Review – Prostate Cancer

Anatomical Extent of Pelvic Lymphadenectomy in Patients Undergoing Radical Prostatectomy

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Abstract

Objectives: The rationale for locoregional staging lymphadenectomy in prostate cancer (pCA) lies in the accurate diagnosis of occult micrometastases to stratify patients who might benefit from adjuvant therapeutic measures. In pCA, the issues of the necessity and the therapeutic advantage of pelvic lymphadenectomy (PLND) in patients with low-, intermediate-, and high-risk disease are still discussed controversially. The aim of this review manuscript is to critically evaluate the current status on PLND in pCA.

Methods: A review of the literature was performed concerning radical prostatectomy and PLND with respect to anatomical extent, oncological outcome, and associated complications.

Results: The anatomical lymphatic drainage of the prostate includes the obturator fossa, and the external and internal iliac arteries; therefore, at least these areas should be included in PLND. According to the current clinical studies, extended PLND (ePLND) significantly increases the yield of both total lymph nodes and lymph node metastases independent of the risk classification of pCA. Lymph node metastases will be detected in about 5–6%, 20–25%, and 30–40% of low-, intermediate-, and high-risk pCA, respectively. Exclusively 25% of all positive lymph nodes are located in the area around the internal iliac artery. With regard to progression-free and cancer-specific survival, retrospective analysis of the SEER data and additional case-control studies indicate a direct positive relationship between the number of removed lymph nodes and long-term oncological outcome in patients with limited lymph node involvement or negative lymph nodes. In these patients, cancer-specific survival is improved by about 15–20%. On the basis of results of large case-control studies, complication rates of ePLND are not significantly increased.

Conclusions: On the basis of current data, the following conclusions can be drawn: (1) If performed, PLND has to be done in the extended, anatomically adequate variant. (2) The frequency of lymph node metastases in low-risk pCA is low, and the issue of PLND has to be discussed with the patient. (3) If radical prostatectomy is performed in intermediate- and high-risk pCA, an ePLND should be option of choice. For the future, ongoing prospective trials have to demonstrate a benefit in terms of biochemical-free and cancer-specific survival.

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1. Introduction

The role and the potential benefit, if any, of pelvic lymphadectomy (PLND) in prostate cancer (pCA) are still discussed controversially. It is generally accepted that PLND at time of radical prostatectomy is the only reliable diagnostic procedure to achieve as much individual pathohistological staging information as possible to trigger postoperative adjuvant management. However, the extent of PLND (limited vs. extended) and the candidates most suitable for this procedure are still a matter of intense debate. Some authors base their decision for the need for PLND on preoperative nomograms considering preoperative prostate-specific antigen (PSA) serum levels, clinical stage, number of positive biopsies, and Gleason score of prostate biopsies for risk calculations [2–4]. Others favour performing PLND in all patients, thereby subjecting a distinct number of patients to potential complications associated with the surgical procedure.

Many of these nomograms might be imprecise because the calculations have been based on standard LNDs with a mean of <10 lymph nodes removed and analysed. Recently, two nomograms based on the data of extended PLND (ePLND) have been published [5,6]; however, prospective multi-institutional validation must be performed before it can be recommended for general use [7].

It is the purpose of the current review to critically reflect (1) the anatomy of lymphatic drainage pattern of the prostate, (2) the potential diagnostic benefit of PLND in the various risk groups of pCA, (3) the association of PLND with progression-free and cancer-specific survival, and (4) potentially increased perioperative complications and their prevention.

2. Locoregional lymphadenectomy and radical cancer surgery

The primary intention of locoregional lymphadenectomy is to obtain detailed information with regard to the local extent of a given cancer to accurately calculate the risk for progression and to discuss the necessity of adjuvant therapeutic measures. Furthermore, anatomically adequate lymphadenectomy might help to improve cancer-specific survival or progression-free survival as has been demonstrated for various cancer types [8–10]. In a recent retrospective analysis of 484 patients undergoing radical cystectomy and PLND, Leissner et al [8] demonstrated that the total number of lymph nodes retrieved had a significant impact on recurrence-free survival (p < 0.01). The 5-yr recurrence-free survival was 25% and 53% in patients with ≤14 and ≥15 lymph nodes being removed, respectively.

