Single tertiary cancer center experience on the management of pT3b prostate cancer after robotic-assisted laparoscopic prostatectomy

Arvind Nayak, Omar El-Tajj, Sugeeta Sukumar, John Pieda, Aruni Ghose, Roberto Alonzia, Peter Ostler, Anand Sharma, Tim Lane, Jim Adshead, Nikhil Vasdev

Abstract

Background: Pathological involvement of the seminal vesicle poses a treatment dilemma following robotic prostatectomy. Margin status plays an important role in deciding further management. A wide range of treatment options are available, including active monitoring, adjuvant radiotherapy, salvage radiotherapy, and occasionally androgen deprivation therapy. Patients undergoing postoperative radiotherapy tend to have higher risk of urinary and bowel morbidities. The recent RADICALS-RT concluded that adjuvant radiotherapy did not have any benefit compared with salvage radiotherapy. We aim to audit the incidence, margin status, and management of T3b cancer cases at our center.

Materials and methods: A retrospective analysis was conducted of all patients diagnosed with pathological T3b (pT3b) prostate cancer following robotic-assisted laparoscopic prostatectomy from January 2012 to July 2020. Preoperative parameters analyzed included prostate-specific antigen (PSA), T stage, and age. A chi-square test and 2-tailed t-test were used to determine the relationship between categorical and continuous variables, respectively. Kaplan-Meier survival curves were generated to assess overall survival in patients with pT3b prostate cancer and used to compare unadjusted progression-free survival among those who underwent adjuvant and salvage radiotherapy.

Results: A total of 83 (5%) of 1665 patients who underwent robotic prostatectomy were diagnosed with pT3b prostate cancer between January 2012 and July 2020. Among these, 36 patients (44%) did not receive any radiotherapy during follow-up, compared with 26 patients (31%) who received adjuvant radiotherapy and 21 (25%) who received salvage radiotherapy. The median age of our cohort was 64 (SD, 6.4) years. Mean PSA at presentation was 12.7 μg/L. Positive margins were seen in 36 patients (43%); however, there was no statistically significant difference between treatment groups (p = 0.49). The median overall survival was 96%. There was no significant difference between the adjuvant and salvage groups in terms of biochemical progression-free survival (p = 0.66). Five-year biochemical progression-free survival was 94% for those in the adjuvant radiotherapy group and 97% for those in the salvage radiotherapy group.

Conclusions: Our audit corroborates with the recently concluded RADICALS-RT study, although we had fewer patients with positive margins. Radiotherapy can be avoided in patients with T3b prostate cancer, even if margin is positive, until there is definitive evidence of PSA recurrence. In keeping with the conclusion of RADICALS-RT, salvage radiotherapy may be preferable to adjuvant radiotherapy.

Keywords: Prostate cancer; Radiotherapy; Robotic prostatectomy; Seminal vesicle; T3b

1. Introduction

Clinically localized prostate cancer can be treated successfully with a robotic radical prostatectomy (RP). Clinical diagnosis is currently based on prostate-specific antigen (PSA), digital rectal examination, and now with multiparametric magnetic resonance imaging (mpMRI) followed by prostate biopsy. A prebiopsy prostate MRI is now used as an accurate modality to stage prostate cancer pre-treatment. The sensitivity of MRI to diagnose seminal vesicle (SV) invasion T3b prostate cancer is in the range of 60%, whereas the specificity is 95%. The incidence of T3b prostate cancer reported on MRI is approximately 10%, as compared with 5% to 18% of patients having SV invasion on pathologic examination after RP.

The invasion of the SV (T3b disease) is usually associated with adverse clinical outcomes in patients with prostate cancer and is believed to be associated with occult micrometastatic disease, earlier biochemical relapse, and progression of disease. Biochemical recurrence was reported to be approximately 60% in a previous analysis of 300 men with SV invasion. A wide range of treatment options are available, including active monitoring, adjuvant radiotherapy (RT), salvage RT, and occasionally androgen deprivation therapy (ADT). The standard of care for patients with SV invasion has traditionally been RT combined with 2 to 3 years of ADT. The treatment for high-risk prostate cancer (HRPCa) is not yet standardized because of the...
lack of evidence to prove the superiority of a single option with regard to oncological outcomes. Therefore, the choice of treatment is currently guided by individual scenarios, concerns for adverse effects, and impact on quality of life (QOL) for the patient.

