What is the Role of Surgery for Locally Advanced Disease?

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Abstract

Among the optimal options recommended for locally advanced prostate cancer, radical prostatectomy (RP) with or without adjuvant radiotherapy or hormone therapy is a possible but relatively infrequent option. The role of radical prostatectomy in locally advanced prostate cancer is still controversial and has not been extensively assessed despite numerous recent series provided by great US and European institutions. Nevertheless, in selected patients with cT3a tumours, surgery can provide good oncologic results with 10-yr and 15-yr prostate cancer survival rates of about 85% and 75%, respectively. Moreover, approximately 20–30% of patients who initially present with cT3 tumours ultimately have organ-confined disease on pathologic examination. RP for locally advanced prostate cancer provides similar short-term biochemical-free survival compared to the of combination radiotherapy and androgen ablation. Morbidity of the procedure is similar to RP for organ-confined tumours. The impact of radical prostatectomy on local progression and local recurrence is also important in well-selected patients with low- or intermediate-grade tumours. Preoperative analysis of clinical stage, biopsy data, Gleason score, endorectal magnetic resonance imaging, and nomograms may enhance the choice of the best option in young and healthy patients with locally advanced prostate cancer. RP should be considered as a viable alternative to radiotherapy and hormone therapy in patients with long life expectancy presenting with cT3 prostate cancer. Combined treatments with RP have to be prospectively evaluated in terms of oncologic outcome and quality of life. This approach should be investigated in clinical and comparative trials.

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1. Introduction

Treatment of locally advanced prostate cancer is complex and the optimal option remains to be clearly defined. One of the main reasons is explained by the heterogeneity of these T3–4 tumours characterised by the extension of the disease beyond the confines of the prostatic capsule. Despite dramatic stage migration due to widespread prostate-specific antigen (PSA) screening, many patients continue to present with locally advanced disease and current incidence is reported at about 15–20% in routine
urologic practice [1–4]. Nowadays, clinical stage T3 tumours (cT3) are diagnosed with lower tumour volume than in the past, enhancing the opportunity for radical prostatectomy (RP) indications in many selected cases [5].

The goal of therapy in patients with locally advanced prostate cancer includes prolongation of survival but also control of local tumour progression [6]. Local control is important, particularly in locally advanced prostate cancer due to the increased risk of symptomatic progression. Moreover, patients with cT3 prostate cancer have a higher probability of death from recurrent prostate cancer than from other causes [6].

The most common local treatments for locally advanced prostate cancer include external-beam radiation therapy (EBRT) associated with hormone therapy followed by RP alone or combined with other modalities. When RP is indicated as local treatment, the procedure should be adapted to the situation. Usually, it is an extended RP, enlarged to include periprostatic tissue and combined with an extended lymphadenectomy because of the risk of pelvic nodal involvement [7–9].

Oncologic and functional outcomes of RP for locally advanced tumours reported in the literature for 10 yr are sometimes difficult to analyse because of the heterogeneity of non-comparative studies. These series provided data issued from some great monocentric US or European institutions. Despite comparative and randomised studies, the results of RP with or without adjuvant therapy in recent publications are similar to those of radiotherapy combined with hormone therapy in terms of biochemical-free, specific, and overall survival [4–6,10,14,20].

Moreover, the morbidity of the procedure seems comparable to RP for localised prostate cancer, when it is performed by experienced surgeons [4,6,7,10–14].

Regarding the lack of data on the pathologic outcome of RP compared to EBRT combined with hormone therapy, it is up to the urology community to start randomised trials including RP in combined treatments of locally advanced prostate cancer.

### 2. Definition of clinically advanced tumours

The usual definition of locally advanced prostate cancer includes the tumours that have involved the periprostatic tissue through the capsule, seminal vesicles, urethra, and bladder neck without clinical lymph node involvement or distant metastases (T3–T4 N0 M0) [15].

In the TNM 2002 classification, cT3 is defined as a palpable tumour extended beyond the prostatic capsule: T3a extracapsular extension, T3b extension to the seminal vesicles [16]. The term extraprostatic extension was accepted by the Conference of International Consensus [17].

Locally advanced prostate cancer includes heterogeneous tumours between localised and metastatic disease; 30–50% of the patients have a potential risk of pelvic lymph node involvement and 40% progress to a metastatic stage at 5 yr and 65% at 10 yr [18].

### 3. Results of RP in locally advanced prostate cancer

Until recently, RP alone was not adapted to cure locally advanced tumours because of the tumour volume and the high incidence of positive pelvic lymph nodes. Poor long-term survival rates were reported in several series with a 5-yr biochemical recurrence of 70% [10,14,19]. However, RP alone can be acceptable in well-selected tumours classified T3a with low Gleason score (<8) on biopsies and an initial PSA value of <15 ng/ml, in young patients or in men with associated urinary obstruction disorders [5,6,10,14,20].

