What's known on the subject? and What does the study add?

Despite a lack of randomised controlled trials, most men with locally advanced prostate cancer are recommended to undergo external beam radiotherapy (EBRT), often combined with long-term androgen-deprivation therapy (ADT). Many of these men are not offered radical prostatectomy (RP) by their treating urologist. Additionally, it is known that EBRT with long-term ADT does provide good cancer control (88% at 10 years). We have previously published intermediate-term follow-up of a large series of men treated with RP for cT3 prostate cancer.

We report long-term follow-up of a large series of men treated with RP as primary treatment for cT3 prostate cancer. Our study shows that with long-term follow-up RP provides excellent oncological outcomes even at 20 years. While most men do require a multimodal treatment approach, many men can be managed successfully with RP alone.

OBJECTIVE

- To present long-term survival outcomes after radical prostatectomy (RP) for patients with cT3 prostate cancer, as the optimal treatment for patients with clinical T3 prostate cancer is debated.

PATIENTS AND METHODS

- We identified 843 men who underwent RP for cT3 tumours between 1987 and 1997.
- Survival was estimated using the Kaplan–Meier method.
- Cox proportional hazards regression models were used to evaluate the association of clinicopathological features with outcome.

RESULTS

- The median (range) postoperative follow-up was 14.3 (0.1–23.5) years.
- Down-staging to pT2 disease occurred in 26% (223/843) at surgery.
- Local recurrence-free, systemic progression-free and cancer-specific survival for men with cT3 prostate cancer after RP was 76%, 72%, and 81%, respectively, at 20 years.
- On multivariate analysis, increasing RP Gleason score (hazard ratio [HR] 1.8; \( P = 0.01 \)), non-diploid chromatin content (HR 1.8; \( P = 0.01 \)), positive surgical margins (HR 2.1; \( P = 0.007 \)), and seminal vesicle invasion (HR 2.1; \( P = 0.005 \)) were associated with a significant risk of prostate cancer death, while a more recent year of surgery was associated with a decreased risk of cancer-specific mortality (HR 0.88; \( P = 0.01 \)).

CONCLUSIONS

- RP affords accurate pathological staging and may be associated with durable cancer control for cT3 prostate cancer, with 20 years of follow-up presented here.
- RP as part of a multimodal treatment strategy therefore remains a viable treatment option for patients with cT3 tumours.

KEYWORDS

clinical T3, prostate cancer, radical prostatectomy, extraprostatic extension, seminal vesicle invasion

INTRODUCTION

A significant stage migration has occurred with the introduction of routine PSA screening for prostate cancer. Accordingly, most newly-diagnosed tumours are now organ-confined (cT2), with only a small subset of patients presenting with locally advanced (cT3) disease [1]. As a result, the optimal treatment for these patients remains unclear and highly controversial. Interestingly, despite a lack of prospective randomised clinical trials comparing treatment methods for men with high-risk prostate cancer, these patients have been found to be significantly less likely to undergo surgery [2,3].

Indeed, external beam radiotherapy (EBRT) combined with hormonal therapy has been associated with 5-year cancer-specific survival (CSS) rates of 94% for men with locally advanced prostate cancer, and in fact has become a preferred treatment in this setting [4]. The use of concomitant long-term androgen-deprivation therapy (ADT) has been found to be critical in optimising outcomes for high-risk tumours treated with EBRT, as results from the EORTC Phase III trial 22961 found a 10-year
prostate cancer mortality rate of 31% for patients treated with EBRT alone, vs 11.2% after EBRT combined with long-term ADT [5].

Radical prostatectomy (RP) has been evaluated for patients with cT3 in several single-institution series to date, including a previous report from our centre [1,6–8]. Data from these studies suggest that RP may afford long-term cancer control for cT3 tumours. However, these studies have largely contained relatively few patient and/or short-term follow-up, and have variously included patients treated with adjuvant therapies. Here, then, we provide long-term follow-up from a large cohort of men who underwent RP for cT3 prostate cancer.

PATIENTS AND METHODS

After Institutional Review Board approval was obtained, we reviewed our Prostatectomy Registry to identify 7883 consecutive patients who underwent RP at Mayo Clinic between 1987 and 1997. This era was chosen to allow for reporting of extended follow-up. Of these patients, 4812 (61%) patients had cT2 and 843 (15%) presented with cT3 disease, which was determined based on DRE. RP was performed by various surgeons using standard techniques. All patients included here underwent an open retropubic approach. The Mayo Clinic protocol for preparing and reporting serially sectioned prostate has been previously reported [9].

Postoperative assessments, including physical examinations and serum PSA measurements, were done quarterly for the initial 2 years, semi-annually for an additional 2 years, and annually thereafter. Adjuvant therapy was defined as treatment received ≤90 days of RP, and was given at the discretion of the treating physician. Biochemical recurrence was defined as a PSA level of ≥0.4 ng/mL [10,11]. Local recurrence was defined as cancer on biopsy of the prostate bed or clinically evident disease within the prostatic fossa on physical examination or imaging studies. Systemic progression involved demonstrable metastasis on radionuclide bone scan or on biopsies outside the prostatic bed. Vital status was identified from death certificates or physician correspondence. For patients followed elsewhere, the Mayo Clinic Prostatectomy Registry prospectively monitors outcomes annually by correspondence.

