Prostate Cancer

Good Outcome for Patients with Few Lymph Node Metastases After Radical Retropubic Prostatectomy

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Abstract

Background: Conflicting results exist regarding the value of an extended pelvic lymph node dissection (PLND) in node-positive patients undergoing radical retropubic prostatectomy (RRP) for clinically localized prostate cancer.

Objective: To assess the long-term outcome in node-positive patients who underwent extended PLND followed by RRP.

Design, setting, and participants: A consecutive series of 122 node positive patients with negative preoperative staging examinations, no neoadjuvant hormonal or radiotherapy, and who underwent extended PLND (≥10 lymph nodes in the surgical specimen) followed by RRP were analyzed. None of the patients received immediate androgen deprivation therapy (ADT).

Intervention: All patients underwent extended PLND followed by RRP.

Measurements: Biochemical recurrence-free survival, cancer-specific, and overall survival were assessed using the Kaplan-Meier technique.

Results and limitations: Median prostate-specific antigen (PSA) was 16 ng/ml. At pathological examination 76% of the 122 patients had pT3–pT4 tumours, 50% seminal vesicle infiltration. A median of 22 nodes were removed per patient.

Median cancer-specific survival at 5 and 10 yr was 84.5% and 60.1%, respectively. In patients with ≥2 or ≥3 positive nodes removed, median cancer-specific survival at 10 yr was 78.6% and 33.4%, respectively (p < 0.001).

After a median period of 33 mo, 61 of the 122 patients (50%) received ADT, particularly those (69%) with ≥3 positive nodes removed. This retrospective study includes a significant percentage of patients with high tumour burden, and therefore may not reflect current patient series.

Conclusions: Patients with ≤2 positive nodes detected after extended PLND followed by RRP had good long-term results and should not be denied treatment with curative intent. In contrast, prognosis was poor in patients with ≥3 positive nodes, despite extended PLND and despite ADT in 69% of patients.

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1. Introduction

Surgical excision and histologic examination of the pelvic lymph nodes provides the most accurate staging information regarding pelvic lymph node status in patients undergoing radical retropubic prostatectomy (RRP) for clinically localized prostate cancer. The role of extended pelvic lymph node dissection (PLND) in relation to survival, however, remains unclear.

Until recently, the presence of lymph node metastasis in patients with prostate cancer was associated with poor prognosis because chances of cure were slim in the setting of positive nodes [1–3]. Furthermore, it was thought that PLND could be used to justify cancellation of the subsequent prostatectomy if positive nodes were found, sparing the patient the morbidity of an unnecessary radical prostatectomy [4]. There is also growing evidence that extended PLND in patients with prostate cancer may confer a survival benefit not only for node-positive, but also for node-negative patients [5,6].

We report the long-term survival rates in node-positive patients with clinically localized prostate cancer who underwent extended PLND followed by RRP without immediate androgen deprivation therapy (ADT).

2. Patients and methods

A total of 122 consecutive patients with positive nodes detected at extended PLND were identified from a series of 602 patients with clinically localized prostate cancer (N0M0) based on negative staging examinations (bone scan, computerized tomography of pelvis, chest x-ray). The 122 patients were treated by open RRP between April 1989 and January 2007. None of the patients had undergone prior therapy for prostate cancer.

Applying a prospective protocol, a standardized extended extraperitoneal PLND was performed via a lower abdominal midline incision followed by RRP. The boundaries of the extended PLND were as follows: laterally, the upper limit of the external iliac vein (leaving the periarteric tissue untouched to avoid lymphedema of the lower extremities should subsequent radiotherapy to the pelvis be required for local tumour recurrence) [7]; distally, the femoral canal; proximally, the bifurcation of the common iliac arteries; medially, the side wall of the bladder; laterally, the obturator fossa; and dorsally, along the lateral and medial side of the internal iliac (hypogastric) vessels. Some lymphatic tissue was also removed from the presacral/pararectal area (Fig. 1).

The lymphatic tissue taken from the three different locations (external iliac vein, obturator fossa, internal iliac artery) on each side was sent for separate histologic analysis. The specimens were fixed in neutral buffered 4% formaldehyde for 24 h and then placed in acetone to dissolve the fatty tissue. Lymph nodes were counted according to their specific location and side during pathologic examination. Each node was cut into 3 mm sections, embedded separately in paraffin, and stained with hematoxylin and eosin. All sections were microscopically analyzed for metastatic disease. The total number of lymph nodes and the number of diseased nodes removed from each surgical specimen were documented according to location. A surgical specimen was considered representative if ≥10 nodes were detected by the uropathologist; only patients with representative specimens were included in the present study. Gleason score, tumour stage, and grade of the prostatectomy specimens were determined applying the 1997 TNM classification.