Moreover, in recent RP series for cT3 prostate cancer clinical over-staging occurred in 20–30% of the cases and presented as organ-confined tumours (pT2) on pathologic examination, whereas 30–40% of T2 tumours are ultimately pT3 [4–6,10,14,21].

Oncologic outcomes of RP in cT3 prostate cancer reported in the literature are heterogeneous because they rely on retrospective series and are often from single institutions (Table 1). Moreover, it is not mentioned if patients had adjuvant treatment by radiation or hormone therapy [19–22]. A review of eight international studies showed an overall survival rate at 5 yr ranging from 64% to 86% and at 10-yr from 36% to 70%; disease-specific survival rates at 5-yr and 10 yr ranged from 83% to 92% and 72% to 82%, respectively [14].

In the largest surgical series of cT3 treated in a single institution and reported to date, approximately 50% of patients had not developed a PSA recurrence at 15 yr after surgery and only 16% of patients died of prostate cancer [4]. However, it is difficult to evaluate the real impact of RP on survival in this series because some patients received neoadjuvant hormone therapy or secondary treatments or both [4]. In another cT3 series, previous RP was associated with a significant decrease in the risk of death compared to those who did not undergo RP [23].
Nevertheless, more recent surgical series of selected patients with locally advanced prostate cancer have reported comparable survival rates with a combination of radiation therapy and hormone treatment, which is the most common therapeutic option in this stage of disease, with 5-yr, 10-yr, and 15-yr prostate cancer-specific survival rates of 85–99%, 72–92%, and 76–84%, respectively [3,5,6,10,24]. Bolla et al have previously shown that EBRT with 3 yr of adjuvant hormone therapy improves clinical disease-free survival and overall survival rates with 5.5 yr follow-up of 74% versus 40% and 78% versus 62%, respectively [25].

Some authors proposed extensive indications of RP with immediate adjuvant treatment. A recent single-surgeon study showed excellent 7-yr overall survival and cancer-specific survival rates (77% and 90.2%, respectively) in patients with T3–4, N0–1 disease who underwent RP and immediate adjuvant treatment with radiotherapy or hormone therapy (in 89.5% of cases) [26]. A nonrandomised US study has compared patients who underwent RP for cT4 prostate cancer to those receiving radiotherapy alone, hormone therapy alone, or radiotherapy combined with hormone therapy. A comparable survival was found between the RP group and combined treatment group [27].

### 4. Surgical aspects

Surgical technique is usually an extended RP to include surrounding periprostatic tissue and in most of cases a non–nerve-sparing technique must be used [5–7]. The success of RP for clinically advanced cT3 prostate cancer relies on the removal of all local tumour-bearing tissue [28]. The technique was previously described with several detailed points different from the standard technique for organ-confined tumours [5,28,29]. In fact, the aim is to have negative surgical margins [5,7,10,14,21,29]. The majority of palpable tumours originate in the peripheral zone and, consequently, they are more likely to extend into the posterolateral and rectal periprostatic soft tissue. In this way, the neurovascular bundles are usually resected widely on the side of the cancer. Moreover, the posterior plane of resection should be deep enough and must include the complete excision of the two layers of Denovilliers fascia to reduce the risk of positive surgical margins [28].

Unilateral or bilateral nerve-sparing surgery is feasible in very selected young patients with small cT3a tumours who desire to keep the erectile function despite the increased risk of positive surgical margins and incomplete tumour excision [12]. However, it cannot be a systematic procedure because it is carried out more frequently in RP for localised prostate cancer.

Regarding the increased risk of lymph node involvement in locally advanced disease, standard lymphadenectomy limited to the ilio-obturator fossa is not sufficient to define accurately the lymph node status [8,9,30,31]. Extended iliac lymphadenectomy does not have an impact on survival, but it optimises pathologic staging with an increased number of lymph nodes removed and number of positive nodes [9]. Moreover, a good staging based on an extended lymphadenectomy will help to introduce adjuvant hormone therapy when needed. Such treatment has shown significant benefit on overall survival in patients with positive lymph nodes after RP [32].

### 5. Who are the “good candidates” for surgery in locally advanced prostate cancer?

The European Association of Urology (EAU) 2007 guidelines on prostate cancer state that RP can be proposed to selected healthy patients with locally
advanced tumours presenting these clinical parameters: PSA < 20 ng/ml, ≤T3a, and biopsy Gleason score ≤8 [33].