The primary endpoints were local recurrence-free survival, systemic progression-free survival, CSS, and overall survival. Postoperative survival was estimated using Kaplan–Meier method. Patients were censored at last follow-up or death if the end point of interest was not attained. Univariate and multivariate analysis of features associated with outcomes were conducted using Cox proportional hazards regression models.

All tests were two-sided, with $P \leq 0.05$ considered to indicate statistical significance.

RESULTS

Clinical and pathological demographics of the study population are shown in Table 1. The median age was 65 years and median body mass index was 27.2 kg/m². The median preoperative PSA level and tumour volume were 10.2 ng/mL and 5.2 mL³, respectively. Interestingly, as can be seen, clinical over-staging occurred in 26% (223/843) of patients, as these men were in fact found to have organ-confined (pT2) disease at RP. In all, 198 (24%) of the men with cT3 prostate cancer received neoadjuvant hormonal therapy. A total of 344 (40.8%) men received adjuvant hormonal therapy, while 109 (12.9%) were treated with adjuvant radiation. As such, 356 (42%) men in the cT3 cohort were treated with RP without neoadjuvant or adjuvant therapy.

The median (range) postoperative follow-up was 14.3 (0–23.5) years. During this time, 501 (59%) men had biochemical recurrence, 156 (19%) developed local recurrence, and 197 (23%) had systemic progression. In all, 454 (54%) had died at last follow-up, with 126 (15%) dying from prostate cancer (Table 2). The resulting survival estimates at 20 years after RP, then, were 76%, 72%, 81%, and 36% for local recurrence-free, systemic progression-free, prostate CSS, and overall survival, respectively (Figs 1–4). Overall, 170 (20.2%) patients received

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
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<tbody>
<tr>
<td>Median (IQR):</td>
<td></td>
</tr>
<tr>
<td>Age at RP, years</td>
<td>65.0 (60–69)</td>
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<tr>
<td>Preoperative PSA level, ng/mL</td>
<td>10.2 (4.7–23.7)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.2 (25.1–29.6)</td>
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<tr>
<td>N (%):</td>
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<tr>
<td>Biopsy Gleason score:</td>
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<tr>
<td>6</td>
<td>201 (45)</td>
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<td>7</td>
<td>161 (36)</td>
</tr>
<tr>
<td>8–10</td>
<td>84 (19)</td>
</tr>
<tr>
<td>Receipt of neoadjuvant ADT</td>
<td>198 (24)</td>
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<tr>
<td>RP Gleason score:</td>
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<tr>
<td>6</td>
<td>305 (41)</td>
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<td>7</td>
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<td>8–10</td>
<td>128 (17)</td>
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<td>Pathological stage:</td>
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<tr>
<td>T2N0</td>
<td>223 (26)</td>
</tr>
<tr>
<td>T3a</td>
<td>191 (22.7)</td>
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<tr>
<td>T3b</td>
<td>199 (23.6)</td>
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<tr>
<td>T4</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>TxN1</td>
<td>227 (27)</td>
</tr>
<tr>
<td>Positive surgical margin</td>
<td>472 (56)</td>
</tr>
<tr>
<td>Median (IQR) tumour volume, mL³</td>
<td>5.2 (2.3–11)</td>
</tr>
<tr>
<td>Ploidy, n (%):</td>
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<tr>
<td>Diploid</td>
<td>421 (52)</td>
</tr>
<tr>
<td>Tetraploid</td>
<td>285 (35)</td>
</tr>
<tr>
<td>Aneuploid</td>
<td>112 (14)</td>
</tr>
</tbody>
</table>

**TABLE 1**

Clinicopathological demographics of patients with cT3 tumours treated with RP.
salvage radiotherapy for biochemical recurrence, while 319 (37.8%) patients were treated with salvage ADT during clinical follow-up.

We next evaluated variables associated with death from prostate cancer among men with cT3 disease undergoing RP. On multivariate analysis (Table 3), we found that increasing RP Gleason score (hazard ratio [HR] 1.8; \( P = 0.01 \)), non-diploid chromatin content (HR 1.8; \( P = 0.01 \)), positive surgical margin (HR 2.1; \( P = 0.007 \)), and seminal vesicle invasion (HR 2.1; \( P = 0.005 \)) were associated with a significantly increased risk of prostate cancer death. On the other hand, more recent year of surgery (HR 0.88; \( P = 0.01 \)) was associated with a decreased risk of prostate-cancer mortality.