![Fig. 1 – Boundaries of the pelvic lymph node dissection field in our study divided into external iliac vein, obturator fossa, and internal iliac vessels (hypogastric vessels). In the 122 node-positive patients, positive nodes were found exclusively in the area of the external iliac vein in 9%, the obturator fossa in 16%, and the internal iliac vessels in 21%. Positive internal iliac nodes alone (21%) or in combination with positive nodes in other locations (49%) were found in 70% of our patients.](image-url)
The decision to initiate salvage ADT or radiotherapy was left to the treating urologist and was recommended only in patients with rapid PSA doubling time, evidence of metastases, or if symptoms of disease progression were present, ie, bone pain, risk of pathologic fractures, or ureteric obstruction.

3. Statistical analysis

Actuarial long-term biochemical recurrence (BCR)-free survival, cancer-specific survival, and overall survival were assessed according to the Kaplan-Meier technique with patients censored at last follow-up or death. Biochemical failure was defined as a PSA value ≥0.2 ng/ml. Group survival rates were compared using the log rank test (Mantel-Cox). A p value of <0.05 was considered statistically significant. The interaction between the number of positive nodes, number of total nodes, pT-stage, Gleason score of the prostate specimen, seminal vesicle infiltration, and year of surgery with respect to cancer-specific survival were examined by Cox regression proportional hazard models (multivariate analysis). All statistical analyses were performed using a statistical package for the social sciences (SPSS) v 15 software package (Chicago, Illinois, USA).

4. Results

Median age of the 122 node-positive patients was 64 yr (range 44–75 yr). Median preoperative PSA was 16 ng/ml (range 1.9–172 ng/ml) [Table 1]. A median of 22 nodes (range 10–75) were removed per patient. Of these node-positive patients, 47 (39%) had 1 positive node, 27 (22%) had 2 positive nodes, and 48 (39%) had ≥3 positive nodes.

4.1. Localizations of positive nodes detected in the surgical specimens

Positive lymph nodes were located exclusively along the external iliac vein in 11/122 (9%) patients, in the obturator fossa in 20/122 (16.4%), and along the internal iliac artery (presacral) in 26/122 (21.3%) patients (Fig. 1). In 60/122 (49.2%) patients, positive nodes were found along the internal iliac vessels in combination with positive nodes either in the area of the obturator fossa and/or the external iliac vein. Thus, positive internal iliac nodes alone or in combination with positive nodes in other locations were found in 86/122 (70.5%) patients, whereas positive nodes along the external iliac vein and in the obturator fossa, but not along the internal iliac vessels, were detected in only five patients (4%).

4.2. Complication associated with extended PLND

Complications in relation to the extended bilateral PLND in the node-positive patients were: temporary secondary drainage of a symptomatic lymphocele (ie, oedema of the lower extremity, pain, or deep venous thrombosis) detected by ultrasound or computerized tomography in 4 of the 122 patients (3.2%); transitory obturator nerve paralysis in 1 patient. Deep venous thrombosis occurred in 2 of the 122 patients (1.6%).

4.3. Node-positive patients and ADT

Postoperatively, 61 of the 122 node-positive patients (50%) received ADT, 61 (50%) did not. Of patients with 1, 2, or ≥3 positive nodes, ADT was required in 36%, 41%, and 69%, respectively. Salvage ADT after RRP was initiated after a median period of 3.8 yr (range 1.8–7.9 yr), 4.6 yr (range 0.3–9.4 yr) and 2.1 yr (range 0.3–9.5 yr) in patients with 1, 2, and ≥3 positive nodes, respectively (Table 2). Cancer-specific survival curves with regard to salvage ADT vs
no ADT in patients with 1, 2, and ≥3 positive nodes are shown in Fig. 2.

Chemotherapy in patients treated with salvage ADT was given in 1 of 17 (6%) patients with 1 positive node, in 1 of 11 (9%) with 2 positive nodes, and in 7 of 33 (21%) with ≥3 positive nodes. No chemotherapy was given to patients without prior ADT (Table 2).

### 4.4. Outcome in node-positive patients

Median follow-up of the 122 lymph node-positive patients was 67 mo (range 3–175 mo). Their median cancer-specific and overall survival at 10 yr was 60.1% (95% CI 0.43–0.71) and 52.4% (95% CI 0.39–0.66) (Table 3).

