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European Association of Urology

Platinum Priority – Review – Prostate Cancer

Editorial by Judd W. Moul on pp. 1266–1268 of this issue

Pelvic Lymph Node Dissection in Prostate Cancer

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Article info

Article history:
Accepted March 3, 2009
Published online ahead of print on March 10, 2009

Keywords:
Prostate cancer
Pelvic lymph node dissection
Radical prostatectomy
Imaging
Complications

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Abstract

Context: Pelvic lymph node dissection (PLND) is considered the most reliable procedure for the detection of lymph node metastases in prostate cancer (PCa); however, the therapeutic benefit of PLND in PCa management is currently under debate.

Objective: To systematically review the available literature concerning the role of PLND and its extent in PCa staging and outcome. All of the existing recommendations and staging tools determining the need for PLND were also assessed. Moreover, a systematic review was performed of the long-term outcome of node-positive patients stratified according to the extent of nodal invasion.

Evidence acquisition: A Medline search was conducted to identify original and review articles as well as editorials addressing the significance of PLND in PCa. Keywords included *prostate cancer, pelvic lymph node dissection, radical prostatectomy, imaging*, and *complications*. Data from the selected studies focussing on the role of PLND in PCa staging and outcome were reviewed and discussed by all of the contributing authors.

Evidence synthesis: Despite recent advances in imaging techniques, PLND remains the most accurate staging procedure for the detection of lymph node invasion (LNI) in PCa. The rate of LNI increases with the extent of PLND. Extended PLND (ePLND; ie, removal of obturator, external iliac, hypogastric with or without presacral and common iliac nodes) significantly improves the detection of lymph node metastases compared with limited PLND (lPLND; ie, removal of obturator with or without external iliac nodes), which is associated with poor staging accuracy.

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0302-2838/$ – see back matter doi:10.1016/j.eururo.2009.03.012

Because not all patients with PCa are at the same risk of harbouring nodal metastases, several nomograms and tables have been developed and validated to identify candidates for PLND. These tools, however, are based mostly on findings derived from lPLND dissections performed in older patient series. According to these prediction models, a staging PLND might be omitted in low-risk PCa patients because of the low rate of lymph node metastases found, even after extended dissections (<8%). The outcome for patients with positive nodes is not necessarily poor. Indeed, patients with low-volume nodal metastases experience excellent survival rates, regardless of adjuvant treatment. But despite few retrospective studies reporting an association between PLND and PCa progression and survival, the exact impact of PLND on patient outcomes has not yet been clearly proven because of the lack of prospective randomised trials.

Conclusions: On the basis of current data, we suggest that if a PLND is indicated, then it should be extended. Conversely, in view of the low rate of LNI among patients with low-risk PCa, a staging ePLND might be spared in this patient category. Whether this approach is also safe from oncologic perspectives is still unknown. Patients with low-volume nodal metastases have a good long-term prognosis; to what extent this prognosis is the result of a positive impact of PLND on PCa outcomes is still to be determined.

1. Introduction

Pelvic lymph node dissection (PLND) represents the most accurate and reliable staging procedure for the detection of lymph node invasion (LNI) in prostate cancer (PCa) [1]. Unfortunately, imaging procedures such as computed tomography (CT) and standard magnetic resonance imaging (MRI) have very limited ability to predict LNI [2–4]. Other interesting imaging techniques such as [^{11}C]choline positron emission tomography/CT or MRI with lymphotropic superparamagnetic nanoparticles are currently under investigation [5–9]. The latter technique is not yet available on the market, and the use of these sophisticated imaging techniques is limited by significant costs. Thus, for the time being, PLND remains the gold standard for nodal assessment. Which candidates to select for this procedure and the optimal extent of PLND (limited vs extended) are still points of discussion. Debate centres on three issues. First, not all patients are at the same risk of harbouring PCa nodal metastases [10–29]. Second, a meticulous PLND is a time-consuming and challenging procedure which requires skilled surgeons [30–32]. Third, the impact of PLND on PCa outcome is currently unknown. Indeed, no prospective randomised clinical trial has ever tested the impact of PLND on PCa outcomes, not even in the high-risk patient group. Although one may object that several surgical procedures which are currently considered as standard treatment were never proved efficacious in randomised clinical trials, this requisite undoubtedly remains important. Some authors base their decision on the need for PLND on preoperative nomograms which are mainly based on routinely available preoperative variables [10–29]. Such nomograms allow them to identify those patients for whom a routine staging PLND might be omitted; however, whether this reasonable approach is also safe from an oncologic perspective is still unknown because of the lack of prospective randomised clinical trials. Conversely, other authors favour performing PLND in all patients for whom a radical prostatectomy (RP) is truly indicated [33]. This approach is clearly associated with higher staging accuracy, especially if an extended PLND (ePLND) is performed [34–40]. The aim of this paper is to systematically review the available literature concerning the role of PLND and its extent in PCa staging and outcome. The potential benefits as well as the side-effects of PLND in PCa are presented. All of the existing recommendations and staging tools determining the need for PLND are also critically evaluated. Moreover, the long-term outcome of node-positive patients is reviewed and stratified according to the extent of nodal invasion.