3. Anatomical extent of PLND for staging purposes

In pCA, multiple variations of LND are described, including the minimal variant considering the obturator fossa only, the standard variant including lymph nodes in the obturator fossa and the external iliac artery, and the extended variant with a complete lymph node dissection along the obturator fossa, and the external, internal, and common iliac vessels up to the iliac crossing of the ureter [11–14]. The last variant is the only technique that considers anatomical studies [1], which have shown that the prostate gland drains lymphatically into the peri-prostatic subcapsular network from which three groups of ducts originate: the ascending duct from the cranial gland running to the external iliac nodes, the lateral duct running to the hypogastric nodes, and the posterior duct running to the lateral and subaortic sacral nodes of the promontory.

In an autopsy study, Weingärtner et al [15] found that a mean of 20 dissected pelvic lymph nodes can be considered a representative sampling that enables exact locoregional staging of pCA. These data are matched perfectly by the proponents of ePLND, which removes a mean of 21–28 lymph nodes, whereas in limited PLND only a mean of 10–11 lymph nodes are removed [5,6,12–14,16,17]. The number of dissected lymph nodes is directly associated with an increase in the detection of positive lymph nodes as has been demonstrated in a number of studies (Table 1). Stone et al [16]
compared limited and extended laparoscopic PLNDs and found a 2-fold increase in the number of removed lymph nodes (9 vs. 18) and a 3-fold increase in the frequency of lymph node metastases (7% vs. 23%). Our group has recently demonstrated that a mean of 28 and 11 lymph nodes is removed by the extended and the limited technique, respectively; the number of positive lymph nodes increased from 12% to 26% [13,14]. These data have been corroborated by Wawroschek et al [17] and finally by Briganti and coworkers [5,6], who demonstrated positive lymph nodes in 32% and 20% of their patients, respectively. These data, however, can only be achieved if the surgeon sticks to the concept to meticulously dissect all lymph nodes located in the primary landing zone of the prostate.

Besides the mere number of lymph nodes being removed, the regional distribution of occult metastatic disease is of utmost importance. Several studies have demonstrated that about 50% and 25% of lymph node metastases are located along the internal iliac artery or along the internal iliac artery only [5,6,12–14,17].

In summary, there is significant advantage of an ePLND that includes the nodes along the obturator fossa, and the external, internal, and common iliac arteries in terms of diagnostic accuracy with regard to an exact lymph node staging.

3.1 When to perform PLND?

On the basis of preoperative nomograms, Partin tables, and so on, most institutions will not perform PLND in patients with a preoperative PSA serum level <10 ng/ml, a biopsy Gleason score <7, and a clinical stage ≤T2a because the incidence of positive lymph nodes is said to be approximately only 1–5% [2–4].

On the basis of the retro- and prospective evaluation of 4690 patients with pCA having undergone radical prostatectomy and PLND, Crawford et al [2] identified men with a biopsy Gleason score ≤6, a preoperative PSA serum level ≤10.6 ng/ml, and stage cT1c as predictors for a low risk of lymph node metastases. In a prospective validation, the false-negative rate with regard to the prediction of positive lymph nodes was only 0.7%. Using logistic regression analysis, Narayan et al [18] and Bluestein et al [19] described similar findings, demonstrating that men with a preoperative serum PSA level ≤10 ng/ml and biopsy Gleason score ≤6 harbour a 1–2% risk for micrometastatic lymphonodular disease.