BCR-free survival for patients with 1, 2, and ≥3 positive nodes at 5 yr was 24.7% (95% CI 0.39–0.11), 11.8% (95% CI 0.27–0.03), and 4.9% (95% CI 0.09–0.02), respectively (Fig. 3). Median time to PSA recurrence in patients with 1, 2, and ≥3 positive nodes was 27 mo (range 3–135 mo), 18 mo (range 3–83 mo), and 12 mo (range 1–115 mo), respectively.

In 47 patients with 1 positive node cancer-specific survival at 10 yr was 72.1% (95% CI 0.50–0.94); in 27 patients with 2 positive nodes it was 79.1% (95% CI 0.52–0.97); in 48 patients with ≥3 positive nodes it was 33.4% (95% CI 0.16–0.51) (Table 3). Kaplan-Meier survival probabilities in relation to the number of positive nodes detected in the surgical specimen are shown in Fig. 4.

On multivariate analysis, the total number of positive nodes (HR 1.38; \( p < 0.001 \)), ≥3 positive nodes (HR 5.64; \( p < 0.001 \)), high tumour stage (pT4) (HR 4.05, \( p = 0.021 \)), and high Gleason score of the prostatectomy specimen (≥7) (HR 2.42, \( p = 0.02 \)) were significant predictors of negative outcome (Table 4).

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**Table 2 – Comparison of clinicopathologic characteristics in node-positive (1 pN+, 2 pN+, ≥3 pN+) patients with and without salvage ADT after extended PLND followed by RRP**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Patients with 1 pN+ (n = 47)</th>
<th>Patients with 2 pN+ (n = 27)</th>
<th>Patients with ≥3 pN+ (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salvage ADT (n %)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>17 (36.2)</td>
<td>11 (40.7)</td>
<td>33 (68.8)</td>
</tr>
<tr>
<td>Median age at surgery in years (range)</td>
<td>66 (51–73)</td>
<td>65 (57–73)</td>
<td>63 (45–74)</td>
</tr>
<tr>
<td>Median preoperative PSA level (ng/ml) (range)</td>
<td>15.6 (8.4–42.1)</td>
<td>21 (9–64.8)</td>
<td>22 (5.2–172)</td>
</tr>
<tr>
<td>Median number of nodes removed (range)</td>
<td>21 (13–75)</td>
<td>16 (13–74)</td>
<td>22 (10–48)</td>
</tr>
<tr>
<td><strong>Pathologic tumour stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT1/pT2</td>
<td>6 (35.3)</td>
<td>4 (36.4)</td>
<td>2 (6.1)</td>
</tr>
<tr>
<td>pT3a</td>
<td>3 (17.6)</td>
<td>1 (9.1)</td>
<td>7 (21.2)</td>
</tr>
<tr>
<td>pT3b</td>
<td>6 (35.3)</td>
<td>4 (36.4)</td>
<td>19 (57.6)</td>
</tr>
<tr>
<td>pT4</td>
<td>2 (11.8)</td>
<td>2 (18.1)</td>
<td>5 (15.2)</td>
</tr>
<tr>
<td><strong>Gleason score of the prostatectomy specimen</strong></td>
<td></td>
<td></td>
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<tr>
<td>&lt;7</td>
<td>7 (41.2)</td>
<td>6 (54.5)</td>
<td>8 (24.2)</td>
</tr>
<tr>
<td>≥7</td>
<td>10 (58.8)</td>
<td>5 (45.5)</td>
<td>25 (75.8)</td>
</tr>
<tr>
<td><strong>Number of patients with seminal vesicles invasion</strong></td>
<td>9 (52.9)</td>
<td>5 (45.5)</td>
<td>9 (24.2)</td>
</tr>
<tr>
<td>No</td>
<td>8 (47.1)</td>
<td>8 (54.5)</td>
<td>24 (75.8)</td>
</tr>
<tr>
<td>Yes</td>
<td>111 (46–147)</td>
<td>119 (54–175)</td>
<td>58 (15–155)</td>
</tr>
<tr>
<td>Median follow-up time in mo (range)</td>
<td>46 (21–94)</td>
<td>56 (3–113)</td>
<td>25 (2–113)</td>
</tr>
<tr>
<td>Median time interval between RRP and ADT in mo (range)</td>
<td>1 (5.9)</td>
<td>1 (9.1)</td>
<td>7 (21.2)</td>
</tr>
<tr>
<td>Number of patients with adjuvant chemotherapy (%)</td>
<td>2 (11.8)</td>
<td>3 (27.3)</td>
<td>9 (27.3)</td>
</tr>
<tr>
<td>Number of patients with adjuvant radiation (%)</td>
<td>2 (11.8)</td>
<td>2 (12.5)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td><strong>Number of deaths:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>6 (35.3)</td>
<td>3 (27.3)</td>
<td>21 (63.6)</td>
</tr>
<tr>
<td>Other cause</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (6.1)</td>
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We present long-term survival data on patients with lymph node-positive disease treated with extended PLND followed by RRP. In our series, the overall 10–15 yr actuarial survival rates after extended PLND followed by RRP are in line with other recently published results [8–11]. Detailed lymph node mapping was performed in all patients and a median of 22 nodes were detected in the surgical specimen per patient. Patients with 1 or 2 positive nodes had a significantly better prognosis than those with higher nodal tumour burden (≥3 positive nodes) even without immediate ADT.

