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Review Article

Role of Pelvic Lymph Node Dissection in Prostate Cancer Treatment

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Pelvic lymph node dissection (PLND) is the most accurate and reliable staging procedure for detecting lymph node invasion (LNI) in prostate cancer. Recently, [^{11}C]-choline positron emission tomography imaging and magnetic resonance imaging with lymphotropic superpara-magnetic nanoparticles have shown potential for detecting LNI but are still under investigation. The risk of LNI in low-risk groups could be underestimated by use of the current nomograms, which rely on data collected from patients who underwent only limited PLND. Extended PLND (ePLND) shows higher lymph node yield, which leads to the removal of more positive nodes and fewer missed positive nodes. It may be possible to refrain from performing PLND on low-risk patients with a prostate-specific antigen value <10 ng/ml and a biopsy Gleason score ≤ 6, but the risk of biopsy-related understaging should be kept in mind. Theoretically, meticulous ePLND may also impact prostate cancer survival by clearing low-volume diseases and occult micrometastasis even in pN0. The therapeutic role of PLND in prostate cancer patients is still an open question, especially in individuals with low-risk disease. Patients with intermediate- to high-risk disease are more likely to benefit from ePLND.

Key Words: *Lymph node dissections; Prostate cancer; Prostatectomy*

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INTRODUCTION

Radical prostatectomy and pelvic lymph node dissection (PLND) and removal are important treatment options for men with clinically localized prostate cancer. The prognostic significance of lymph node (LN) metastases is well established [1-4]. Pelvic LN metastasis is a strong prognostic factor for disease progression and survival. Initially, PLND was performed in all patients during radical prostatectomy. Historically, men who underwent surgery for clinically localized prostate cancer have a 20% to 40% prevalence of pelvic LN involvement [5,6]. With the advent of prostate-specific antigen (PSA) testing and more widespread prostate cancer screening programs since 1987, this rate has now decreased to 4% to 6% [7,8]. Currently, the objective of a staging lymphadenectomy is to identify micrometastatic spread to LNs for prognostic evaluation and to identify patients with LN metastasis who would benefit from immediate androgen deprivation therapy [9].

At present, some urologists apply well-known nomograms when they determine the need for PLND during radical prostatectomy [10-15]. Such nomograms help to identify those patients who need staging PLND but not when performing radical prostatectomy. However, the diagnostic accuracy of the nomograms and their safety from an oncologic perspective are still unknown because of the lack of prospective randomized clinical trials. In contrast, others favor performing PLND in all patients for whom a radical prostatectomy is truly indicated [16]. To clarify this confusion, the present study reviewed the available current literature on PLND to determine appropriate PLND candidates, the optimal extent of PLND, and the clinical benefits of PLND.

CLINICAL STGING FOR LYMPH NODE METASTASES

Despite advances in radiological technology, conventional computed tomography (CT) and magnetic resonance imaging (MRI) are generally unreliable in detecting LN meta-

stases due to their low sensitivity (0-30%). Positron emission tomography (PET) scanning can detect molecular changes as a result of metabolic changes found via the use of radiolabeled molecular probes that have different rates of cellular uptake. de Jong et al evaluated the tracer [^{11}C]-choline with PET imaging in 67 prostate cancer patients [17]. In 15 patients with biopsy-proven LN metastasis, the tracer had a sensitivity rate of 80% and a specificity rate of 96%. Another novel technique is high-resolution MRI used in tandem with the intravenous administration of lymphotropic superpara-magnetic nanoparticles, which potentially enables the identification of otherwise undetectable LN disease. Among 80 patients with localized and locally advanced prostate cancer, this technique had a 90.5% sensitivity rate and a specificity rate of 97.8% compared with conventional MRI, which had a sensitivity rate of 35.4% and a specificity rate of 90.5% [18]. However, all false-negative nodes had a short-axis diameter of <5 mm when the sensitivity was only 41.1%. This promising technique cannot be used for routine application and requires further clinical validation before its widespread use [18]. Initially, several studies reviewing the ^{111}indium-labeled murine monoclonal antibody scan (ProstaScint^{TM} scan) showed that this technique has superior sensitivity and specificity compared with CT scans [19,20]. However, in patients with a lower stage (mean PSA, 16 ng/ml), ProstaScint^{TM} showed a very low positive predictive value (11%) and sensitivity (17%) for predicting LN invasion (LNI) [21].