In another attempt to identify patients with a potential risk of metastatic disease to the pelvic lymph nodes, Conrad et al [20,21] published a diagnostic algorithm based on a variety of preoperative parameters of more than 600 patients undergoing radical prostatectomy. On the basis of number of biopsy cores harbouring pCA with Gleason score ≥7, three risk groups were identified. Risk for lymph node metastases was 45%, 19%, or 2% if 4–6, 1–3, or no biopsy was involved with Gleason score 8–10 pCA, respectively. Haese et al [22] analysed this diagnostic algorithm prospectively in a cohort of 443 consecutive patients and confirmed the validity and reproducibility of this model. In another retrospective analysis of preoperative markers including 695 patients, Naya and Babaian [23] the number of biopsies involved with Gleason grade 4–5 pCA and a preoperative PSA serum level >15 ng/ml as significant predictors for positive lymph nodes. The incidence of lymph node metastases was 20–9% if more than four biopsy cores were involved or PSA was >15 ng/ml, respectively. In contrast, less than four biopsy cores with Gleason grade 4–5 pCA and PSA <15 ng/ml were associated with a low risk of only 2.8% and 2.1%, respectively.

However, all of these nomograms are based on data of a limited PLND including only the obturator fossa, and the external, internal, and common iliac arteries in terms of diagnostic accuracy with regard to an exact lymph node staging.

### Table 2 – Frequency of lymph node metastasis in patients undergoing extended pelvic lymphadenectomy and radical prostatectomy for prostate cancer <T2b based on preoperative PSA and biopsy Gleason score (modified from Refs. [13,14])

<table>
<thead>
<tr>
<th></th>
<th>Gleason 2–4</th>
<th>Gleason 5–7</th>
<th>Gleason 8–10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA &lt; 10 ng/ml</td>
<td>19 (6%)</td>
<td>263 (82%)</td>
<td>39 (12%)</td>
</tr>
<tr>
<td>pN+</td>
<td>0</td>
<td>11 (10%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>PSA 10–20 ng/ml</td>
<td>3 (1%)</td>
<td>82 (26%)</td>
<td>10 (3%)</td>
</tr>
<tr>
<td>pN+</td>
<td>0</td>
<td>24 (29%)</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>PSA &gt; 20 ng/ml</td>
<td>3 (1%)</td>
<td>70 (22%)</td>
<td>22 (7%)</td>
</tr>
<tr>
<td>pN+</td>
<td>0</td>
<td>27 (39%)</td>
<td>12 (55%)</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>263</td>
<td>39</td>
</tr>
</tbody>
</table>

PSA = prostate-specific antigen.
studies, the risk of lymph node metastases is substantial and varies between 3.2% and 10.2%. Even the group from the Johns Hopkins University [25] demonstrated a significant diagnostic benefit of ePLND in a group of 2135 men with low-risk pCA compared with a group of 1835 men undergoing radical prostatectomy and limited PLND. Extended PLND removed more lymph nodes (11.6 vs. 8.9, \(p < 0.0001\)) and detected more lymph node metastases (3.2% vs. 1.1%, \(p < 0.0001\)) than limited PLND. Similar results have been reported by Joslyn and Konety [26], who observed a direct correlation between the number of removed nodes and the frequency of lymph node metastases (\(p < 0.0001\)).

In a recent study, our group analysed the predictive accuracy of Partin tables and CART analysis in patients undergoing radical prostatectomy and ePLND [13,14]. A good correlation between predicted lymph node positivity and lymph node metastases was found in the very low-risk group of patients with cT1c, Gleason 2–4, and PSA < 10 ng/ml with no lymph node metastases being detected. In the intermediate-risk group of patients with pCA ≤ cT2a, a biopsy Gleason score of 5–7, and a preoperative PSA serum level of <10 ng/ml, Partin tables and pathohistological findings at the time of ePLND did not differ significantly; however, with increasing preoperative PSA serum levels, significantly more patients with positive lymph nodes were identified than predicted (Tables 3 and 4). Similar findings were observed in patients with Gleason score 8–10 pCA, whereas the Partin tables predicted a frequency of positive lymph nodes in the range of 8% to 34%. However, we actually found lymph node metastases in 55–87% of the patients.

Data from Schuhmacher et al [28] and Weckermann et al [27] corroborate our findings; the authors found a 10% risk of pelvic lymph node metastases in patients with clinically localised pCA in the low-risk group.

Furthermore, we compared the reliability of the recently published CART analysis with regard to its accuracy to predict lymph node metastases [13,14]. We found a significant difference between the predicted frequency of positive lymph nodes in the low- and intermediate-risk group, whereas the data in the high-risk group were comparable (Tables 3 and 4). Frequencies of 2.2% and 19.4% were predicted in the low- and intermediate-risk groups, respectively; however, lymph node metastases were detected in 17% and 46%, respectively.