Long-term cancer-specific survival in patients with prostate cancer depends largely on the number of diseased nodes involved [10–13]. Our findings substantiate this, and show that patients in whom ≥10 nodes were removed, and with 1 or 2 positive nodes in the surgical specimen, had surprisingly good cancer-specific survival rates at 10 yr of 72% and 79%, respectively. This is in line with Daneshmand and Skinner, who reported clinical recurrence-free survival of 70% and 73% at 10 yr in patients with 1 or 2 positive nodes, respectively [11]. Boorjian et al, in a large series of 507 node-positive patients, reported cancer-specific survival rates of 90% and 79% at 10 yr in patients with 1 or ≥2 positive nodes, respectively [10].

By contrast, prognosis was poor in our patients with ≥3 positive nodes removed, with cancer-specific survival rates decreasing to 46% and 26% at 10 yr.
specific survival rates of only 33% at 10 yr. Daneshmand et al reported clinical recurrence-free survival rates of 49% at 10 yr in patients with ≥5 positive nodes [11]. These results underscore the fact that patients with minimal lymph node metastasis can have a good prognosis and that lymph node status should not be used to justify abortion of radical prostatectomy [11,13,14]. We therefore recommend that no frozen sections be performed during surgery (RRP), which should be continued

<table>
<thead>
<tr>
<th>Feature</th>
<th>All 122 node positive patients</th>
<th>Patients with 1 pN+ (n = 47)</th>
<th>Patients with 2 pN+ (n = 27)</th>
<th>Patients with ≥3 pN+ (n = 48)</th>
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<tr>
<td>Median biochemical recurrence-free survival (95% CI)</td>
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<tr>
<td>5 yr</td>
<td>13.9% (0.07–0.21)</td>
<td>24.7% (0.39–0.11)</td>
<td>11.8% (0.27–0.03)</td>
<td>4.9% (0.09–0.02)</td>
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<tr>
<td>10 yr</td>
<td>2.9% (0.01–0.07)</td>
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<tr>
<td>15 yr</td>
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<tr>
<td>Median cancer-specific survival (95% CI)</td>
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<tr>
<td>5 yr</td>
<td>84.5% (0.77–0.92)</td>
<td>94.9% (0.88–1.00)</td>
<td>93.2% (0.85–1.00)</td>
<td>67.7% (0.54–0.82)</td>
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<td>10 yr</td>
<td>60.1% (0.43–0.71)</td>
<td>72.1% (0.50–0.94)</td>
<td>79.1% (0.52–0.97)</td>
<td>33.4% (0.16–0.51)</td>
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<td>15 yr</td>
<td>45.4% (0.27–0.64)</td>
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<tr>
<td>Median overall survival (95% CI)</td>
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<tr>
<td>5 yr</td>
<td>83.3% (0.77–0.91)</td>
<td>92.8% (0.85–1.00)</td>
<td>88.5% (0.78–1.00)</td>
<td>67.7% (0.54–0.82)</td>
</tr>
<tr>
<td>10 yr</td>
<td>52.4% (0.39–0.66)</td>
<td>70.5% (0.49–0.92)</td>
<td>71.9% (0.44–0.99)</td>
<td>27.2% (0.10–0.44)</td>
</tr>
<tr>
<td>15 yr</td>
<td>41.9% (0.24–0.56)</td>
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CI = confidence interval.

Fig. 4 – Cancer-specific survival rates in 47 patients with 1 positive node (1 pN+), 27 patients with 2 positive nodes (2 pN+), and in 48 patients with ≥3 positive nodes (≥3 pN+) treated with extended PLND followed by RRP, and in whom ≥10 lymph nodes were detected in the surgical specimen (log rank p < 0.001).
independently of the intraoperative lymph node status. In addition, the striking difference in survival rates at 10 yr in node-positive patients after removal of the pelvic nodes and the primary tumour (60–87%) [10,11,14–17] or after PLND without removal of the primary tumour (23–45%) [2,16,18] supports continuing with RRP. Although these were nonrandomised and retrospective studies, their results are to a certain extent comparable, in that all patients had the same preoperative status N0M0, all were operated on with the intent to perform an RRP, and all underwent PLND.