The sentinel LN concept has in recent years been applied to prostate cancer and was first introduced by Wawroschek et al [22]. This concept has an apparent sensitivity rate of 96% for detecting lymphatic spread in node-positive patients [23]. However, this technique has its drawbacks. Only nodes in close contact with the collimator can be detected. If these nodes are not directly accessible, there is a large chance of them being missed.

In summary, [^{11}C]-choline PET imaging or MRI with lymphotropic superpara-magnetic nanoparticles are promising but are still currently under investigation for clinical use. At present, there is no accurate or reliable imaging modality that can precisely detect LNI in prostate cancer patients. Thus, PLND represents the most accurate and reliable staging procedure for the detection of LNI in prostate cancer.

EXTENT OF PLND

Anatomical studies have demonstrated that the prostate gland drains lymphatically into the periprostatic subcapsular network; this has been confirmed by nuclear medicine mapping studies [24-27]. For accurate diagnosis of nodal metastasis and possible cure of nodal disease, several templates for PLND have been described [28,29]. The most commonly used template for PLND in prostate cancer includes the removal of tissue along the external iliac vein and in the obturator fossa (Fig. 1) and is considered limited

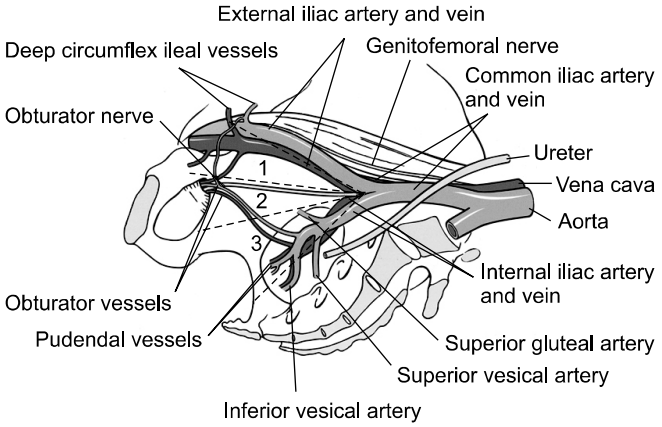

FIG. 1. Pelvic lymph node dissection field including the (1) external iliac node, (2) obturator node, and (3) internal iliac node. Reproduced with permission [32].

PLND (lPLND). The boundaries of the obturator fossa are the bladder (medially), the external iliac vein (laterally), the node of Cloquet (inferiorly), the bifurcation of the common iliac (superiorly), and the obturator nerve (posteriorly); these are collectively known as the external iliac nodes (diagram area 1). Standard PLND (sPLND) includes LNs in the obturator fossa and LNs deep and proximal to the obturator nerve (the obturator nodes; diagram area 2), whereas extended PLND (ePLND) also generally includes the tissue along the internal iliac vessels posteriorly (the internal iliac nodes; diagram area 3). Although some surgeons include the additional removal of subaortic and presacral nodes in their definition of ePLND [30,31], ePLND is most commonly considered to be a node dissection that involves bilateral resection of the external iliac, obturator, and internal iliac nodal groups (1, 2 and 3, respectively in Fig. 1) [32].

The total number of LNs removed during PLND is important for maintaining the accuracy of the staging procedure. More extensive dissections result in a greater LN yield. Weingärtner et al compared nodal counts in cadavers without prostate cancer subjected to PLND with actual counts resected during radical prostatectomy and PLND [33] and reported that, on average, 20 LNs must be removed for pathologic analysis to ensure an adequate and representative sample. An ePLND that involves the removal of this volume of nodes provides enhanced accuracy as a staging procedure. An average LN yield of 21 nodes during ePLND was reported in one study [34], whereas another study described an ePLND template including presacral and common iliac nodes in which the yield averaged 28 LNs [31].

To determine optimal templates of PLND in terms of accurate diagnosis and possible cure of nodal disease, many studies of pelvic LNs have been performed. Bader et al showed data for positive LN location following ePLND along the external iliac vein, obturator nerve, and internal iliac vessels in 365 patients [32,34]. The most common site

for metastasis (60%) was the obturator fossa. Overall, however, 58% and 36% of the patients had deposits in the internal iliac and external iliac nodal areas, respectively, whereas 19% had positive nodes distributed in the internal iliac vessels alone. Thus, if pelvic lymphadenectomy was confined to the obturator fossa, it would miss approximately 60% of the metastases, because most of the histopathologically proven metastatic LNs were found in the external and internal iliac node packets. Similar results were reported in a study that compared a historical series of patients who underwent lPLND with a contemporary series who underwent ePLND. That study reported that 42% of positive nodes were located outside the limited template [28,31]. Moreover, the authors determined that 25% of all positive LNs were exclusively located in the area around the internal iliac artery.