2. Evidence acquisition

A Medline search was conducted to identify original articles, review articles, and editorials addressing the role of PLND in PCa. Keywords included *prostate cancer, pelvic lymph node dissection, radical prostatectomy, imaging*, and *complications*. All of the keywords are within the Medical Subject Headings (MeSH) database, which represents the controlled vocabulary used for indexing articles for Medline and PubMed. The articles with the highest level of evidence were identified with the consensus of all of the collaborative authors and were critically reviewed.

3. Evidence synthesis

3.1. *Improving the detection of lymph node metastases in prostate cancer: critical assessment of currently available imaging techniques*

Currently, none of the standard radiologic techniques predicts the presence of LNI accurately when compared with ePLND. Some innovative techniques, however, might overcome this clinically significant staging problem in the near future. Reported CT sensitivity for the detection of lymph node metastases is typically in the range of about 35% [2]. This low sensitivity can be attributed to the fact that a lymph node size >1 cm in diameter is required for the identification of lymph node metastases [2]. Similarly, standard MRI, dynamic enhanced MRI, and even magnetic resonance spectroscopic imaging (MRSI) have shown no advantage over CT in predicting the presence of LNI [3–4]. Conversely, the use of lymphotropic paramagnetic iron oxide nanoparticles with a size of 30–50 nm as a contrast agent at MRI (ie, lymphotropic nanoparticle–enhanced MRI [LNMRI]) might improve the detection of nodal disease [5–7]. Initial results in a group of 30 patients with genitourinary malignancies demonstrated a significantly improved sensitivity and specificity of 100% and 80%, respectively, for accurately detecting pelvic lymph node metastases [6]. In a more recent trial in 80 men with clinically localised PCa, LNMRI was shown to increase the sensitivity for detecting lymph node metastases from 35% when using MRI alone to 90% [5]. Specificity also increased from 90% to 98%, making LNMRI a potentially useful imaging technique for preoperative staging of the small pelvis. Similarly, the sensitivity and negative predictive value (NPV) of magnetic resonance lymphoangiography (MRL) using ferumoxtran-10 as a contrast agent were as high as 82% and 96%, respectively, in 375 patients with intermediate- to high-risk PCa [7]. These studies, however, have some limitations which have to be addressed in the near future before LNMRI will become a routine staging method for PCa. Patients enrolled in these trials underwent a limited PLND (lPLND). An ePLND was performed in a few cases only in the presence of suspicious lymph nodes outside the boundaries of lPLND. Therefore, the high reported sensitivity and NPV of LNMRI might have been falsely inflated because of the significant understaging associated with lPLND [34–41]. Moreover, the conventional LNMRI has its own limitations. First, in the presence of fibrosis or lipomatosis within the lymph node, it is difficult to discriminate benign tissue from cancer. In such cases, there also might be a lack of contrast agent uptake. Second, the reading time required for this technique is long (several hours per patient), and high interobserver variability can be found. Third, small nodal micrometastases can be missed. To solve these issues, a novel approach consisting of MRI enhanced with ultrasmall superparamagnetic particles of iron oxide (USPIO) combined with diffusion-weighted MRI (DW-MRI) has been proposed. This approach has been shown to be a fast and accurate method for detecting pelvic lymph node metastases in patients with prostate and/or bladder cancer, even in normal-sized nodes [9]. Similarly, [^{11}C]choline positron emission tomography (PET)/CT has also been tested recently in the detection of PCa nodal metastases [8]. Interestingly, this imaging technique showed high accuracy in detecting LNI in intermediate- and high-risk PCa patients treated with ePLND. The sensitivity, specificity, NPV, and number of correctly recognised cases at PET/CT were 60.0%, 97.6%, 87.2%, and 87.7%, respectively [8].

Sentinel lymphoscintigraphy (SLN) has been described as an imaging staging tool for planning the necessity and the extent of PLND in patients undergoing RP. Planar films are taken preoperatively, and intraoperatively, the use of gamma probe facilitates dissection of all lymph nodes storing the technecium (^{99m}Tc) nanocolloid. This has led to the concept of laparoscopic or open sentinel lymph node dissection in PCa, which would eventually decrease the rate of unnecessary ePLNDs [42–48]. Interestingly, the sensitivity of the radioguided sentinel lymph node dissection for detecting patients with positive nodes is extremely high (96%) [42]. This approach, however, has some significant limitations. First, in about 5% of patients, no marker is taken up on one pelvic sidewall, and ePLND has to be performed [43]. Second, SLN is not able to identify all metastatic lymph nodes either

due to the presence of micrometastases with a diameter below the resolution of SLN or due to macrometastases blocking the lymphatic drainage of ^{99m}Tc-nanocolloid into the lymph nodes [47]. Indeed, 32% of positive nodes were falsely negative [48]. Third, technecium-containing nodes can only be found intraoperatively with the collimator if it is in direct contact with the lymph node.

Single photon emission CT (SPECT) fused with CT or MRI has been shown to improve spatial resolution and orientation, thus allowing for a more precise localisation of ^{99m}Tc-containing lymph nodes [49]. The procedure, however, is time consuming and depends on the skills and endurance of the reader. Moreover, experience with this tool is limited, and it cannot overcome the problem of false-negative nodes.