In an attempt to improve the currently available nomograms, Briganti et al [6] developed multivariate nomograms in patients with low-risk and intermediate/high–risk pCA undergoing ePLND. The nomogram for low-risk pCA was developed in 781 patients and internally validated in 200 patients; multivariate analysis identified clinical stage, biopsy Gleason sum, and number of lymph nodes removed as significant predictors for occult lymphnodular metastases, and resulted in an accuracy of 78.6%. However, prior to the nomogram’s general use, the data have to be externally validated, which is currently under way.

In summary, most of the available nomograms cannot accurately predict the frequency of positive lymph nodes in patients with clinically localised or locally advanced pCA. Extended PLND is recommended in patients with unfavourable preoperative findings such as PSA > 10 ng/ml, >cT1c, biopsy Gleason score >6, more than two biopsy cores involved with cancer, and any core containing Gleason 4 or 5 pCA. In patients with low-risk pCA (PSA < 10 ng/ml, cT1c, Gleason score <6), the risk for lymphnodular disease is between 8% and 10%, and the need for PLND has to be discussed on an individual basis with the patient.

### Table 3 – Predicted and observed frequency of lymph node metastases in patients with clinical stage T1c–2a prostate cancer based on preoperative Partin tables (modified from Refs. [13,14])

<table>
<thead>
<tr>
<th>PSA &lt; 10 ng/ml</th>
<th>pN+ predicted</th>
<th>pN+ observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason 2–4</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Gleason 5–7</td>
<td>2–8%</td>
<td>10%</td>
</tr>
<tr>
<td>Gleason 8–10</td>
<td>8%</td>
<td>57%</td>
</tr>
<tr>
<td>PSA 10–20 ng/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gleason 2–4</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Gleason 5–7</td>
<td>12%</td>
<td>29%</td>
</tr>
<tr>
<td>Gleason 8–10</td>
<td>27%</td>
<td>80%</td>
</tr>
<tr>
<td>PSA &gt; 20 ng/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gleason 2–4</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Gleason 5–7</td>
<td>27%</td>
<td>39%</td>
</tr>
<tr>
<td>Gleason 8–10</td>
<td>34%</td>
<td>55%</td>
</tr>
</tbody>
</table>

PSA = prostate-specific antigen.

### Table 4 – Predicted and observed frequency of lymph node metastases in patients with clinical stage T1c–2a prostate cancer based on preoperative CART analysis (modified from Refs. [13,14])

<table>
<thead>
<tr>
<th>Biopsy Gleason grade 4–5</th>
<th>pN+ predicted</th>
<th>pN+ observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/6 biopsies</td>
<td>2.2%</td>
<td>17%</td>
</tr>
<tr>
<td>1–3 biopsies</td>
<td>19.4%</td>
<td>46%</td>
</tr>
<tr>
<td>4–6 biopsies</td>
<td>45%</td>
<td>62%</td>
</tr>
</tbody>
</table>

CART = classification and regression tree.
3.2. Complications of ePLND in pCA

Surgeons are often deterred from performing an ePLND because of the potentially high incidence of complications. However, the high complication rate of 10–20% derives only from old series published in the 1970s and 1980s [29]. Clarke et al [30] and Briganti et al [31] described an overall complication rate of 10.5% and 19.8% after ePLND, respectively. According to the authors, 75% of the complications derived from ePLND might be due to the extensive dissection of lymphatic tissue lateral to the external iliac artery—an area that has never been shown to include positive lymph nodes in anatomical mapping studies [13,14] and that drains primarily the lower extremity. In recent series (Tables 5 and 6), the frequency and severity of intra- and perioperative complications did not differ significantly between the limited and the extended variant of PLND [12–14,25]. If performed by an experienced surgeon, the frequency of peri- and postoperative complications attributable to PLND is around 7%, with symptomatic lymphocele (2–4%) representing the most common type of complication. Deep venous thrombosis, pulmonary emboli, injuries to the obturator nerve and the ureter, and lymphoedema of the lower extremity have also been described, but in a rare frequency.

