# Radical prostatectomy in high-risk prostate cancer

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**Objective:** Different treatment modalities are considered in treating locally advanced prostate cancer in men. This review discusses the long-term follow-up data of patients who underwent radical prostatectomy with or without adjuvant therapy. The value of an (extended) pelvic lymphadenectomy in these patients is also discussed. **Methods:** Relevant information was identified through a literature search of published studies and review articles. **Results:** Radical prostatectomy alone in locally advanced prostate cancer seems to produce acceptable results. A

#### Introduction

Despite implementation of screening using prostatespecific antigen (PSA) tests, up to half of patients who are being diagnosed with prostate cancer present with clinical stage T3 disease and/or high-grade cancer .<sup>1,2</sup> Treatment of this group of patients is challenging, and there are many controversies and uncertainties. Therapeutic options range from watchful waiting to conservative surgical management with transurethral resection of the prostate (TURP) with or without nerve-preserving procedure in these patients, however, is not an option. Pretreatment with hormonal therapy does not seem to result in prolonged, progression-free or disease-specific survival. Adjuvant therapy after surgery seems to provide good survival rates.

**Conclusions:** Although no guidelines exist for the treatment of high-risk prostate cancer patients, real benefit seems to occur from radical prostatectomy to control the local tumor and prevent morbidity associated with tumor growth. Since studies clearly demonstrated the benefits of adjuvant therapy along with radical prostatectomy, this should be the preferred course of action.

**Key Words:** prostate cancer, radical prostatectomy, adjuvant therapy

hormonal therapy to external-beam radiotherapy with or without hormonal ablation to externalbeam radiotherapy with brachytherapy to radical surgery with or without adjuvant therapy. Table 1 summarizes some studies of patients with clinical stage T3 cancer.

Treatment of patients with a locally advanced highrisk prostate cancer should not only lead to improved survival, but also to control of local tumor progression, resulting in a decrease in morbidity and thus improved quality of life. The value of performing "radical" surgery on patients with clinical stage T3 disease is debatable mainly because the high risk for incomplete excision of the tumor, and high incidence of lymph node metastasis. To date, most patients with T3 prostate cancer have been treated predominantly

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Series	Number of	Survival (%)			
	patients	5 years	10 years	15 years	
Radical surgery					
Mayo Clinic <sup>17</sup>	1090	89	72	50	
Definitive radiotherapy					
Bagshaw <sup>3</sup>	348	-	-	20	
Scardino <sup>8</sup>	117	74	34	17	
Scardino <sup>8</sup>	65	86	44	30	
Zagars <sup>9</sup>	551	72	47	27	
Androgen ablation					
DeVere White <sup>23</sup>	73	-	17	-	

TABLE 1. Overall survival rate of patients with clinical stage T3 prostate cancer treated with primary radical surgery, radiotherapy, or androgen ablation

with external beam radiotherapy alone. In a literature search, it was the most frequently used modality for treating locally advanced prostate cancer. This treatment has not, however, been proven to be effective in controlling the local tumor burden or providing durable, disease-free survival.<sup>3-8</sup> The reason that radical surgery was not a preferred option for so many years was that outcomes in early reports were rather poor. These poor results can be partly explained because many staging modalities that are available today, were not previously available. For example, (extended) pelvic lymphadenectomy was not common; radionuclide bone scanning was not performed in all cases; and PSA assays were not available, and thus the less accurate serum acid phosphatase assay was used to determine the severity of the disease. Probably a significant number of patients who underwent surgical treatment for locally advanced prostate cancer already had lymphatic and/ or visceral metastasis. For this reason, radiation therapy was frequently used in preference to radical surgery.<sup>3,4,9</sup> In the next paragraph, we discuss the management approach and surgical treatment of highrisk prostate carcinoma. This type of high-risk prostate carcinoma is referred to as being clinical stage T3, and/or having a PSA of >10 ng/mL, and/or a Gleason score of 7 or higher. Long-term follow-up data are reviewed from patients who received radical prostatectomy with or without adjuvant therapy.