3.2. *Importance of the extent of pelvic lymph node dissection in prostate cancer staging*

Several studies have shown that the rate of LNI in PCa patients almost linearly increases with the extent of PLND [34–41]. Indeed, ePLNDs might be necessary to detect occult lymph node metastases that would not otherwise be detected by lPLNDs, as PCa nodal metastases do not follow a predefined pathway of spread [50]; however, what does represent an ePLND in PCa is still a matter of debate. Some authors consider ePLND to be the removal of obturator, external iliac, and hypogastric nodes [14,37,39]. Others include the removal of presacral nodes [36,51], which are part of the hypogastric package in some series [33,38]. Golimbu et al showed that the deep presacral–presciatic nodes were involved almost as often as the more superficial external iliac-obturator group, which demonstrates that ePLNDs excluding the presacral region still have a substantial likelihood of overseeing positive nodes [51]. Finally, other authors advocate the additional removal of common iliac nodes, at least up to the ureteric crossing, on the basis of imaging studies [38,49]. Yet, even in the presence of such extensive nodal dissections, approximately 25% of lymph nodes potentially harbouring PCa nodal metastases would not be removed [49]. Regardless of the definition used, general agreement has been reached on the fact that an extended nodal dissection should always include removal of lymph nodes along the hypogastric artery. Indeed, several studies have demonstrated that up to 50% of lymph node metastases are located in this landing site [38,40,49–52]. Therefore, removal of lymph nodes located in the obturator fossa alone or in conjunction with the lymphatic tissue along the external iliac vessels might significantly underestimate the true incidence of nodal metastases in PCa. Heidenreich et al [36] as well as Bader et al [38] pioneered a systematic assessment of the concept of PLND extent and LNI rate. Heidenreich et al [36] found twice as many positive nodes using the extended versus limited technique in a historical control group (26% vs 12%; $p < 0.03$). Similarly, ePLND with a mean count of 13.1 lymph nodes was associated with a 2.8-fold higher LNI rate versus lPLND (mean: 10.1 removed lymph nodes; 11.4% vs 4.1%; $p = 0.009$) in another recent retrospective laparoscopic series [39]. Interestingly, the rate of false-negative findings associated with lPLND (restricted to external iliac area and obturator fossa) would have been 19% and 16% in Bader et al's [38] and Heidenreich et al's [36] series, respectively; this rate increases up to 60% if only patients with lymph node metastases are considered [38]. Other investigators confirmed these findings [49–52]. The relationship between PLND extent and the rate of LNI was also examined by Briganti et al [34,35]. These authors showed that the ability correctly to predict the likelihood of LNI increases when the number of removed nodes is increased [34]. Interestingly, the probability of correctly predicting the rate of LNI was close to zero when <10 nodes were removed. Conversely, a virtually perfect ability was reported when ≥ 30 lymph nodes were removed. These results seem indirectly to confirm the results of an autopsy study which found that an average of 20 dissected pelvic lymph nodes can be considered a representative sampling that enables exact loco-regional staging of PCa [53]. Taken together, these data show that lPLND is associated with a dismal staging accuracy that is falsely biased towards low rates of LNI due to inadequate nodal sampling. The only prospective randomised study assessing the rate of LNI in 123 patients randomly assigned to either lPLND or ePLND did not find a significant difference in the rate of LNI between the two surgical approaches (3.2% vs 4%, respectively; $p = 0.1$) [31]. This study, however, is flawed by several limitations. First, the vast majority of patients included had low-risk PCa, which is associated with a low rate of LNI, even in patients treated with ePLND. Second, ePLND was performed on only one side. Third, the field of ePLND was not defined, and no data are given regarding the number of lymph nodes removed in each group or the pathologic assessment performed in detecting lymph node metastases. Fourth, the study was seriously underpowered to allow for a conclusion of noninferiority. Taken together, these limitations strongly restrict the validity of this trial. Therefore, available data seem to support the statement that if PLND is planned in

Table 1 – Available preoperative staging tools predicting the presence of lymph node metastases in prostate cancer

Study	No. of patients	Predictors	Extent of PLND	Prevalence of LNI, %	Predictive accuracy, %
Cagiannos et al [11]	7014	PSA, clinical stage, biopsy Gleason score	Limited	3.7	76
Kattan et al [12]	697	PSA, clinical stage, biopsy Gleason score	Limited	8	76.8
Makarov et al [13]	5730	PSA, clinical stage, biopsy Gleason score	Limited	1	88
Briganti et al [14]	602	PSA, clinical stage, biopsy Gleason score	Extended	11	76
Briganti et al [15]	278	PSA, clinical stage, biopsy Gleason score, percentage of positive cores	Extended	10.4	83
Bluestein et al [16]	1632	PSA, clinical stage, biopsy Gleason score	Limited	NA	NA
Bishoff et al [17]	481	PSA, clinical stage, biopsy Gleason score	Limited	7.7	NA
Narayan et al [18]	932	PSA, biopsy Gleason score	Limited	11	NA
Conrad et al [22]	344	No. of positive biopsies, no. of biopsies containing any Gleason grade 4 or 5 cancer	Limited	8.1	NA
Roach et al [23]	212	PSA, biopsy Gleason score	Limited	17	NA
Crawford et al [24]	4133	PSA, clinical stage, biopsy Gleason score	Limited	NA	NA
Batuello et al [25]	6135	PSA, clinical stage, biopsy Gleason score	Limited	4.6	81
Han et al [26]	5744	PSA, clinical stage, biopsy Gleason score, age	Limited	5	88
Poulakis et al [27]	201	PSA, clinical biopsy Gleason score, and pelvic coil MRI findings	Limited	10	91
Karam et al [28]	425	PSA, clinical stage, biopsy Gleason score, preoperative plasma endoglin	Limited	3.3	97.8
Wang et al [29]	411	PSA, clinical biopsy Gleason score, and pelvic coil MRI findings	Limited	5	89.2

PLND = pelvic lymph node dissection; LNI = lymph node invasion; PSA = prostate-specific antigen; MRI = magnetic resonance imaging; NA = not available.

patients with PCa, it should be extended. This approach significantly increases the nodal staging accuracy by decreasing the rate of false-negative findings associated with lPLNDs.