Various researchers have investigated the toxicities and impact on QOL of different management options for prostate cancer, whereas some have also compared baseline patient profiles with posttreatment QOL to definitively implicate treatment toxicities. Patients undergoing postoperative RT tend to have higher risk of urinary and bowel morbidities.

Interestingly, most of these articles have focused on localized disease, where single-modality treatment is optimal, and the need for multimodal therapy is unusual. Therefore, RP alone is compared with brachytherapy alone and/or external beam RT alone. On the contrary, in the case of HRPCa, most international guidelines recommend multimodal management. There exists a compelling need for evidence with regard to toxicities and impact on QOL in this subset of patients.

Randomized trials from the 1980s, European Organisation for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group, compared combined long-term ADT and RT treatment of HRPCa with RT alone, concentrating on physician-reported classic toxicities and oncological outcomes. They found combination therapy to be superior in terms of survival, with no significant differences with regard to genitourinary and gastrointestinal toxicities. However, effects on sexual QOL were not analyzed. Recent randomized controlled trials have reconfirmed these findings, but data on QOL impact are absent in these studies also.

Case series from Centers of Surgical Excellence have found that 75% to 80% of patients who underwent initial RP for treatment of HRPCa needed either early adjuvant RT and/or ADT or late salvage RT. Hence, it is imperative to counsel patients with HRPCa about the need for multimodal therapy and the risks associated with each modality. Randomized controlled trials comparing immediate postoperative RT with observation have shown no increased risk of genitourinary or gastrointestinal toxicities. But monoinstitutional series have suggested a delayed time to continence recovery associated with RT following both nerve-sparing and non-nerve-sparing RP.

The recent RADICALS-RT concluded that adjuvant RT did not have any benefits compared with salvage RT. In this study, we aim to audit the incidence, margin status, and management of T3b cancer cases at our center.

### 2. Materials and methods

The Lister Hospital database (2012 to present) was queried for men with pT3b disease. A retrospective analysis was conducted of all patients diagnosed with pT3b prostate cancer following robotic-assisted laparoscopic prostatectomy from January 2012 to July 2020. Seminal vesicle invasion was defined as tumor invading the muscular wall of the SV, which can occur by extraprostatic extension at the base of the prostate, direct tracking along the ejaculatory duct complex, or via isolated, noncontiguous SV deposits.

Preoperative parameters analyzed included PSA, T stage, and age. Postoperative margin status and pathological stage were examined. Patients were categorized based on margin status and RT treatment plan accordingly (no RT, adjuvant RT, and salvage RT).

Demographic and pathologic data were compared between patients who had T3b prostate cancer and underwent salvage, adjuvant, and no RT. A chi-square test and 2-tailed t test were used to determine the relationship between categorical and continuous variables, respectively. Kaplan-Meier survival curves were generated to assess overall survival in patients with pT3b prostate cancer and used to compare the unadjusted progression-free survival between those who underwent adjuvant and salvage RT. Biochemical failure was defined as a PSA of >0.4 μg/L. All statistical tests were 2-sided by default, and the significance level was set at 0.05, unadjusted for multiple comparisons. All statistical analyses were conducted using Prism 6 (GraphPad Software, Inc, San Diego, CA).

### 3. Results

A total of 83 subjects were identified with T3b prostate adenocarcinoma, with a median follow-up of 36 months (Table 1). Thirty-six patients (44%) did not receive any RT during follow-up, 26 patients (31%) received adjuvant RT, and 21 patients (25%) received salvage RT. The median age of our cohort was 64 (SD, 6.4) years, with no statistically significant difference between the groups (p = 0.34). Mean PSA at presentation was 12.7 μg/L, with no statistically significant difference between groups (p = 0.26). Among all patients, 38 (46%) had a Gleason score of 3 + 4, which was the most common pathological pattern. However, there was a lower proportion of patients (12%) who had a Gleason score of ≥8 who received adjuvant RT when compared with those not receiving RT (25%) or those receiving salvage RT (33%). Positive margins were seen in 36 patients (43%); however, there was no statistically significant difference between treatment groups (p = 0.49).