With respect to primary lymphatic landing sites, Mattei et al mapped the prostatic nodal landing zones by injecting Tc-99-labeled colloid into patients' prostates [35]. They found that, even by using the extended template, approximately one-third of the primary landing sites would still be missed and advocated including the tissue along the common iliac vessels up to the crossing of the ureter. For accurate staging including all primary lymphatic draining sites, the field of LN dissection should theoretically include tissue up to the origin of the inferior mesenteric artery.

In contrast, Clark et al performed a prospective randomized evaluation of 123 patients undergoing radical prostatectomy to assess the diagnostic value of an ePLND involving the presacral area compared with sPLND for detecting nodal metastasis [30]. On the basis of eight patients in whom LN metastasis was confirmed histopathologically, they concluded that ePLND did not improve the accuracy of LN staging compared with sPLND. This is the only study to date that was designed to be prospective and randomized; however, the majority of the patients presented with low-risk prostate cancer with a low rate of LNI. Furthermore, ePLND was performed on only one side, and no data were given regarding the number of LNs removed from each group.

To measure the exact LN yield following PLND, an additional factor to consider is the pathological examination method. In bladder cancer studies, greater nodal yields have been noted when lymphadenectomy specimens are sent as separate packets (such as external iliac and obturator) rather than en bloc [36,37]. Separate examination of specimens is an important procedure for optimizing LN detection and provides an accurate determination of nodal tumor burden [36,38].

In summary, more extensive dissection results in increased LN yield. As more nodes are removed, more positive nodes are found and fewer positive nodes are missed. For more accurate staging and a possible cure for minimal nodal disease, more extensive PLND could be used. However, based on the knowledge of primary lymphatic landing sites, many lymph nodes would still be missed even with ePLND.

FOR WHICH PATIENTS IS PLND NECESSARY?

After the introduction of PSA testing, the rate of LNI dramatically decreased to about 4% to 6% [7,8]. In Korea, the reported incidence of LNI by sPLND is between 4% and 6%. Kim et al reviewed their experience with 1,324 radical prostatectomy cases and reported that that 6% of patients had LNI [39]. Ham et al investigated 273 patients who underwent robotic prostatectomy. Among them, 11 patients (4%) showed LNI [40]. In our institution, of 351 patients who underwent limited or standard PLND, LNI was determined in 20 (5.7%) patients (unpublished data). With lower rates of pelvic LN metastasis [7,8] and the potential complications that can develop after PLND [30,41], knowing which prostate cancer patients need to undergo PLND regrettably remains undetermined. Several nomograms have been designed to predict LNI (Table 1) and to identify patients who may derive the most benefit from PLND [10-15, 42-51]. Most nomograms, including the well-known Partin tables [12,52] and Memorial Sloan-Kettering nomograms [42], predict pathologic stage by using preoperative clinical stage, biopsy Gleason scores, and preoperative PSA levels [12-14,42,53,54]. However, although these nomograms are well established and are certainly useful for the clinical decision making process, the predictive ability of most nomograms, except for two, is limited by the data used to create them. Most datawere obtained from series of lPLND with a mean of 6 to 9 LNs removed (Table 1) [10-15,42-52]. Therefore, the true prevalence of LNI may be significantly underestimated owing to the limited nodal sampling. Heidenreich et al compared 103 patients who underwent ePLND with 100 patients who received only sPLND in which no significant differences in age, preoperative PSA levels, or mean biopsy Gleason scores existed [31]. They reported that ePLND was associated with a high rate of LN metastasis outside of the fields of sPLND in cases of clinically localized prostate cancer [31]. Similarly, other studies also found that nomograms based on sPLND, where internal iliac nodes were not sampled, could not be considered a reliable method because sPLND could miss 25% to 50% of the positive nodes compared with extended dissection [31,32,53,55,56].