3.3. *Critical evaluation of predictive models used to assess the need for pelvic lymph node dissection in prostate cancer*

Several nomograms and predicting tables [10–29] have been developed to predict LNI and to assess the need for PLND (Table 1). Most of these tools were based on routinely available variables such as preoperative prostate-specific antigen (PSA) level, clinical stage, and biopsy Gleason sum. These tools can identify patients at low risk of LNI and have contributed to a steep and unrelenting decrease in the utilisation of routine PLND at RP [54]. All of these tools, however, except for two [14,15] were developed and validated in patients treated with lPLND. Therefore, despite their apparently high accuracy (range: 76–97.8%; Table 1), they may significantly underestimate the true prevalence of LNI due to the limited nodal sampling. Makarov et al [13] published an update of the Partin tables developed to predict pathologic stage (including LNI) using preoperative PSA, clinical stage, and biopsy Gleason score. In this study, LNI rate and predictive accuracy were 1% and 88%, respectively. Conversely, lower accuracy was reported when LNI predictions from the Partin tables were validated in a population-based cohort

Table 2 – Currently available guidelines regarding the need for and the extent of pelvic lymph node dissection in prostate cancer

Guidelines	Indication for PLND	Extent of PLND
European Association of Urology [1]	Men with intermediate (cT2a, PSA 10–20 ng/ml, biopsy Gleason score 7) or high risk (>cT2b, PSA >20 ng/ml, Gleason score ≥8) prostate cancer	Extended
American Urological Association [55]	PLND generally reserved for patients with higher risk of nodal involvement	Not indicated
National Comprehensive Cancer Network [56]	PLND can be excluded in patients with <7% predicted probability of lymph node metastases by nomograms, although some patients with nodal metastases will be missed. An extended PLND is preferred when PLND is performed.	Extended

PLND = pelvic lymph node dissection; PSA = prostate-specific antigen.

and in European patients, in which accuracies of 76% were found [20,21]. Cagiannos et al also reported a preoperative nomogram aimed at identifying patients at low risk of LNI based on PSA, clinical stage, and biopsy Gleason sum [11]. The bootstrap-corrected accuracy of this model was 76%. None of these studies, however, provided the number of removed lymph nodes. Moreover, all mainly relied on lPLNDs, which limits their validity and applicability in cohorts treated with ePLND. To circumvent this limitation, Briganti et al developed a nomogram predicting the rate of LNI in patients who underwent an ePLND at a single high-volume centre [14]. Their nomogram was 76% accurate and relied on PSA, clinical stage, and biopsy Gleason sum. This nomogram represents the first tool based on ePLND patients, but it still awaits prospective external validation. Even higher LNI predictive accuracy can be reached if data on tumour volume, such as percentage of positive cores, are included in multivariable models and applied to ePLND-treated patients [15]. All of these findings were recently reviewed and included in the currently available PCa guidelines (Table 2) [1,55,56].

3.4. *Is there a need for pelvic lymph node dissection in low-risk prostate cancer patients?*