### Table 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No radiotherapy (n = 36)</th>
<th>Adjuvant radiotherapy (n = 26)</th>
<th>Salvage radiotherapy (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range), yr</td>
<td>63 (55–74)</td>
<td>62 (46–72)</td>
<td>60 (51–72)</td>
</tr>
<tr>
<td>Mean PSA at presentation, mean (SD), μg/L</td>
<td>11.4 (6.2)</td>
<td>14.4 (8.2)</td>
<td>13.1 (7.1)</td>
</tr>
<tr>
<td>Gleason score, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>3 + 4</td>
<td>16 (44)</td>
<td>14 (54)</td>
<td>8 (38)</td>
</tr>
<tr>
<td>4 + 3</td>
<td>11 (31)</td>
<td>8 (31)</td>
<td>6 (29)</td>
</tr>
<tr>
<td>&gt;8</td>
<td>9 (25)</td>
<td>3 (12)</td>
<td>7 (33)</td>
</tr>
<tr>
<td>Positive margin, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>23 (64)</td>
<td>13 (50)</td>
<td>11 (52)</td>
</tr>
<tr>
<td>Present</td>
<td>13 (36)</td>
<td>13 (50)</td>
<td>10 (48)</td>
</tr>
<tr>
<td>Lymph nodes, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node positive</td>
<td>1 (3)</td>
<td>1 (4)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Node negative</td>
<td>11 (31)</td>
<td>10 (38)</td>
<td>13 (62)</td>
</tr>
<tr>
<td>No dissection</td>
<td>24 (67)</td>
<td>15 (58)</td>
<td>7 (33)</td>
</tr>
</tbody>
</table>

PSA = prostate-specific antigen.
Unadjusted Kaplan-Meier estimates for overall survival were generated for patients with pT3b prostate adenocarcinoma, with a median overall survival of 96% ($p = 0$, Fig. 1). Three patients died, of whom only one death was attributed to prostate cancer.

Twenty-four patients (51%) who had negative margins underwent RT (13 [28%] in the adjuvant group and 11 [23%] in the salvage group), whereas the remaining 23 patients (49%) did not receive any RT treatment (Fig. 2). There was no statistically significant difference between patients with negative margins who underwent RT (adjuvant or salvage) compared with no RT ($p = 0.84$). Twenty-three patients (64%) with a positive surgical margin underwent RT (13 [35%] in the adjuvant group and 10 [28%] in the salvage group); the remaining 23 patients (36%) did not receive any RT treatment (Fig. 3). Patients with a positive margin favored RT ($p = 0.03$). There was no statistically significant difference between patients undergoing adjuvant versus salvage RT ($p = 0.8$).

Regarding outcome measures, 8 biochemical progression events were reported: 5 in the adjuvant RT group and 3 in the salvage RT group over an 8-year period (Fig. 4). No difference was found between the adjuvant and salvage groups in terms of biochemical progression-free survival (bPFS) ($p = 0.66$). Five-year bPFS was 94% for those in the adjuvant RT group and 97% for those in the salvage RT group.

### 4. Discussion

Approximately 5% to 18% of patients tend to have pathological involvement of SV following RP.\(^6,15-17\) The use of mpMRI has led to more accurate preoperative staging and has made a significant impact on therapeutic planning.\(^18\) The use of mpMRI has also played an important role in selection of candidates for nerve-sparing and pelvic lymph node dissection. Recent studies have suggested that 43% of patients with pathological T3b have involved pelvic lymph nodes.\(^19\)

Management of patients with pathological T3b can vary from surveillance, to adjuvant and salvage RT and ADT. The presence of a positive margin has a bearing on the most appropriate treatment offered to the patient. Favorable oncological outcomes without adjuvant treatment have been observed in patients with a negative surgical margin and PSA <0.2 $\mu$g/L at 1 month following prostatectomy;\(^20\) however, long-term outcomes are still unclear. Hence, subjecting all patients to RT may lead to overtreatment.