A Korean multi-institutional study developed a nomogram to predict LNI [57]. But, the nomogram was also based on sPLND and so could only predict the pathological stage of the clinically localized prostate cancer. To overcome this limitation, Briganti et al created and validated a nomogram that estimates the optimal number of nodes that should be removed based on clinical parameters and the number of nodes removed during ePLND [53,55]. From internal validation with 602 patients, their nomogram demonstrated an accuracy of 76% based on ePLND [53]. Within the same groups of risk from the D'Amico classification system [58], significantly higher LNI predictions using the Brigantin nomogram are likely, in part due to the ePLND data used to generate them. However, its reliability may be decreased by the fact that the majority of pa-

TABLE 1. Nomograms for predicting the lymph node involvement in prostate cancer

Study	No. of patients	Predictors	Extent of PLND	Prevalence of LNI, %	Predictive accuracy, %
Cagiannos et al [42]	7,014	PSA, clinical stage, biopsy Gleason score	Limited	3.7	76
Kattan et al [4,10,11,33,51]	697	PSA, clinical stage, biopsy Gleason score	Limited	8	76.8
Makarov et al [12]	5,730	PSA, clinical stage, biopsy Gleason score	Limited	1	88
Briganti et al [13,41,53,55]	602	PSA, clinical stage, biopsy Gleason score	Extended	11	76
Briganti et al [13,41,53,55]	278	PSA, clinical stage, biopsy Gleason score, percentage of positive cores	Extended	10.4	83
Bluestein et al [14]	1,632	PSA, clinical stage, biopsy Gleason score	Limited	NA	NA
Bishoff et al [43]	481	PSA, clinical stage, biopsy Gleason score	Limited	7.7	NA
Narayan et al [44,45]	932	PSA, biopsy Gleason score	Limited	11	NA
Conrad et al [54,15]	344	No. of positive biopsies, no. of biopsies containing any Gleason grade 4 or 5 cancer	Limited	8.1	NA
Roach et al [45]	212	PSA, biopsy Gleason score	Limited	17	NA
Crawford et al [9,46,47]	4,133	PSA, clinical stage, biopsy Gleason score	Limited	NA	NA
Batuello et al [46,47]	6,135	PSA, clinical stage, biopsy Gleason score	Limited	4.6	81
Han et al [8,47,48]	5,744	PSA, clinical stage, biopsy Gleason score, age	Limited	5	88
Poulakis et al [49]	201	PSA, clinical biopsy Gleason score, and pelvic coil MRI findings	Limited	10	91
Karam et al [50]	425	PSA, clinical stage, biopsy Gleason score, preoperative plasma endoglin	Limited	3.3	97.8
Wang et al [51]	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

TABLE 2. Guidelines for determining the need for and extent of pelvic lymph node dissection for treating prostate cancer

Guidelines	Indication for PLND	Extent of PLND
European Association of Urology	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	PLND generally reserved for patients with higher risk of nodal involvement	Not indicated
National Comprehensive Cancer Network	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

tients qualified as low-risk patients, and only 9% (71 patients) were LN-positive and ePLND was performed in only 23% of patients.

The necessity for PLND has been questioned, particularly in low-risk groups, on the basis of studies of lPLND. On the contrary, studies with ePLND have shown that LN metastases can occur even in patients with a PSA level <10 ng/ml. Schumacher et al showed that following ePLND and radical prostatectomy in patients with PSA <10 ng/ml, there was a 25% incidence of LN metastases in those with a specimen Gleason score ≥7, whereas only 3% of patients with a Gleason score ≤6 were node-positive [59]. Heidenreich et al reported a 2.4% incidence of LN metastasis in patients with a PSA level <10.5 ng/ml and biopsy Gleason scores ≤6, whereas Bhatta-Dhar et al found that the LN metastasis risk was <1% after lPLND in a series of patients with organ-confined disease, PSA <10 ng/ml, and a biopsy Gleason score ≤6 [31,60]. However, the inherent risk of understaging, which is approximately 30% [61], has to be taken into account. In the study of Bhatta-Dhar et al, 40% of patients had their Gleason scores upgraded to >6 [60].