## Primary radical surgical therapy

As stated earlier, radical prostatectomy for clinical stage T3 prostate cancer has not been widely accepted, due to the potential risk for incomplete excision of the local tumor and the high incidence of lymph node

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metastasis. Most clinically palpable prostate cancers (70% to 80%) originate in the peripheral zone.<sup>10</sup> These tumors tend to extend into the posterolateral and rectal perineural spaces. These areas represent an area with "locus resistencia minorus," because they facilitate the spread of tumors. Mainly for this reason, a nervesparing procedure in a T3 tumor, when performed during a radical prostatectomy, is a poor option, especially since 60% of radical prostatectomy specimens with positive posterolateral margins contain tumor in the resected ipsilateral neurovascular bundle.<sup>11</sup> Accurate excision of the tumor related to key anatomic points (such as "en bloc"' excision of the neurovascular bundles and precise apical dissection and removal of both ampullae's of the vas deferens and seminal vesicles) is very important in improving cancer removal and local tumor control. This raises the issue of determining under which conditions a properly executed radical prostatectomy in clinically advanced prostate cancer might provide a better course of action. Van den Ouden et al presented a report of a series of 83 patients with clinical stage T3 tumors who underwent radical prostatectomy with radical lymphadenectomy as monotherapy.<sup>12</sup> These patients were divided into subgroups with T3 G1-2 and T3 G3 tumors and evaluated for clinical progression, local recurrence, distant metastasis, and biochemical progression. The results were compared to a group of patients with locally confined tumors (190 patients). The patients' mean age was 63 years (range, 47 to 74). After radical prostatectomy, 18% of the patients had a pT2; 77% had a pT3; and 4% had a pT4. Of these patients, 12% had positive lymph nodes, and 66% had positive margins. At 5 and 10 years postprostatectomy, overall survival in the patients with positive lymph nodes and in those with positive

margins was 75% and 60%, respectively; clinical progression was 41% and 69%, respectively; local recurrence was 18% and 44%, respectively; distant metastasis was 31% and 50%, respectively; and biochemical progression at 5 years was 71% in both groups. Tumor differentiation mattered: poorly differentiated tumors showed significantly lower progression rates compared to well or moderately differentiated tumors. Surprisingly, tumor progression and survival in patients with T3 G1-2 tumors were not significantly different from those for patients with locally-confined tumors. This series suggests that radical prostatectomy in patients with a clinical T3 tumor produces acceptable results in those with a G1 or G2 grade tumors. A precise selection of patients undergoing radical prostatectomy is therefore needed. Furthermore, patients with T3 G3 tumors do have early progression and therefore need adjuvant therapy.

### Radical prostatectomy and adjuvant therapy

In managing stage T3 prostate cancer patients, it remains to be clarified whether adjuvant therapy should be given with radical prostatectomy, and, if so, whether it should be given before (as neoadjuvant therapy), or after this surgery. Since no consensus guidelines exist, pathologic T3 disease is generally managed on a case-by-case basis. In clinically T3 staged patients, the potential usefulness of androgen ablation before surgery to reduce tumor bulk, facilitate surgical removal, and downstage the tumor is appealing. However, its actual efficacy in producing a significantly larger progression- or disease-free interval in such patients has been disappointing. Amling et al<sup>13</sup> performed a case-controlled retrospective review; 72 patients who underwent pretreatment with hormonal therapy followed by radical prostatectomy were compared to a control group of patients who underwent surgery alone. Extracapsular extension was present in 61% of patients treated with hormonal therapy and in 81% of untreated patients; 31% of treated patients had organ-confined lesions compared to 19% of untreated patients. No difference in the incidence of lymph node involvement in both groups was observed in patients with clinical T3 prostate cancer. But what is more revealing is that no difference in progression-free or disease-specific survival was observed at 5 years, despite the perceived favorable pathologic status of the group treated with hormonal therapy. An explanation for this unexpected effect could be in the fact that after androgen withdrawal, both benign and malignant prostate glandular cells undergo shrinkage, together with cytoplasmic changes. This makes it very difficult for

cells.<sup>14</sup> Furthermore, it was hypothesized that patients with advanced cancer respond less well to androgen withdrawal than do patients with a localized prostate cancer, as shown earlier in a rat model.<sup>15</sup> The major factor playing a significant role here may be the larger volume of the tumor in T3 prostate cancer: hormonal responsiveness of the cancer decreases with increasing tumor bulk and dedifferentiation. Could giving adjuvant therapy after performing a radical prostatectomy lead to better results? Lerner et al<sup>16</sup> studied 812 patients with a clinical stage T3 prostate cancer who underwent radical prostatectomy; all patients had low co-morbidity and a life expectancy of at least 10 years. There were no distant metastases. A total of 479 patients (60%) received adjuvant therapy, including external beam radiation in 61 patients (7%), and rogen ablation in 348 patients (43%), and both in 82 patients (10%). The decision of whether to implement adjuvant therapy was made by the individual urologist and was often based on the pathological grade and stage of the tumor. The mean patient age was 65 years (range, 40 to 78) and the mean follow-up was 4.5 years (range, up to 24 years). The disease was stage pT2c or lower in 17% of patients and pT3a to c in 49% of patients, and 33% had positive lymph nodes. The pathology-determined Gleason score of the primary tumors was 7 or higher in 62% of patients. Positive margins were found in 48% of the specimens. This series suggests that a very good survival rate with low morbidity can be achieved by performing radical prostatectomy and giving adjuvant therapy.