Treatment-associated morbidity can be reduced significantly when (1) all lymphatics lateral to the external artery are saved, (2) the distal ends of the lymphatics are either ligated or clipped with small clips exerting a higher pressure to the lymphatic vessels than large clips, (3) two drains are placed in each side of the pelvis, (4) drains are left in place until <50 ml/d is drained, and (5) low-molecular heparin is injected into the upper arm.

There is some discussion whether ePLND might have a negative impact on the results of nerve-sparing radical prostatectomy with regard to potency and continence. However, parasympathetic nerve fibres running to the cavernosal bodies are usually not touched during PLND. No definite answer can be given because the majority of groups in favour of ePLND do not report data on postoperative potency. Sympathetic nerve fibres supporting continence by influencing the resting tonus of the urethra are located medial to the internal iliac artery and might be damaged during LND. With regard to continence data of men undergoing limited and ePLND, no difference has been shown between the groups. However, the few studies available argue against this hypothesis. Burkhard and coworkers [32] report no different results with regard to the preservation of erectile function after ePLND compared with others [33]. The use of the internal iliac artery for renal transplantation had no significant impact on postoperative erectile function as assessed by the International Index of Erectile Function if patients were potent preoperatively [34].

3.3. Therapeutic benefit of ePLND

With regard to pCA, the possibility of a therapeutic benefit for PLND has been suggested by some studies, but the results have been inconsistent. Earlier reports on biochemical relapse rates of patients undergoing radical prostatectomy for low-risk pCA with and without PLND have suggested that lymph node dissection is apparently unnecessary [35–37]. Fergany et al [35] compared biochemical relapse rates of 372 and 203 patients with low-risk pCA undergoing radical prostatectomy with and without PLND, respectively. The 4-yr progression-free survival rates were 91% and 97% following radical prostatectomy with and without lymphadenectomy, respectively. However, one has to consider that all authors performed a limited LND with only a mean of less than nine lymph nodes surgically removed. It is evident that a significant advantage in terms of oncological control cannot be expected in comparisons of no PLND versus anatomically minimal PLND with only a few lymph nodes removed.
Although no prospective randomised clinical trials are available, several studies have indicated the possibility of long-term survival even in the presence of limited lymph node metastases [12,25,26,38,39]. Bader et al [12] demonstrated the beneficial effect of ePLND in terms of biochemical progression-free survival and cancer-specific survival in a cohort of 243 lymph node-positive patients who did not undergo immediate androgen deprivation. After a mean follow-up of 45 mo, cancer-specific survival was 78%, PSA progression-free survival was 24%, and symptom-free survival was 47%. Performing a multivariate analysis, the group identified only the number of positive lymph nodes to be significantly associated with systemic relapse. Of patients with only one positive lymph node, 75% remained without tumour progression and only 14% died from pCA. In a series of 4000 consecutive patients undergoing radical prostatectomy for clinically localised disease, Allaf et al [25] demonstrated the therapeutic benefit of ePLND in patients with limited lymph node disease. Among men with lymph node metastases involving less than 15% of extracted nodes, the 5-yr PSA progression-free survival was 43% versus 10% for the limited PLND \((p = 0.01)\). The concept of lymph node density and its prognostic significance has been investigated only rarely in men undergoing radical prostatectomy. Steinberg et al [40] and Daneshmand et al [41] report that patients with a lymph node density >20% are at a significantly higher risk of progression than those with a density <20%. Recently, Joslyn and Konety [26] obtained data from the Surveillance Epidemiology and End Results (SEER) program on 13,020 patients who underwent radical prostatectomy with or without PLND between 1988 and 1991 to evaluate the impact of the extent of PLND on survival. The key finding of the analysis was that extensive PLND reduces the long-term risk of cancer-related death by 23% \((p = 0.007, \text{Tables 7 and 8})\). More extensive PLND (≥10 lymph nodes removed) was associated with a 15% lower risk of pCA death even after restricting the analysis to patients with negative lymph nodes \((p = 0.038)\). In a similar approach, our group has recently performed a case-control study analysing PSA progression-free survival after a minimum follow-up of 5 yr in a cohort of 100 consecutive patients with pN0 disease having undergone limited PLND compared with a group of 100 consecutive patients having undergone ePLND. First data indicate that the PSA relapse rate differs significantly between both groups with 23% and 8% in the limited and extended pLA groups, respectively, indicating a therapeutic benefit of PLND. Similar findings were reported by Bader et al [42] with 16%, 12%, 8%, and 8% of 243 patients demonstrating PSA progression after a short follow-up if 0–4, 5–9, 10–14, and >14 lymph nodes, respectively, were removed during radical prostatectomy. Since only a minority of patients harboured lymph node metastases, one potential explanation for these findings is that a meticulous PLND eliminates lymph nodes metastases that were not detected by routine pathohistological analysis. Retrospective analysis of 4611 patients undergoing radical prostatectomy and PLND demonstrated a significant correlation between the number of removed lymph nodes and freedom from biochemical recurrence in men without nodal involvement [43]. These data, however, are in contrast to the single institutional data analysis of DiMarco et al [44], who did not find a benefit of PLND in a cohort of 7034 consecutive patients undergoing radical prostatectomy with or without PLND. However, as the authors state, the mean number of removed lymph nodes was 9 with a significant decrease of 14 nodes taken in 1987–1989 to 5 in 1999–2001 \((p < 0.001)\). As demonstrated by Joslyn and Konety [26], the beneficial effect of PLND comes true only if ≥10