DISCUSSION

For men with cT3 prostate cancer, RP offers durable oncological outcomes, with long-term follow-up, now up to 20 years. Additionally, over-staging of cT3 disease was 26%, suggesting that while most patients with cT3 tumours will probably require a multimodal treatment strategy, more than a quarter of patients may be able to be managed with RP alone, thereby delaying if not avoiding the costs and toxicities of secondary therapies. This series represents, what is to our knowledge, the largest single institution series reported to date, with the longest postoperative follow-up, for patients with cT3 prostate cancer treated with RP.

While routine PSA screening has resulted in a significant stage migration of prostate cancer, a small percentage of men continue to be diagnosed with locally advanced tumours. The optimal treatment approach for men with high-risk/locally advanced disease remains unknown and continues to be the subject of much debate. The long-term postoperative CSS for men with cT3 disease in the present study (90% at 10 years) compares favourably with the reported rates achieved with EBRT combined with long-term ADT in the EORTC phase III trial 22961 [88% at 10 years] [5]. The present study further shows that RP continues to achieve durable oncological outcomes, with a CSS of 81% at 20 years (=1%/year after 10 years). One potential benefit from RP for patients with cT3 disease is the ability to obtain pathological...
staging, as >25% of these men were found to be clinically over-staged. As such, the pathological staging information from RP may guide a more selective application of secondary therapies, including ADT, which carries significant adverse consequences on health-related quality of life and non-cancer morbidity [12,13]. Although the exact association remains unclear and has recently been questioned [14], there is recent increased awareness of the potential for increased risk of cardiac death in men receiving ADT as well [15].

Others have examined the impact of RP for locally advanced prostate cancer. Carver et al. [6] reported on 176 men with cT3 cancer treated with RP. One third of patients received neoadjuvant while none received adjuvant therapy. The 15-year probability of death from prostate cancer in that series was low (24%); however, follow-up was short (median 6.4 years). In another series from Johns Hopkins of cT3a only, Freedland et al. [7] reported on 61 patients with a median follow-up of 10.3 years. Estimated 15-year survival was 84% with no men having received adjuvant therapies. Meanwhile, Hsu et al. [16] reported on a series of 235 men with cT3 prostate cancer treated with RP. Of these men, 22% received adjuvant and 34% received salvage treatments. Nonetheless, with a relatively short follow-up (5.8 years), actuarial 10-year prostate cancer survival was 91.6%.

In the present series, despite nodal metastases in >25%, 28% of men with cT3 prostate cancer did not receive any form of ADT during treatment or follow-up, while 48% did not receive any form of adjuvant therapy. Thus, a significant percentage of men with cT3 tumours may achieve durable oncological outcomes with RP alone. Nevertheless, it is important to note that RP for cT3 prostate cancer is often part of a multimodal treatment strategy. Interestingly, for the impact of the sequence of treatments in such a multimodal approach, initial treatment with RP followed by salvage radiation has been associated with improved health-related quality of life outcomes, particularly for erectile dysfunction and urinary incontinence, than initial treatment with radiation therapy followed by salvage RP [17].

While no prospective randomised trials have been conducted for RP vs radiation therapy in men with high-risk prostate cancer, several retrospective series have examined this issue. When controlling for case mix, these series have noted a significantly increased risk of mortality among patients treated with EBRT vs RP [18,19]. It has been postulated that this finding may be related in part to a potential increased risk of cardiac death, particularly in men with coronary artery disease, receiving ADT together with EBRT [15]. However, the need remains for prospective clinical trials to define the optimal multimodal management approach for patients with high-risk prostate cancer.

We recognise the present study is limited by its retrospective and non-randomised design. As such, administration of secondary cancer treatments with regard to the choice, timing, and duration of therapy was subject to individual physician discretion. In addition, the present series represents a historical cohort of patients, largely treated before the stage migration that has occurred as a result of aggressive PSA screening. As increasing year of surgery was significantly associated with a decreased risk of prostate cancer death, it is unclear whether these results will continue to be applicable in contemporary cT3 patients. Moreover, it remains to be seen how increased use of preoperative MRI for more accurate staging of high-risk patients will affect the rates of over-staging seen in the present study [20,21]. While the present study is devoid of a control group for comparison, nonetheless we feel that RP as part of a multimodal treatment strategy for patients with cT3 disease offers durable cancer control and survival rates 20 years after RP and compares favourably with the outcomes that have been reported after EBRT + ADT for locally advanced tumours.

In conclusion, although patients with cT3 prostate cancer may have additional adverse pathological features, RP affords accurate pathological staging and identifies a substantial proportion of patients who in fact have organ-confined tumours, and may thereby be spared the toxicities and cost of adjuvant therapy. Moreover, RP may be associated with durable cancer control, frequently as part of a multimodal treatment strategy, for patients with locally advanced disease, and should therefore remain a viable treatment option for such patients.

CONFLICT OF INTEREST
None declared.

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Correspondence: R. Jeffrey Karnes, Department of Urology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. e-mail: karnes.r@mayo.edu

Abbreviations: ADT, androgen-deprivation therapy; CSS, cancer-specific survival; EBRT, external beam radiotherapy; HR, hazard ratio; RP, radical prostatectomy.