Several trials have assessed the rate of LNI in low-risk PCa patients treated with either lPLND or ePLND [13,57–62]. Despite a lack of uniformity in defining the low-risk PCa group, the rate of LNI in lPLND series is invariably low, ranging between 0.5 and 0.7% [13,56–59]. In the largest low-risk PCa series focussing on patients with cT1 PCa and PSA $\leq$6 ng/ml, the rate of LNI was as low as 0.7% [60]. These results have been confirmed by the most recently updated Partin tables, where the rate of LNI was <1% in patients with favourable cancer characteristics (PSA <10 ng/ml, T1c PCa, and biopsy Gleason sum $\leq$6) [13]. Similarly, the rate of LNI was as low as 0.7% in a recent low-risk PCa series (defined by PSA $\leq$10 ng/ml, biopsy Gleason score $\leq$6, and clinical stage T1 or T2a) [59]. Such negligible LNI rates found in the low-risk group significantly contributed to a continuous decrease in the rate of PLND performed in this subset of patients [54]; however, all of these studies are biased by the inclusion of patients treated with lPLNDs. Interestingly, when considering ePLND series, the rate of LNI seems to increase slightly, even in the low-risk PCa group [40,61,62]. Weckermann et al reported on a retrospective study in which the rate of LNI was 7.4% among patients with PSA <10 ng/ml and biopsy Gleason sum $\leq$6 who were treated with ePLND [61]. The rate of LNI was even higher (11%) in a recent study by Schumacher et al based on a cohort of 231 patients with PSA <10 treated with ePLND [62]. This rate, however, significantly decreased to 3% when only patients with clinical stage T1–T2 and biopsy Gleason score $\leq$6 were considered [33]. Similarly, the rate of LNI was 5.8% in another ePLND series including patients with PSA <10 ng/ml, T1c PCa, and biopsy Gleason score $\leq$6 [40]. Taken together, these data showed that the overall LNI rate in the low-risk PCa group (PSA <10, clinical stage T1–T2a, and biopsy Gleason sum $\leq$6) never exceeded 8%, even among patients treated with more extensive nodal dissections [13,40,57–62]. Based on the results of these studies, all of the available PCa guidelines do not routinely recommend a staging PLND in the presence of these preoperatively favourable PCa characteristics (Table 2) [1,55,56]. Nevertheless, it is still unknown whether PLND might confer significant biochemical recurrence (BCR) survival benefit in low-risk PCa due to the lack of prospective randomised trials. Indeed, only a few retrospective studies to date have assessed the impact of PLND on the outcome of low-risk PCa patients. Bhatta-Dhar et al [57] compared the BCR-free survival of low-risk patients not randomly assigned to either lPLND or no lPLND. After a mean follow-up of 60 mo, there was no difference in 6-yr biochemical failure rates in patients receiving PLND compared with patients not treated with lPLND (86% and 88%, respectively; $p = 0.28$). The authors also re-evaluated the same groups of patients at a longer follow-up [58]. Again, they did not find any difference in the 10-yr BCR-free survival rates between the two groups (83.8% vs 87.9%, respectively; $p = 0.33$). Similarly, in another multicentre study, the BCR-free survival rates of low-risk patients were 81% versus 82% in the no-PLND group versus the PLND group, respectively ($p = 0.83$) [59]. These results, however, must be interpreted with caution because the studies were limited by several scientific flaws. First, all patients had inadequate nodal dissection in that they were treated with lPLND (mainly an obturator). Second, the vast majority of the patients enrolled were probably at very low risk of dying from progressive disease, even if left untreated. Third, no standardised pathologic assessment of lymph nodes was performed. Finally, from a statistical perspective, the number of events was too small to allow for an equivalence study.

Therefore, these data do not formally rule out the possibility that more extensive PLND might favourably affect patient survival, even in the low-risk group. Indeed, a significant inverse association between the number of nodes removed and the rate

Table 3 – Complication rates of pelvic lymph node dissection (PLND)

Study	No. of patients enrolled	Rate of complications, %	PLND extent	Mean number of lymph nodes removed
Stone et al [30]	189	35.9 vs 2	Extended vs limited*	17.8 vs 9.3
Clark et al [31]	123	8.1 vs 2.4	Extended vs limited	NA
Briganti et al [32]	963	18.9 vs 7.3	Extended vs limited	17 vs 7
Heidenreich et al [36]	203	8.7 vs 9	Extended vs limited	28 vs 11
Bader et al [38]	365	2.1	Extended	21^
Jeschke et al [43]	71	7	Extended*	NA
Schumacher et al [62]	122	4.8	Extended	22^
Herrell et al [63]	68	20	Limited	9.2
Keller et al [64]	90	7.8	Extended	19
Wyler et al [65]	123	4	Extended*	21
Pepper et al [66]	260	3.5	Extended	NA
McDowell et al [67]	217	22	Extended	NA
Paul et al [68]	150	51	Extended	NA

NA = not available.
^ Median number of lymph nodes removed.
* Laparoscopic series.

of BCR has been reported in node-negative patients [41]. Future prospective randomised trials including patients treated with ePLND are needed to confirm these preliminary, potentially biased findings.

3.5. *Complications of pelvic lymph node dissection*

Surgeons are often deterred from performing an ePLND because of the potentially high incidence of complications. When the cumulative PLND complication literature is examined, the rate of complications ranges from 2% to 51% (Table 3) [30–32,36,38,45,63–70], but controversies exist with regard to the rate of PLND-related complications according to the extent of PLND. Clark et al found an increased risk of complications attributable to PLND on the side of extended dissection [31]. Stone et al [30] also reported a strikingly higher complication rate when they compared laparoscopic ePLND with laparoscopic lPLND (35.9% vs 2%; $p < 0.001$). The largest contemporary series ($n = 963$) addressing complications after PLND showed that in patients treated with ePLND, the overall rate of complications was 19.8% versus 8.2% in those treated with lPLND ($p < 0.001$) [32]. Alternatively, when individual PLND complications were assessed, only the rate of lymphocele was significantly higher in patients subjected to ePLND (10.3% vs 4.6%, respectively; $p = 0.01$). Complications were not invariably high in all ePLND series, as evidenced by Bader et al [38]: In this study, an overall complication rate requiring prolonged hospitalisation of 2.1% was recorded. Conversely, a higher complication rate (8.8%) was reported by Heidenreich et al [36]. Nevertheless, the frequency and severity of intra- and perioperative complications did not differ significantly between the lPLNDs and the ePLNDs (9% vs 8.7%, respectively). Despite the presence of discordant results in the literature, all of these data seem to suggest that PLND may not be an entirely innocuous procedure, even in the hands of the most experienced surgeons. To minimise PLND-related morbidity, some key steps need to be followed. Heidenreich et al [40] suggested that all lymphatics lateral to the external artery should be saved. Additionally, the distal ends of the lymphatics should be either ligated or clipped with small clips that exert a higher pressure on the lymphatic vessels than large clips. Two drains should also be placed in each side of the pelvis and left in place until <50 ml/d is drained. Finally, low-molecular heparin should be injected into the upper arm. Although it seems logical to think that surgical expertise may reduce PLND-associated morbidity, this concept still needs to be confirmed in methodologically sound studies.