The clinical assessment of locally advanced prostate cancer relies on several parameters obtained by the digital rectal examination, PSA, and biopsy analysis (number of positive biopsies, tumour length, and total percentage of cancer). The patient should be young and healthy with a life expectancy >10 yr. MRI to detect local regional extension is helpful to evaluate the lymph node status (as well for the computed tomography scan) and the presence or not of extracapsular extension. Bone scintigraphy, in patients with a PSA value >20 ng/ml is required to detect asymptomatic bone metastasis [18,34,35]. The evaluation of tumour volume can be improved by modern imaging techniques using new endorectal MRI to assess extracapsular extension, seminal vesicles extension, and nodal involvement [36]. Specificity and sensibility of the new generations of MRI (3 Tesla) are 75–95% and 60–70%, respectively [36,37]. Numerous nomograms available today are helpful to improve the preoperative assessment of the patients [38].

It is clear that healthy patients <70 yr old with cT3a stage are the best candidates for surgery with a reduced risk of positive surgical margins and pelvic lymph node metastasis. It was shown that in select men with cT3a, RP can result in very good long-term cancer control. Moreover, 20–30% of men undergoing RP for cT3 tumours have pathologic organ-confined disease [4,7,10,14,19].

6. How to improve the oncologic outcomes of RP in stage cT3 tumours?

6.1. Neoadjuvant hormonal therapy

Neoadjuvant hormonal therapy before RP, even in case of cT3 tumours, is not recommended in current practice because no study showed a benefit on survival. Previous studies have shown a 30% clinical down-staging and a 25% pathologic down-staging in men treated with neoadjuvant hormone therapy (mean time 3 mo). But this treatment has not shown any statistical difference in disease-free or overall survival between men with or without neoadjuvant therapy [39–42].

Neoadjuvant combination of chemotherapy and hormone therapy before RP has been reported in locally advanced prostate cancer and high-risk tumours [43]. These new modalities can be effective and used in the future to improve local oncologic issues of local treatments.

6.2. Adjuvant and salvage radiotherapy

Poorly differentiated tumours in cT3 prostate cancers are associated with increased clinical and biochemical progression rates after RP [4]. In these cases, patients may benefit from adjuvant therapy following RP [6,14]. Similar approaches can be developed when examination of the RP specimen shows extensive and multifocal positive surgical margins or lymph node involvement.

A benefit of adjuvant EBRT after RP for pT3 disease in prolonging overall survival has not been shown despite the fact that this radiation therapy (60–65 Gy) can prevent or delay biochemical and local recurrence, as was demonstrated in randomised studies [44–46].

In case of presumptive locally recurrent prostate cancer, salvage radiotherapy is also an effective option to improve local control and disease-free survival as long as the postoperative PSA value is <1.5 ng/ml [47].

6.3. Adjuvant hormonal therapy

In case of nodal involvement after RP, it was clearly shown that immediate hormone therapy by luteinising hormone-releasing hormone (LHRH) agonists was beneficial for overall survival (72.5% vs. 49%) and for disease specific survival (87.2% vs. 56.9%) compared to a different hormone therapy at metastasis progression [32,48].

In the Early Prostate Cancer (EPC) trial, with a mean follow-up of 5.4 yr, the risk of clinical and biochemical progression in the group undergoing RP for locally advanced tumours was reduced 25% by bicalutamide 150 mg compared with placebo [49].

6.4. Functional outcomes

With improvements in surgical techniques including the laparoscopic approach, the complication rates are similar to RP for organ-confined tumours [4–7]. The most common postoperative complications are urinary incontinence and sexual dysfunction, which occur immediately after surgery and improve over time [7,12]. Increased overall surgical experience leads to decreased operative morbidity and improves the functional results [4,50].

7. Conclusion

The treatment of clinically advanced prostate cancer remains controversial. RP is an adequate technique and an acceptable option to treat the small cT3a
tumour with high risk of local progression; however, this alternative should be avoided in more advanced disease with a high risk of lymph node involvement and macroscopic residual tumour. In the absence of randomised controlled studies, it is not possible to recommend RP as equivalent to radiotherapy and hormonal therapy that is the treatment of choice in several countries even if a benefit has been shown in several studies. However, with very well-selected criteria, extended RP for locally advanced prostate cancer should be presented as an alternative treatment for young patients. These patients should be informed of possible adjuvant or salvage treatments, when needed, by radiation therapy, hormone therapy, and, perhaps in the future, by chemohormotherapy.

Although EBRT combined with adjuvant hormone therapy remains the most common treatment for cT3 prostate cancer, RP provides an excellent therapeutic procedure for well-selected patients with locally advanced prostate cancer, with a disease-free survival at 10 yr of 85% in the main series from the United States and Europe. These findings should be confirmed in well-conducted clinical trials and multicentre randomised prospective studies.

Conflicts of interest
The author has nothing to disclose.

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References