even an experienced pathologist to recognize viable

#### Pelvic lymphadenectomy in prostate cancer

In malignant disease, appropriate treatment and prediction of prognosis are mainly influenced by precise staging. For prostate cancer, the only way to establish correct lymph node staging is to perform an extended lymphadenectomy Figure 1. But, unfortunately, there has been a large variation in the technique and extent of pelvic node dissections reported to date. The current recommendation is to perform standard pelvic lymphadenectomy in patients who have local prostate cancer, a preoperative PSA level greater than10 ng/mL, a Gleason score higher than 7, and cancer clinical stage of 2A or greater. A standard pelvic lymphadenectomy entails a lymph node dissection of the obturator region and lymphatics around the external iliac artery, although the clinical usefulness of regional lymphadenectomy has been debated for a long time. So, for localized prostate





**Figure 1.** Distribution and localization of fields for extended pelvic lymphadenectomy: right external iliac (1), common iliac (2), oturator fossa (3), internal iliac lymph nodes (4), prescaral lymph nodes (5), left external iliac (6), common iliac (7), obturator fossa (8), internal iliac lymph nodes (9). Adapted from Heidenreich et al.<sup>20</sup>

cancer, pelvic lympadenectomy does have a role in improving local cancer control, aiding decision making for adjuvant therapy, and improving survival, and it may be associated with prolonged, progression-free survival.<sup>17-19</sup> The following question arises. Is there a place for pelvic lymphadenectomy in locally advanced prostate cancer, and if so, should it be a standard or extended one? Heidenreich et al<sup>20</sup> demonstrated a 26.2% incidence of lymph node metastasis in patients who underwent an extended pelvic lymphadenectomy. Of all lymph node metastases, 42% were found outside the regions of a standard pelvic lymphadenectomy. In 69% of the 203 patients who were at high risk of having lymph node metastasis (PSA >10 ng/mL, Gleason score >7), these were proven by histological examination. These studies highlight the need for extended pelvic lymphadenectomy in patients with high-risk, locally advanced prostate cancer. Further trials should be undertaken to determine benefits of decreased recurrence, and disease-free and overall survival in these patients.

It is very difficult to compare the results of various clinical studies, mainly due to possible staging errors, differences in therapeutic techniques, and case selection biases. However, with a lack of prospective randomized clinical trials, important information about the relative merits of various treatments may be gained by making such comparisons. As stated earlier, the previous inferior results obtained by using radiation as monotherapy in treating locally advanced prostate cancer makes us reject this as a viable option: the inability of radiotherapy alone to eradicate the primary tumor has been associated with a very poor prognosis. Therefore, the most impressive advantage of primary radical surgery with or without adjuvant therapy for clinical stage T3 disease lies in its ability not only to cure the patient but also to at least control the local tumor and prevent the inherent morbidity associated with cancer progression and its impact on the patient's quality of life. However, multivariate analysis of previous studies from the Zincke group <sup>21,22</sup> revealed that adjuvant hormonal therapy had a significant impact only on the cancer progression-free interval, but not on the overall or cause-specific survival. Nevertheless, it can be used to achieve local tumor control alone. Local morbidity (massive tumor regrowth causing bladder outlet obstruction, pain, hematuria, and ureteral obstruction) is a frequent occurrence in patients who have uncontrolled primary prostate cancers after definitive radiation therapy and has resulted in significant impairment in the quality of life. In the Mayo Clinics series, 82% and 79% of patients were free of local cancer progression at 10 and 15 years, respectively. This was true for the Lerner study as well: 80% and 71% of patients were free of local cancer progression at 10 and 15 years, respectively. Therefore, radical prostatectomy with or without adjuvant therapy clearly provides excellent control of the primary tumor. Since the benefits of choosing combination therapy (radical prostatectomy with hormonal and/or radiation therapy) over monotherapy alone — be it radical prostatectomy, radiotherapy, androgen ablation, or watchful waiting - have been clearly demonstrated, implementing this treatment modality in patients with T3 prostate carcinoma is the preferred course of action. 

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