-specific survival (CSS) rate after RP at 5- and 10-year follow-up is 85%–100% and 57%–72%, respectively. The overall survival (OS) rate at 5- and 10-year follow-up is >75% and 60%, respectively [4, 16, 17].

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-year biochemical recurrence-free survival rate exceeding 60% [13]. Other authors evaluated 83 surgically treated cT3a patients at a mean follow-up of 68.7 months 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 [17].

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 few serious events were reported.

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 a study by Ward et al. [12], 78% of patients eventually needed adjuvant or salvage RT or HT compared to 56% of patients in a recent study from Hsu et al. [18]. These studies reveal excellent 5-, 10-, and 15-year OS and CSS rates, comparable to those obtained in cT2 patients. In addition, the Ward and Hsu studies had similar survival rates, with 5-year CSS rates of 95% and 98.7%, respectively, and 10-year CSS rates of 90% and 91.6%, respectively [12,18]. Ward et al. [12] also reported a 15-year CSS rate of 79%.

In a recent study by Gontero et al. [19], RP appears to be a valid treatment with acceptable morbidity in patients with locally advanced prostate cancer of any T ≥ 3, N0-1. The 7-year OS and CSS rates were 77% and 90%, respectively; 89.5% of the patients received immediate adjuvant treatment after RP [19]. This is also the opinion of Lange [20], who expressed the need for a randomised study testing the efficacy of RT and RP as initial therapy for locally advanced prostate cancer. In the meantime, RP
series revealed survival rates that surpass those for RT alone and comparable to those of 3 years of androgen-deprivation therapy combined with external RT.

Two randomised studies compared postoperative RT with RP alone for locally advanced prostate cancer. Bolla et al. [21] reported an improved biochemical progression-free survival (BPFS) in patients treated with adjuvant postoperative RT (74% vs. 52.6%, p < 0.0001) with an extended follow-up, but no improved cancer-specific survival. Thompson et al. [22] showed that adjuvant postoperative RT significantly reduced the risk of PSA relapse (median PSA relapse-free survival, 10.3 years for RT vs. 3.1 years for observation, p < 0.001) and disease recurrence (median recurrence-free survival, 13.8 years for RT vs. 9.9 years for observation, p = 0.001).

Our belief that RP has a place in the treatment of locally advanced prostate cancer is supported by a few studies conducted in the United States [23–28]. Another 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 [29].

4. High-grade prostate cancer

4.1. Studies with radical prostatectomy monotherapy

A Gleason score ≤ 7 in an 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 [30]. In a study from Manoharan et al. [31], the incidence of downgrading was reported as 31%, with patients having a lower biochemical recurrence rate (32% vs. 41%). Grossfeld et al. [32] assessed the surgical outcome of 114 men with high-grade prostate cancer and noted downgrading in 38% of the patients. In a study from Bastian et al. [33], 34% of men in the patient cohort were downgraded and had a 5- and 10-year 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-year estimated BPFS of 34% and 34%, respectively.

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. A number of reports have addressed the success rates of RP monotherapy in high-grade cancer. Donohue et al. [30] examined the outcome of RP monotherapy in 238 patients with high-grade prostate cancer and found a 5- and 10-year BPFS of 51% and 39%, respectively, in agreement with rates reported in other series [34–36]. Mian et al. [37] assessed the outcome of patients with a specimen Gleason score ≥ 8 treated with RP alone. The reported 5- and 7-year BPFS of 71% and 55%, respectively, are better than the rates reported by Donohue et al. [30] and other studies [34–36]. In addition, the rate of lymph node metastasis was only 6% compared to 20% in the Donohue study. In a study analysing 79 high-grade patients treated with RP at a mean follow-up of 55 months, the overall biochemical failure rate was 38% (41% if Gleason score was ≥ 8, and 32% if it was ≤ 7). Manoharan et al. [31] 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.

Serni et al. [38] evaluated the outcome of 116 patients with Gleason scores ≥ 8 who underwent RP. The 3- and 5-year progression-free survival rates for all patients were 84.6% and 78.1%, respectively. The 5-year BPFS for those with Gleason scores of 8 and 9 were 72.1% and 38.2%, respectively (p ≤ 0.05).

Bastian et al. [33] 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-year estimated BPFS rates of 40% and 27%, respectively, for the Johns Hopkins cohort, and 32% and 28%, respectively, for those within the SEARCH database. 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 [39].

PSA screening enables detection of high-grade tumours with smaller volume at an earlier stage, thus improving the organ- and specimen-confined disease rates [37]. Two separate studies reported the incidence of organ-confined disease at 26% [34] and 31% [37]. Mian et al. [37] showed that patients with organ- and specimen-confined disease had a higher 5-year 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. Bastian et al. [33] found higher 5- and 10-year estimated BPFS among men with organ-confined disease and negative surgical margins (79% and 50% vs. 40% and 27% for the entire cohort, respectively).

Serni et al. [38] reported that the incidence of organ-confined node-negative disease is 11.2%. At a mean follow-up of 46 months, 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 those have been reported in other series [35,36,40]. Serni et al. [38] reported that the 5-year 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 rate [38].

Grossfeld et al. [32] noted a 5-year disease-free survival rate of 47% in high-grade patients with PSA <10 ng/mL vs. 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%.

A study by Hurwitz et al. [41] assessed the surgical outcome of 168 men with high-grade prostate cancer. Patients with PSA <10 ng/mL and % PBCs <50% had a 5-year BPFS probability of 67% vs. 23% for all other patients. 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

Tewari et al. [42] 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 year, for RT it was 6.7 year, and for RP it was 9.7 year. Median CSS was 7.8 year for conservative treatment and 14 year 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).

From a recently published large observational study analysing data of the Swedish prostate cancer registry, it was shown that after 15 years surgery in men with non-metastatic prostate cancer leads to better survival than does radiotherapy. The authors concluded that younger men and those with less comorbidity who have intermediate or high risk localised prostate cancer may have a greater benefit from surgery [43].

### 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. [34] reported that treatment with adjuvant HT in patients with high-grade cancer appears to improve the 10-year progression-free survival rate after RP but does not significantly reduce death from prostate cancer within 10 year. 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. [44] reported a 5-year 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%). 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-year follow-up [34, 35]. Loeb et al. [26] 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-year progression-free survival, CSS rate, and OS rate were 37%, 88%, and 75%, respectively. Patients received adjuvant or salvage treatment when needed.

Bastian et al. [33] 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 [33]. A recent paper reviews the use of a combination of external-beam RT and systemic agent with RP for HRPC patients [45].

### 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-year CSS rates of >85% and 57%, respectively. The OS rates at 5- and 10-year 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-year 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 downgraded 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 author declares no conflict of interest.

References