<table>
<thead>
<tr>
<th>No. of LNs examined</th>
<th>Hazard ratio (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.00 (Ref)</td>
<td></td>
</tr>
<tr>
<td>1–3</td>
<td>0.85 (0.68–1.06)</td>
<td>0.158</td>
</tr>
<tr>
<td>4–6</td>
<td>0.77 (0.64–0.93)</td>
<td>0.0069 *</td>
</tr>
<tr>
<td>7–9</td>
<td>0.62 (0.67–0.99)</td>
<td>0.039</td>
</tr>
<tr>
<td>≥10</td>
<td>0.81 (0.70–0.94)</td>
<td>0.0047 *</td>
</tr>
</tbody>
</table>

CI = confidence interval; LN = lymph node; Ref = reference.
* Statistically significant value.

<table>
<thead>
<tr>
<th>No. of LNs examined</th>
<th>Hazard ratio (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.00 (Ref)</td>
<td></td>
</tr>
<tr>
<td>1–3</td>
<td>0.96 (0.76–1.21)</td>
<td>0.7373</td>
</tr>
<tr>
<td>4–6</td>
<td>0.86 (0.70–1.05)</td>
<td>0.1321</td>
</tr>
<tr>
<td>7–9</td>
<td>0.87 (0.71–1.07)</td>
<td>0.1957</td>
</tr>
<tr>
<td>≥10</td>
<td>0.85 (0.72–0.99)</td>
<td>0.0382 *</td>
</tr>
</tbody>
</table>

CI = confidence interval; LN = lymph node; Ref = reference.
* Statistically significant value.
nodes are removed. Therapeutic outcome in terms of biochemical recurrence was the same between the patients operated earlier with a more extensive PLND and those operated 10 yr later with a minimal PLND despite a significant shift in tumour stage. It cannot be excluded that a more extensive PLND might have had an influence on recurrence and survival because one would expect a poorer outcome for the earlier group, considering the higher frequency of locally advanced pCA.

On the basis of the aforementioned studies, radical prostatectomy in the presence of microscopic positive lymph node involvement can yield long-term survival in a substantial number of patients. Furthermore, dissection of involved lymph nodes might be beneficial for adjuvant treatment purposes. In a retrospective analysis of 322 patients undergoing immediate adjuvant androgen deprivation for lymph node-positive pCA following radical prostatectomy, Cheng et al [38] observed no statistically significant difference in the cancer-specific mortality between the control group of pN0 patients and men with only one lymph node involved. Only a more extensive involvement of positive nodes is associated with a significantly increased mortality risk despite adjuvant endocrine manipulation. In another clinical trial, Messing et al [45,46] documented a therapeutic benefit in terms of progression-free and cancer-specific survival of immediate adjuvant hormonal therapy in patients with gross lymph node-positive pCA undergoing radical prostatectomy.