3.6. *Impact of pelvic lymph node dissection on prostate cancer outcome*

The issue of whether PLND might affect PCa outcome has been an argument of extreme interest in the urologic community. Unfortunately, the question remains unanswered because of the lack of prospective randomised trials. Moreover, the impact of PLND on cancer outcomes remains controversial, even in retrospective studies. Masterson et al [41] found a significant inverse association between the number of removed lymph nodes and BCR-free survival in node-negative patients ($p = 0.01$). These results might be attributable to the removal of micrometastatic nodal disease, which may support the therapeutic role of PLND in this

patient category. Patients with nodal micrometastases would be those who are more likely to receive a possible curative benefit from PLND. This hypothesis is still pending definitive approval, since no immunohistochemistry evaluation aimed at identifying occult nodal disease has been performed in the study.

Another retrospective trial found a significant association between the extent of PLND and cancer-specific survival. Interestingly, patients undergoing removal of at least four lymph nodes (node-positive and node-negative patients) or >10 nodes (only node-negative patients) had a lower risk of PCa-specific death at 10 yr compared with patients who did not undergo PLND [71]. The main limitation of this multicentre study is the lack of an homogeneous and standardised pathologic assessment of the removed lymph nodes, which is key for determining reliable nodal counts. In contrast, Di Marco et al [72] found no survival benefit associated with an increasing number of removed lymph nodes in node-negative patients in a large, single-institution series collected over a 13-yr time span. Patients who underwent surgery at the beginning of these authors' experience had more nodes removed and showed an oncologic outcome similar to patients operated on 10 yr later. Taking the stage-shift into account, patients operated on earlier should have had poorer outcomes; as this is apparently not so, one might hypothesise a beneficial role for PLND. This possibility, however, cannot be considered as more than food for thought. We feel that the question of whether a meticulous nodal dissection can have an impact on node-negative PCa still needs to be elucidated.

Furthermore, it should be acknowledged that the positive association between PLND extent and cancer outcome in node-negative patients might be based on a misinterpretation of these data caused by the *Will Rogers phenomenon* [73,74], a well-known phenomenon in the medical literature. Will Rogers (1879–1935), the great American humorist, drew attention to the apparent mathematical paradox that the movements of elements from one set to another can increase the average value of both sets. In medicine, the Will Rogers phenomenon describes an apparent improvement in outcome for groups of patients with no actual improvement for any individual patient [73]. In the context of PLND, if the number of removed negative lymph nodes is investigated as a prognosticator, it is clear that patients treated with ePLND have a higher likelihood of being really node negative without overlooked metastases. If a patient has a positive node in an area that is covered by an extended dissection but not by a limited dissection, this patient is excluded from the analyses in the group of ePLND patients (as he is node positive, and only node-negative patients are left in the analyses) but is included in the group with a limited dissection. This means that different groups are compared at a certain disease stage, and the benefit of the group with an extended dissection can be explained by the different disease stages. In other words, after a limited dissection, the likelihood of overlooked metastases is higher, and it is these overlooked positive nodes, instead of the removal of negative nodes, that influence the prognosis [73,74]. Similar results can be achieved when considering only patients with positive nodes. Indeed, in patients in whom many nodes are removed, the incidence of finding positive nodes would be high, and the outcome of these patients would be relatively good because many patients would have only small-volume metastatic disease. At the same time, when comparing node-positive patients between a series with ePLND or lPLND, the patients with positive nodes would again have a much better outcome in the series with ePLND because they would contain the patients who had small nodal disease. These observations suggest that the only solution to answering the question of whether or not removal of the lymph nodes has a role beyond diagnostic purposes is to conduct a prospective randomised trial in which patients are randomised to either no PLND or ePLND.

Even in the absence of well-designed trials, data available from large series of patients undergoing PLND have shown that the long-term outcome of surgically treated patients with LNI is not invariably poor (Table 4) [75–85]. Bader et al [76] reported a remarkable 74% 5-yr cancer-specific survival rate in a smaller cohort of patients treated with ePLND and RP and with no adjuvant treatment. Data from the same group reported by Schumacher et al indicated a 60% cancer-specific survival rate at 10-yr follow-up [82]. Cheng et al [77] reported a 79% 10-yr cause-specific survival in a large series of 322 patients treated with RP. Of these patients, 92% received prolonged adjuvant androgen deprivation therapy (ADT). Boorjan et al [78] recently updated the same institution's series, which included 505 patients treated with RP and PLND. Again, roughly 90% of those patients received ADT; the 10-yr cancer-specific survival rate was as high as 85.8%. In another series of 100 node-positive patients, the 5- and 10-yr disease-specific survival rates were 94% and 75%, respectively [83]. Interestingly, in the largest node-positive series available ($n = 703$) including patients treated with a multimodal, combined approach, the 15-yr cancer-specific survival rate was 78% [79]; however, when

Table 4 – Outcome of patients with lymph node metastases treated with radical prostatectomy (RP) and pelvic lymph node dissection (PLND) with or without adjuvant treatments in the prostate-specific antigen (PSA) era

