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Treatment of Locally Advanced Prostate Cancer – The Case for Radical Prostatectomy

Abstract

The treatment of clinically locally advanced prostate carcinoma (stage cT3) remains controversial. One of the main reasons for this controversy results from the substantial staging error attached to the clinical diagnosis cT3 with overstaged T2 tumors and understaged node-positive cases. Treatment options in this situation include radical prostatectomy, external beam radiotherapy, immediate or delayed androgen deprivation treatment and the so-called 'watchful waiting'. Acceptable and often surprisingly good tumor-specific survival rates have been reported for radical prostatectomy in pT3 series – based on good clinical case selection – approaching those of pT2 series. In lymph node-positive pT3 cases, adjuvant hormone deprivation seems to prolong survival which it does not in lymph node-negative pT3 disease. A benefit of adjuvant external beam radiotherapy after radical prostatectomy for pT3 cases in prolonging overall survival has not been shown, despite the fact that it can prevent or delay biochemical and local recurrence. External beam radiotherapy as the only treatment for cT3 disease results in unfavorable tumor-specific survival rates, which can be significantly improved with adjuvant hormonal treatment with LHRH agonists. If, in case of advanced age and/or significant comorbidity, primary hormonal treatment is chosen, early hormonal deprivation therapy seems to offer marginal benefits in survival compared to delayed treatment.

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Introduction

The uncertainties inherent in the current staging modalities available for prostate cancer result in significant staging errors regarding clinically locally advanced tumors – the clinical stage T3N0M0. The definition of this stage implies that clinically the cancer has seemed to have progressed locally beyond the prostatic capsule without having metastasized. The diagnostic methods used for staging are digital rectal examination plus transrectal ultrasound. While CT scanning is of little use in locally staging prostate cancer, the emerging possible role of MRI imaging still has to find a defined place in the staging of cT3 prostate cancer.

The insufficient accuracy of clinical staging in cT3 cases and the inability of imaging studies to reliably diagnose pelvic lymph-node metastases (except in cases of very large lymph nodes) result in a significant staging error. Surgical series of cT3 cases reveal that this clinical group consists of T2 as well as T4 cases plus a substantial number of node-positive cases. A reliable separation of these subgroups of patients with cT3 disease is clinically not possible but can only be achieved in surgical series.

The result is that, until better and more reliable diagnostic methods have been found and validated, this uncertainty in the management of cT3 prostate cancer disease will remain. While undoubtedly overstaged patients with actual T2 disease benefit from the application of potentially curative treatment, those with occult systemic disease cannot at present be cured.

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The treatment of patients with true T3 disease therefore remains controversial. It should be remembered that the anatomic prostatic capsule is only a very thin membrane, and that often in pT3 disease extension is via the perineural route. Thus, true locally advanced disease (cT3 without metastatic spread) in prostate cancer may not in itself represent a definite and huge negative leap in prognosis.

In current clinical practice, local radiotherapy with adjuvant hormone deprivation is often the preferred treatment for cT3 disease. In the USA, only 6% of patients with cT3 disease undergo radical prostatectomy, and even in younger patients this proportion amounts to only 19% [1].

The use of validated nomograms such as the Partin tables [2] can help to estimate the risk of locally advanced disease or lymph node metastases based on known predictors of these risks (such as PSA values, clinical stage, biopsy Gleason score). However, these estimations give only likelihoods but not certainty, and can therefore not reliably foretell an individual patient's prognosis. Thus, for the time being, many uncertainties remain which make definite management decisions in cT3 cases often difficult. Randomized trials comparing different treatment modalities in locally advanced prostate cancer are lacking [3]. This review aims at evaluating what is currently known about the different management options for cT3 prostate cancer.

Staging of cT3 Disease

Digital rectal examination remains the basis of clinical staging but is inherently uncertain. Surgical series of cT3 cases have shown that 9–27% represent clinically overstaged pT2 disease [4–7]. Transrectal ultrasound, MRI or other imaging modalities cannot at present substantially improve on the results of digital rectal examination in the local staging of prostate cancer [8–10].