Several studies have been designed to help determine the timing of RT following prostatectomy. The EORTC 22911\(^21\) and Southwest Oncology Group 8794\(^22\) essentially compared adjuvant RT to observation, as not all patients received salvage RT for biochemical progression. Although the Southwest Oncology Group trial was the only trial to show a survival benefit for patients who received adjuvant RT, it could be attributed to the late use of salvage RT. The EORTC 22911 trial did show a bPFS benefit but no overall survival benefit in patients who received adjuvant RT. ARO 96-02 trial\(^23\) and the Finnish Radiation Oncology Group trial\(^10\) were smaller trials, with a total of 557 patients, designed to answer the question of salvage versus adjuvant RT. Both trials demonstrated that adjuvant RT reduced the risk of biochemical progression. Although these studies demonstrated the benefit of adjuvant RT, they did not enlighten us on the optimal timing of RT.
The largest randomized controlled trial \( (n = 1396) \) to date comparing routine adjuvant RT after RP with salvage RT for PSA biochemical progression, RADICALS-RT,\(^24\) showed no benefit with adjuvant RT; however, it did demonstrate an increased risk of urinary and bowel morbidities. Thus, the authors recommended PSA surveillance as opposed to adjuvant RT. In that study population, 19% of patients had T3b disease, and 63% had positive margins, and subgroup analysis showed no difference in outcomes compared with the rest of the study population.

A French multicenter (46 hospitals) open-label, phase 3 trial, GETUG-AFU 17,\(^25\) randomized 424 patients to adjuvant or salvage RT. They found an increased risk of genitourinary toxicity and erectile dysfunction with no oncological benefit in patients receiving adjuvant RT versus salvage RT.

Another multicenter randomized trial of 333 patients across 32 oncology centers in Australia and New Zealand, TROG 08.03/ANZUP RAVES,\(^24\) concluded that biochemical control was similar between salvage RT and adjuvant RT; however, salvage RT spared approximately half of men from pelvic radiation, resulting in significantly lower genitourinary toxicity.

A prospective systematic review and meta-analysis, ARTISTIC,\(^26\) suggested that adjuvant RT does not improve event-free survival in men with localized or locally advanced prostate cancer. Until data on long-term outcomes are available, current evidence suggests that early salvage treatment would reduce the need for pelvic RT in half of the men, therefore reducing associated genitourinary toxicity.

Lymph node positivity in patients with T3b prostate cancer is an important factor that can influence management, as patients with positive lymph nodes may go on to have adjuvant chemotherapy or RT. Studies have shown that 11% to 24% of patients with T3b disease have positive pathological lymph nodes.\(^11,27\)

The 5-year bPFS in patients with T3b prostate cancer has been found to be extremely variable, ranging from 8% to 68%.\(^28\) Biochemical progression-free survival rates are dependent on variability in PSA level, margin status, and Gleason score.\(^29–31\) In our series, 5-year bPFS was 94% in the adjuvant RT group and 97% in the salvage RT group.

Patients with HRPCa represent a highly heterogeneous group. Most patients will require both RT and long-term ADT. A selected subgroup of patients (those with limited local burden of disease, cT3a or initial cT3b, a Gleason score of 7, and PSA <20 ng/mL, for example) may benefit from a dose escalation into the prostate with short-term (6 months) ADT, thus reducing the likelihood of combined adverse effects. Recent data have shown a possibility of cardiac deaths with long-term ADT, particularly for patients with an initial greater burden of comorbidities. These considerations need to be borne in mind when customizing treatment plans for patients. There is an urgent need to stratify HRPCa patients, to better adapt the duration of ADT based on the characteristics of their disease and comorbidities.

Our study has a few limitations, including the retrospective nature of the study. In addition, some of the patients with T3b disease had been recruited in the recently concluded RADICALS-RT study.

5. Conclusions

Our audit corroborates with the recently concluded RADICALS-RT study, although we had fewer patients with positive margins. Radiotherapy can be avoided in patients with T3b prostate cancer, even if margins are positive, until there is definitive evidence of PSA recurrence. In keeping with the conclusion of RADICALS-RT, salvage RT appears preferable to adjuvant RT.

Acknowledgments

None.

Statement of ethics

According to local institutional regulations, we confirm that ethical approval and participants’ consent were not required as ethical approval is not warranted in a retrospective observational study. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest statement

No conflict of interest has been declared by the authors.

Funding source

None.

Author contributions

AN: Data collection and draft of manuscript; OET: Statistical analysis; NV: Conceived the study; SS, JP, AG, RG, RA, PO, AS, TL, JA: Literature review and review of manuscript.
References