Study	No of patients	Median follow-up, yr	Adjuvant therapy	Cancer-specific survival		BCR-free survival		Metastasis-free survival	
				5 yr	10 yr	5 yr	10 yr	5 yr	10 yr
Masterson et al [41]	175	4.4	No	–	–	23%†	19%†	–	–
Daneshmand et al [75]	235	11.4	31% of pts	–	–	54%	39%	80%	65%
Bader et al [76]	92	3.75	No	74%	62%	25%†	10%†	50%†	25%†
Cheng et al [77]	322	6.3	92% of pts	94%	83%	74%^	64%^	–	–
Boorjian et al [78]	507	10.3	89.7% of pts	94.2%	85.8%	69%	55.9%	90.1%	80.1%
Briganti et al [79]	703	9.4	100% of pts	90%	82%	71%	58%	–	–
Gjertson et al [80]	24	6.1	25% of pts	–	–	15%	–	–	–
Zwergel et al [81]	147	3.5	91.9% of pts	86.5%	73.7%	77.4%	53%	72.7%**	49.8%**
Schumacher et al [82]	122	5.6	No	84.5%	60.1%	13.9%	2.9%	–	–
Spiess et al [83]	100	5.2	30% of pts	94%	75%	–	–	84%	69%
Messing et al [84]	98	11.9	HT ($n = 47$) vs observation ($n = 51$)	95%† vs 70%†	85%† vs 50%†	–	–	80%† vs 28%†	65%† vs 18%†
Cadeddu et al [85]	19	5.5	3% of pts	93%	56%	–	–	–	–
Palapattu et al [86]	143	6	No	–	–	26.5%	10.9%*	–	–
Han et al [87]	135	6.3	No	–	–	26%	10%	–	–

BCR = biochemical recurrence; HT = hormonal therapy; pts = patients.
† Approximately.
^ Disease progression defined by elevation of serum PSA >0.4 ng/ml after surgery, development of local recurrence, or distant metastasis documented by biopsy or radiographic examination.
* 7-yr BCR-free survival rate.
** Freedom from any (systemic, local, or biochemical) progression probabilities.

Table 5 – Influence of the extent of nodal invasion on the outcome of patients with lymph node metastases treated with radical prostatectomy (RP) and pelvic lymph node dissection (PLND) with or without adjuvant treatments in the prostate-specific antigen (PSA) era

Study	No. of patients with LNI	Patient characteristics	Median follow-up, yr	Adjuvant therapy	Cancer-specific survival		BCR-free survival		Metastasis-free survival	
					5 yr	10 yr	5 yr	10 yr	5 yr	10 yr
Daneshmand et al [75]	235	<20% vs ≥20% LND	11.4	31% of pts	–	–	–	–	86%† vs 60%†	72% vs 47%
Bader et al [76]	92	1 vs 2 vs ≥2 positive nodes	3.75	No	93%† vs 60%† vs 63%†	84%†* vs 60%†* vs 27%†*	32%† vs 23%† vs 21%†	14%†* vs 12%†* vs 7%†*	52%† vs 52%† vs 35%†	35%†* vs 35%†* vs 20%†*
Cheng et al [77]	322	0 vs 1 positive node	6.3	92% of pts	99.3% vs 99%	97% vs 94%	77%^ vs 79%†^	59%^ vs 66%†^	–	–
Boorjian et al [78]	507	0 vs 1 vs ≥2 positive nodes	10.3	89.7% of pts	99% vs 97% vs 90%	98% vs 90% vs 79%	79% vs 71% vs 67%	68% vs 57% vs 54%	98% vs 94% vs 85%	95% vs 86% vs 73%
Briganti et al [79]	703	≤2 vs >2 positive nodes	9.4	100% of pts	93% vs 81%	85% vs 73%	75% vs 60%	61% vs 45%	–	–
Schumacher et al [82]	122	1 vs 2 vs >2 positive nodes	5.6	No	95%† vs 100%† vs 69%†	72.1% vs 79.1% vs 33.4%	24.7% vs 11.8% vs 4.9%	11%†* vs 2%†* vs 3%†*	–	–
Palapattu et al [86]	143	≥15% vs <15% LND	6	No	–	–	33%† vs 10%†	25%†* vs 3%†*	–	–

BCR = biochemical recurrence; LND = lymph node density (number of positive lymph nodes over total number of lymph nodes removed); LNI = lymph node invasion; pts = patients.
† Approximately.
^ Disease progression defined by elevation of serum PSA >0.4 ng/ml after surgery, development of local recurrence, or distant metastasis documented by biopsy or radiographic examination.
* 7-yr follow-up.