However, patients with suspected locally advanced disease who are considered to be candidates for potentially curative treatment require a complete staging. Whether the rule that with a PSA level <10 ng/ml osseous metastatic spread is unlikely, and therefore a bone scan is not indicated, also applies to locally advanced disease has not been shown. In unselected cases the rate of positive findings on bone scan in prostate cancer patients with a PSA <10 ng/ml is 4% [11].

Surgical series of cT3 cases have also shown node-positive rates of 27–48% [5–7, 12, 13]. The only exception, with a markedly lower rate of pN+ cases, is the series reported by van Poppel et al. [14] with only 11%, perhaps due to a highly selected cohort. The risk of nodal spread in cT3 disease is, as in T2 disease, correlated with Gleason score, PSA value and possible seminal vesicle invasion. Thus the risk of nodal spread in cT3 disease with Gleason 8–10 cancer and PSA values between 4 and 10 ng/ml is already present in 32% [12]. Staging for metastatic disease as well as surgical lymph node staging thus seem absolute requirements in patients with cT3 disease before undertaking a potentially curative local treatment.

Prognosis of Locally Advanced Prostate Cancer

The effect of potentially curative treatment modalities on the course of truly locally advanced prostate cancer is difficult to assess, due to a lack of conclusive randomized studies and the inconsistently selected patients in treatment studies, which mostly are retrospective. In the pre-PSA era, tumor-specific survival rates in cT3 disease after radiotherapy or conservative treatment of 50% and of 80% after radical prostatectomy were observed [15]. A biochemical recurrence after radical prostatectomy in pT3 disease can be expected in 40% within 10 years [16]. However, variability is great depending on the risk factors, biopsy Gleason score, preoperative PSA and seminal vesicle status [17, 18]. This variability ranges between a 10-year recurrence rate of over 90% in poor-risk groups to one of under 10% in low-risk groups. Thus, management decisions in cT3 disease must – as in clinically localized prostate cancer – not only take general prognostic factors for overall survival into account (age, comorbidity and quality of life) but also these tumor-specific known risk factors (tumor differentiation by biopsy Gleason score and PSA).

Radical Prostatectomy in cT3 Disease

Radical prostatectomy in cT3 disease results in incomplete tumor removal (R1) in 22–60% of cases [6, 14, 19], and up to 48% of patients will have lymph node disease. Thus, it can be argued that for these patients surgery does not achieve a great deal while potentially incurring significant morbidity. However, it may be questioned whether this today – in the PSA era and after significant development in the surgical technique of radical prostatectomy – stills holds true.

The group of Zincke and colleagues [7, 20, 21] from the Mayo Clinic have for a long time advocated the use of radical prostatectomy in locally advanced prostate cancer, and have recently published the largest single-center surgical series on radical prostatectomy in cT3 disease with a follow-up of 15 years [6]. They operated on a total of 841 patients with cT3 disease out of over 8,000 radical prostatectomies altogether between 1987 and 1997. For the cT3 patients the mean age was 66 years, mean preoperative PSA 10.2 ng/ml, median biopsy Gleason score 7, and 23% had received neoadjuvant hormonal treatment. Overstaging was substantial with 27% of cT3 cases having pathological stage pT2 disease while positive lymph nodes were also seen in 27%. PSA recurrence-free and disease-specific survivals as well as overall survival in the cT3 group were significantly lower than in the cT2 group, but the actual differences were small. Morbidity due to complications of radical prostatectomy in the cT3 group was not different from that in the cT2 group. In the cT3 group, full continence after 1 year was reported to be 79%, while grade 3 stress urinary incontinence was seen in 6.5%; 75% had complete loss of potency, with 74% having undergone radical prostatectomy without nerve-sparing.

In a retrospective multicenter analysis of 345 radically operated cT3 patients, 41% node-positive cases were seen and the actuarial 10-year disease-specific survival was only 57%. In this series disease-specific survival was clearly dependent on tumor grade and amounted to only 29% in poorly differentiated tumors [5]. Amling et al. [7], however, reported an 84% disease-specific 10-year survival rate in cT3 patients. The group from Rotterdam in their single-center series of surgically treated cT3 patients reported an overall survival of 60% and a disease-specific survival of 72% after 10 years. The latter was again dependent on tumor grade [22]. Van Poppel et al. [14] observed a 5-year biochemical recurrence-free rate of 60% in pT3a patients with a preoperative PSA <10 ng/ml. In a recent series of radical prostatectomy as monotherapy in cT3 patients with a mean follow-up of just over 5 years, Isorna Martinez de la Riva et al. [4] reported a disease-specific survival of 100% and a likewise grade-dependant biochemical progression rate of 36%.