In summary, there is convincing evidence from large retrospective and small case-control studies that ePLND might have a therapeutic impact with significant reduction of pCA-specific death in the long term. A prospective randomised clinical phase 3 trial of limited versus ePLND currently initiated by the Association of Oncological Urology of the German Cancer Society will shed some light on this important issue.

4. Alternative options of lymph node staging in pCA

The idea of lymphoscintigraphy in various organs is to evaluate the individual lymphatic drainage of the tumour-bearing organ and to depict the primary and subordinate landing sites. Wawroschek et al [17,42] described a gamma probe–guided sentinel lymph node identification in pCA patients prior to radical prostatectomy to detect the primary lymphatic landing zone of metastatic disease so as to better identify those patients being at risk for lymph node metastases and, therefore, having to undergo PLND. Combining preoperative lymphoscintigraphy after ultrasound-guided intraprostatic injection of $^{99m}$technetium with intraoperative gamma probe detection of labelled nodes, they found positive lymph nodes in 24%, with 36% of the positive nodes being found outside the fields of standard lymphadenectomy. These data have been corroborated by others with open or laparoscopic surgical techniques [47–51]. If the sentinel nodes are negative on histological evaluation, the other nonsentinel lymph nodes always have been negative; therefore, these patients do not have to undergo an extensive lymph node dissection. If, however, the sentinel nodes are positive, an ePLND has to be performed because other nonsentinel nodes might harbour metastases. On the basis of these data, the concept of SNL might be helpful to better identify patients who might have a diagnostic and/or therapeutic benefit of ePLND in pCA.

In a recent study including 80 patients with clinical stage T1–3 pCA, it was investigated whether highly lymphotropic superparamagnetic nanoparticles, which gain access to lymph nodes by means of interstitial-lymphatic fluid transport, could be used in conjunction with high-resolution magnetic resonance imaging (MRI) to reveal small nodal metastases [52]. Of the 334 lymph nodes that underwent resection or biopsy, 63 (18.9%) from 33 patients (41%) had histopathologically detected metastases. MRI with lymphotropic superparamagnetic nanoparticles correctly identified all patients with nodal metastases, and a node-by-node analysis had a significantly higher sensitivity than conventional MRI (90.5% vs. 35.4%, $p < 0.001$). These preliminary findings, however, have to be substantiated by further prospective multi-institutional trials comparing MRI with ePLND.

5. Conclusion

Extended PLND results in a significant benefit to detect lymph node metastases in patients with pCA undergoing radical prostatectomy. In light of anatomical lymphatic drainage of the prostate, ePLND including the removal of lymphatic tissue around the external iliac vein, the obturator fossa, and the internal iliac arteries represents the surgical technique of choice. On the basis of the 20–25% and the 30–40% chance to detect occult microscopic lymph node metastases in intermediate- and high-risk pCA, respectively, all patients should undergo ePLND for diagnostic and therapeutic purpose. It has been shown in various studies that patients with
limited lymph node metastases can experience long-term survival even without immediate androgen deprivation. In patients with low-risk pCA, the chance to detect lymphatic metastases is between 3% and 9% and has to be considered in preoperative counselling of the patients.

Recent case-control studies indicate that performing a more extensive PLND improves not only the accuracy of staging, but it also reduces the risk of pCA-specific mortality by 23% in lymph node-positive patients and by 15% in patients without lymph node metastases.

**Conflicts of interest**

The authors have no conflicts of interest to report.

**References**


[27] Weckermann D, Goppel M, Dorn R, Wawroschek F, Harzmann R. Incidence of positive pelvic lymph nodes in patients with prostate cancer, a prostate specific antigen (PSA) level of < or = 10 ng/ml and biopsy Gleason score of < or = 6, and their influence on PSA progression-free survival after radical prostatectomy. BJU Int 2006;97:1173–8.