considering BCR-free survival rates of node-positive patients not receiving adjuvant ADT, outcomes seem to be poorer. This finding is expected, since it is well known that not all patients with BCR will eventually die from prostate cancer. Palapattu et al [86] reported on a 16% BCR-free survival rate at a median follow-up of 6 yr in patients undergoing RP left untreated until progression. Similar results were reported by Masterson et al, who showed roughly 19% BCR-free survival rates in 175 node-positive patients not receiving adjuvant therapy [41]. Several studies, however, have shown that not all node-positive patients are at the same risk of PCa progression and death [75–79,82,86,87]. Indeed, patients with a low volume of nodal disease have significantly higher survival rates compared with patients with a higher volume of LNI, regardless of adjuvant treatment administration (Table 5) [75–79,82,86]. Daneshmand et al [75] reported on a large retrospective study in which patients with one and two positive lymph nodes had an overall survival rate of 94% and 96% at 5 yr and 75% and 74% at 10 yr, respectively. Interestingly, when stratified by lymph node density (LND), patients with an LND ≥20% were at higher risk for clinical recurrence compared with those with a density of <20% (relative risk: 2.31; $p < 0.001$). Similarly, Palapattu et al found an LND cut-off of 15% as a significant predictor of cancer progression ($p < 0.0001$) [86]. Interestingly, Cheng et al showed that the 10-yr cancer-specific survival rate was as high as 94% in patients with a single node metastasis [77]. This rate was not significantly different from the cancer-specific survival of patients without nodal involvement. Similar results seem to be achieved in series including patients not receiving any adjuvant treatment. In a study by Bader et al, 39% of patients with one positive node remained free of clinical or biochemical progression, compared to 12% of patients with two or more positive nodes [76]. Schumacher et al recently confirmed these findings and reported significantly higher 10-yr cancer-specific survival rates in patients with two or fewer positive nodes compared with patients with three or more positive nodes not receiving any adjuvant therapy (78.6% vs 33.4%, respectively) [82]. The cut-off of two positive nodes has also been recently studied in a large multi-institutional node-positive series of patients treated with a multimodal approach ($n = 703$) [79]. Patients with two or fewer positive nodes had significantly better cancer-specific survival outcome at 15-yr follow-up compared with patients with more than two positive nodes (84% vs 62%; $p < 0.001$). Patients with more than two positive nodes had a 1.9-fold higher risk of dying of PCa compared with patients with two or fewer positive

nodes after accounting for all the other predictors ($p = 0.002$). Moreover, a significant improvement in cancer-specific survival prediction was reached when the number of positive nodes was considered [79]; however, the evidence of increased survival of patients with low-volume nodal invasion might be explained by a lead-time bias.

Furthermore, the optimal postoperative management of patients with nodal metastases is still controversial. Indeed, although a well-designed prospective randomised trial showed a positive effect of adjuvant ADT in node-positive patients of whom the majority also had positive margins and seminal vesicle invasion [84], it is possible that not all patients with nodal metastases, namely those with minimal nodal disease and a slow PSA doubling time, might benefit from adjuvant ADT [82]. Patients with a low volume of LNI accurately staged with ePLND indeed eventually might be considered for watch-and-wait protocols, which would reduce the risk of overtreatment of patients at lower risk for cancer progression. Moreover, a recent retrospective study has shown a positive impact of adjuvant radiotherapy in patients with nodal metastases [88]. Future prospective studies are needed to clarify these issues.

Taken together, all of these data show that the impact of PLND as a curative treatment remains an open question. Nevertheless, some authors suggest that the extent of PLND in and of itself might have a beneficial effect on symptomatic progression and PCa-specific survival [41,71]. Unfortunately, these assumptions are based on retrospective, uncontrolled trials; nonetheless, it may be the case that some patients may have benefited from the removal of micrometastases that are eventually only detectable at a molecular level. Only future prospective randomised trials comparing the effect of PLND versus no PLND in high-risk patients definitely would assess the role of PLND on PCa outcomes. In view of the substantial amount of indirect evidence that ePLND may benefit, if not cure, particularly those patients with low volume of nodal disease, such studies are hardly feasible.

4. Conclusions

A number of conclusions can be drawn from this review. First, PLND remains the most accurate and reliable approach for detecting the presence of lymph node metastases in PCa. If a PLND is planned at the time of RP, it should be extended. Increasing the extent of lymph node dissection results in a more accurate assessment of LNI and a higher rate of nodal metastases. Limited PLND is associated with a high rate of false-negative findings. Second, the downside of more extensive PLND consists of a higher rate of complications, as reported in some studies. Specifically, the rate of lymphoceles might be higher but the higher rate of complications associated with ePLND has not always been confirmed. Third, previous tools predicting the rate of LNI are based mostly on lPLND and thus are of limited value. Fourth, the rate of LNI is low (<8%) in patients with low-risk PCa (defined as clinical stage T1/T2a, biopsy Gleason sum ≤6, and PSA <10 ng/ml). Despite the absence of prospective randomised trials assessing the impact of ePLND in this patient category, a staging ePLND might be spared in patients with low-risk PCa. Fifth, no data from prospective randomised studies indicate that the extent of PLND improves cancer control or survival; however, outcome of surgically treated node-positive patients is not invariably poor. The extent of lymph node involvement (namely, the number of positive lymph nodes) is one of the strongest predictors of cancer-specific survival. Patients with lymph node metastasis and low nodal burden show excellent long-term outcomes, regardless of the administration of adjuvant treatments.

Author contributions: Alberto Briganti 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.

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Acquisition of data: Briganti, Blute, Eastham, Graefen, Heidenreich, Karnes, Montorsi, Studer.
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Statistical analysis: Briganti, Blute, Eastham, Graefen, Heidenreich, Karnes, Montorsi, Studer.
Obtaining funding: None.
Administrative, technical, or material support: Briganti, Blute, Eastham, Graefen, Heidenreich, Karnes, Montorsi, Studer.
Supervision: Briganti, Blute, Eastham, Graefen, Heidenreich, Karnes, Montorsi, Studer.
Other (specify): None.

Financial disclosures: I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials

discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

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