Beyond survival data, another consideration seems of importance. In addition to offering potential cure, radical removal of the prostate can improve local control and reduce local complications. This in itself may improve quality of life despite eventually progressive disease. The group of Walsh et al. [23] reported a case-control study of pelvic lymphadenectomy alone versus pelvic lymphadenectomy with radical prostatectomy in stage D1 patients. In this study they found a non-significant trend towards improved survival in the prostatectomized group after 10 years. The group of Frohmüller et al. [24] showed already in 1995 in lymph node-positive patients (T1-3pN1-2M0), in a comparative study between pelvic lymphadenectomy followed by hormonal deprivation versus pelvic lymphadenectomy plus radical prostatectomy followed by hormonal therapy, a significant benefit in disease-specific survival as well as local progression and complication rate after 10 years for the prostatectomized group (10-year disease-specific survival 32 vs. 71%, local progression rate 8 vs. 69%) [24]. These studies demonstrate that radical surgery in pT3 patients may in the long run improve quality of life by reducing local progression and complications, despite the fact that cure cannot be achieved.

Thus, patients with cT3 prostate cancer who may be candidates for radical prostatectomy should have favorable risk factors. In addition to a sufficient general life expectancy and low comorbidity, the biopsy Gleason score should be 7 or less, the PSA should not exceed 20 ng/ml and seminal vesicle invasion should clinically be unlikely. Nerve-sparing surgery in this patient group, however, is not an option. A high rate of positive margins is to be expected (up to 60%). This can possibly be reduced with neoadjuvant hormonal treatment which, however, does not influence the biochemical recurrence rate [25].

Positive Lymph Nodes

In case of positive lymph nodes (pN+) in stage cT3 prostate cancer, the disease is systemic and carries a reduced prognosis. In surgical series of cT3 cases the node-positive rate is between 27 and 41% [5–7]. The published retrospective series of node-positive pT3 disease have shown that disease-specific survival is prolonged by adjuvant hormone deprivation. Five- and 10-year progression-free survival rates of 41–83 and 25–71%, respectively, have been reported [23, 24, 26–29]. The ECOG as well as the EORTC studies have shown a significant progression-free survival benefit for an early versus a deferred hormone-deprivation therapy [22, 30].

The finding of positive lymph nodes during surgery in cT3 patients raises the question of whether to perform radical prostatectomy or not. The published studies on this question have yielded a definite answer to this question. Zwergel et al. reported a relatively good disease-specific 10-year survival of 74% after radical prostatectomy

Table 1. Prospective randomized studies on adjuvant hormonal treatment after radical prostatectomy

Group (first author)	Stages	Treatment	Progression	Survival
Messing, 1999 [41], 2003 [30]	pN+	Orchidectomy or LHRH analogues	Advantage for adjuvant treatment	Advantage for adjuvant treatment
Prayer-Galetti, 2000 [56]	Stage C	LHRH analogues	Advantage for adjuvant treatment	No data available
Wirth, 2004 [44]	pT3-4pN0	Flutamide	Advantage for adjuvant treatment	No difference
Wirth, 2001 [57], 2004 [58]; McLeod, 2006 [59]	pT1b-4, N0-1M0	Bicalutamide	Advantage for adjuvant treatment	No difference

in pN+ disease. The risk of progression in this series was proportional to the extent of lymph node metastases. With minimal lymph node spread the risk of disease-specific mortality after radical prostatectomy is only marginally elevated compared to pN0 cases with a hazard ratio of 1.5 in patients with one positive lymph node. In this patient group, disease-specific 10-year survival rates of 94% have been reported [31]. The group from Berne, which stresses the necessity of extensive pelvic lymphadenectomy, has shown this relationship between prognosis and the extent of micrometastatic lymph node spread with, however, less favorable disease-specific survival rates [32].

