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REVIEW

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

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Abstract High risk prostate cancer is a deadly disease that needs aggressive treatment. High risk prostate cancer is often treated with androgen deprivation therapy or combined radiohormonotherapy while there is a place for surgery in cases of operable and resectable locally advanced or high risk disease. This review summarises the results of the different treatment strategies for locally advanced and high risk prostate cancer. Radical prostatectomy monotherapy or in combination with radiotherapy and/or hormonal treatment are analysed. They show that radical prostatectomy is an effective treatment modality for these tumours. After surgery, the results of the pathology and the follow-up of serum PSA may indicate the need of additional adjuvant or salvage treatment strategies.

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 and androgen deprivation therapy), 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

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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. Over-staging (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 $\leq$cT3a, and a biopsy Gleason score $\leq$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 positive surgical margin rates 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 $T \geq 3$, 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