Prognosis in node-positive patients does not depend solely on lymph node status, but also on primary tumour characteristics. In our series, the high incidence of concomitant seminal vesicle infiltration and high Gleason scores of the radical prostatectomy specimens may have been confounding factors. Indeed, we observed that ≥3 positive nodes removed, high tumour stage (pT4) and high Gleason Score (≥7) were negative predictors of outcome. Others have not found an association between pathologic tumour stage and outcome in node-positive patients [10,19].

Our results are more or less comparable to the arm with deferred ADT in Messing’s study, where patients were randomised to immediate or deferred ADT after PLND and RRP [14]. It may appear surprising at first that the outcome in our patients who underwent a rather extensive PLND was not significantly better than in Messing’s study, where PLND in some patients was probably more limited. A possible explanation is that two-thirds of patients in both studies not only had positive nodes but also had extracapsular extension or seminal vesicle infiltration. Thus, these factors may have a larger negative impact than minimal lymph node disease alone. A possible therapeutic benefit of extended PLND may eventually become more apparent in newer patient series with fewer concomitant risk factors.

The results from the Messing trial in a patient population similar to ours with regard to preoperative PSA, seminal vesicle infiltration, and positive margins, indicate that immediate ADT significantly improves overall, cancer-specific, and progression-free survival compared with the withholding of ADT until disease progression occurs [14]. One could
postulate therefore that our results would have been even better if all patients had received immediate ADT as practiced by others [10,14–17]. This is possible, but it must be acknowledged that all studies have reported as good results after 10 yr with immediate ADT as those achieved in the Messing trial [10,20,21]. There is also an inherent risk of overtreatment, particularly in patients with 1 or 2 positive nodes, as a large number of patients will not require ADT before dying of some other cause, as shown in Fig. 2. This implies that, instead of immediate treatment for all patients, a more selective approach to ADT should be taken, namely for patients with minimal nodal disease. Our results (Fig. 2) indicate that many patients with minimal nodal involvement (≤2 positive nodes) and without ADT experienced no evident tumour progression during a follow-up of more than 10 yr. For patients with ≥3 positive nodes, PSA doubling time is an excellent tool for discrimination between low- and high-risk patients, particularly after radical prostatectomy, because there is no interference from normal prostatic tissue. A postoperative PSA doubling time of less than 12 mo is a negative prognostic factor for survival in prostate cancer, and these patients may well be the group most likely to benefit from immediate ADT [22–24].

The extent of lymph node dissection is another relevant factor. It is unlikely that a “limited” PLND can be of benefit, as approximately 62% of all relevant factor. It is unlikely that a “limited” PLND can be of benefit, as approximately 62% of all patients may well be the group most likely to benefit from immediate ADT [22–24].

indeed, in most of our node-positive patients (ie. ≥3 positive nodes), the PLND represented a tumour mass reductive rather than a curative surgery. This is supported by the relatively early BCR indicating residual disease. BCR, however, is not a surrogate end-point for prostate cancer-specific mortality, and is only loosely associated with the occurrence of metastases [26]. In node-positive patients, BCR-free survival has been reported to be around 15% at 10 yr after RRP [14,27,28]. We found in our node-positive patients that 10-yr BCR-free survival after RRP was approximately 5%, most likely because of advanced stage of the primary tumour and high tumour burden.

6. Conclusion

Our long-term results in 122 node-positive patients with prostate cancer treated with extended PLND followed by RRP show that the total number of metastatic nodes, but also the pathologic Gleason score and advanced stage of the primary tumour, significantly predict disease progression and survival. Good long-term survival was found after extended PLND followed by RRP in patients with only minimal lymph node involvement (≤2 positive nodes). In two-thirds of patients with 1 positive node and in one-half of patients with 2 positive nodes ADT was not required for a period of more than 10 yr.

Author contributions: Urs E. Studer had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Schumacher, Studer.
Acquisition of data: Schumacher.
Analysis and interpretation of data: Schumacher, Studer, Burkhard.
Drafting of the manuscript: Schumacher, Studer.
Critical revision of the manuscript for important intellectual content: Schumacher, Studer, Burkhard, Thalmann.
Statistical analysis: Schumacher.
Obtaining funding: None.
Administrative, technical, or material support: Studer.
Supervision: Studer.
Other (specify): Fleischmann, pathologist who analysed all specimens.

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References