Adjuvant Treatment after Radical Prostatectomy for pT3 Disease

Until recently there was no rationale for adjuvant radiotherapy in lymph node-negative pT3 disease, since the majority of locally advanced prostate carcinomas tend to progress systemically rather than locally after radical prostatectomy. However, there are indications that adjuvant radiotherapy (60 Gy over 6 weeks) can probably reduce the rate of biochemical progression and local recurrences [33–35]. Recently, Bolla et al. [36] published the results of a large randomized trial of adjuvant immediate postoperative radiotherapy in pN0M0 patients with pT3 disease and/or positive margins, and found a significantly increased biochemical progression-free survival and an increased clinical progression-free survival within a follow-up period of 5 years. However, it has so far not been possible to show a benefit in disease-specific survival [37]. Also, there is no definitely proven need for adjuvant hormonal treatment in lymph node-negative pT3 prostate cancer. While the EPC study has shown a significant reduction of the progression rate in prostatectomized locally advanced prostate cancers with adjuvant antiandrogenic treatment, this did not result in a prolongation of the disease-specific survival.

While there is thus no proof from randomized studies for a general benefit of adjuvant hormone deprivation treatment after radical prostatectomy, advantages from adjuvant hormone treatment may be seen for specific subgroups of patients (table 1). In a retrospective study a survival advantage was seen in patients with seminal vesicle invasion [38] and in patients with diploid tumors and lymph node-positive disease [39, 40]. A small randomized study with 98 patients only and a median follow-up of 7 years showed a superiority of early versus deferred treatment concerning disease-specific and overall survival in patients with minimal lymph node disease after radical prostatectomy [41]. The results of this study have so far, however, not been confirmed by other trials [42]. An EORTC study with 302 lymph node-positive patients who did not undergo radical prostatectomy showed no advantage for early hormonal treatment, despite a threefold larger study group than the control group [43]. In a randomized prospective controlled multicenter study in Germany and Austria, 352 node-negative patients with locally advanced prostate cancer were treated with either flutamide 750 mg daily or by watchful waiting until clinical progression occurred. After a median follow-up of 6 years, no survival advantage was seen for the adjuvant hormonal treatment [44].

Neoadjuvant Treatment

A definite benefit of neoadjuvant hormonal treatment before radical prostatectomy has never been proven, despite numerous randomized studies undertaken [45–49]. Neoadjuvant treatment specifically for locally advanced prostate cancer, however, has only been examined in a limited number of studies with a small number of patients. Neoadjuvant treatment can reduce the tumor vol-

ume [50] as well as the rate of positive margins [51, 52]. This, however, does not influence survival or progression parameters. In one randomized study, a trend towards a reduced clinical progression rate was seen in patients who received neoadjuvant as well as adjuvant hormonal treatment compared to the control group, which received only adjuvant hormonal treatment [53]. In this study, however, follow-up was limited to only 2 years.

There are still only very few data concerning potential advantages which might be achieved with neoadjuvant chemotherapy in high-risk patients before radical prostatectomy with docetaxel. Toxicity is mild. Histopathologically complete remissions are not to be expected [54, 55] and the use of chemotherapy in this setting should currently only be performed in controlled clinical trials.

Conclusions

In well-selected patients with clinically locally advanced prostate cancer who have a favorable risk factor profile regarding preoperative PSA and biopsy Gleason score and who have limited comorbidity and sufficient life expectancy, curative treatment is advisable. Radical prostatectomy in these patients should be a preferred option, also considering the large staging error which occurs in this setting. Pelvic lymphadenectomy in cT3 disease is indispensable, due to a high number of node-positive cases which must be expected. Recent series, however, have demonstrated that in node-negative pT3 prostate cancer, radical prostatectomy achieves biochemical progression and disease-specific survival rates in patients with well to moderately differentiated disease which are only marginally worse than in those with pT2 disease. In addition, there are data demonstrating a reduction in local complication rate in patients with cT3 prostate cancer after radical prostatectomy, which improves quality of life and reduces hospital time during the remaining life span of incurable patients with progressive disease. Adjuvant hormonal treatment is of proven benefit only in node-positive surgically treated patients. Adjuvant radiotherapy after radical prostatectomy in pT3pN0M0 patients improves biochemical and clinical progression-free survival.

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