Expert panels from the American Urological Association, National Comprehensive Cancer Network, and European Association of Urology have created guidelines for PLND based on such nomograms and other available data (Table 2). In summary, several well-known nomograms can be used to accurately predict who is at risk for LN-positive prostate cancer and to potentially predict who might derive therapeutic benefit from PLND. However, by depending on these nomograms, we may fail to properly stage patients with apparently low-risk disease because

these nomograms rely on data collected from patients who only underwent lPLND. Overall, the existing data suggest that it may be possible to refrain from performing PLND on low-risk patients with a PSA <10 ng/ml and a biopsy Gleason score ≤ 6, but the inherent risk of biopsy-based understaging should be kept in mind.

THERAPEUTIC ROLE OF PLND

Aside from providing clinicians with the most accurate LN staging, the therapeutic role of PLND in prostate cancer is another main issue. Some evidence suggests that ePLND might also have a positive impact on survival. Early studies suggested that radical prostatectomy and removal of involved regional LNs was beneficial for survival [62,63]. A subsequent study confirmed a 68% 10-year metastasis-free survival rate in patients with LN micrometastasis who were managed without adjuvant therapy [64], indicating that radical prostatectomy with PLND could be curative even for LN-positive disease. Theoretically, these results are supported by the fact that meticulous nodal resection removed micrometastases not detected by routine pathologic examination, which may in part be explained immunohistochemically [65]. The latter study was a careful review of 3, 914 negative nodes from 274 pT3 patients by immunohistochemical staining. The authors reported that 13.3% of 180 patients who were originally defined as being N0 actually harbored occult LN metastasis. These patients had significantly poorer survival rates than did patients who were truly LN-negative and had outcomes comparable to men who had been LN-positive on initial staging. Ferrari et al used a real-time polymerase chain reaction (PCR) assay that revealed and quantified occult micrometastases in pathologically negative LNs before primary therapy for prostate cancer [66]. Terakawa et al also found that real-time PCR increased the detection rate of LNI by more than three-fold compared with routine immunohistochemistry [67]. These authors also demonstrated a statistical correlation between occult (real-time PCR-detected) LNI and patient outcomes.

With respect to the correlation between the burden of positive node removal and prognosis following radical prostatectomy and PLND, Bader et al determined the progression and survival rates of 92 patients with positive nodes following radical prostatectomy and ePLND without adjuvant therapy [32]. Following a median follow-up of 45 months, 15 of 39 patients (38.5%) with a single positive node did not show signs of progression, whereas only 10% and 14% of patients with two or more positive LNs, respectively, remained disease free. Other studies reported the possibility of long-term survival despite the presence of limited LN metastasis with PLND and poorer prognosis with greater LN invasion [8,28,68-72]. Daneshmand et al reported that patients who had one or two positive LNs had a clinical recurrence-free survival rate of 70% and 73%, respectively, after 10 years compared with men with five or more involved nodes, who had a recurrence-free survival rate of only 49% [68]. A positive node density $<20\%$ was associated with improved disease progression rates and survival. Allaf et al reported that among men with LN-positive disease involving $<15\%$ of extracted nodes, the 5-year PSA progression-free rate for ePLND was 43% compared with 10% for the more limited PLND [69]. Boorjian et al retrospectively reviewed a large series of patients with positive LNs after radical prostatectomy and PLND with a limited number of nodes (median 11) removed and found that 56% of the patients had a 10-year biochemical progression-free survival period. A solitary LN metastasis increased the risk of cancer-specific death almost four-fold; in patients with two or more positive LNs, this was increased two-fold compared with patients with only one positive node [71]. Palapattu et al found that 52% of men with a positive node density of $<15\%$, a Gleason score ≤ 7, and no seminal vesicle invasion remained free of biochemical failure after 5 years [72].

Furthermore, in patients with pN0 prostate cancer, Masterson et al found that an increased number of nodes removed significantly correlated with the absence of biochemical recurrence [73]. Similarly, Joslyn and Konety, using the SEER database, revealed that when age, race, stage, grade, and radiotherapy were controlled for, the risk of cancer-specific death was significantly lower (23%) for patients who had more than four LNs removed [70]. Furthermore, more extensive lymphadenectomy (>10 nodes removed) was associated with a 15% lower risk of prostate cancer death even after the analysis was restricted to patients with negative lymph nodes. Early data from a recent case-control series by Heidenreich et al [28] also demonstrated a therapeutic benefit of ePLND. By comparing a cohort of 100 consecutive patients with pN0 disease who underwent lPLND with a group of 100 consecutive patients who underwent ePLND with minimum of 5 years of follow-up, the initial data obtained indicated a PSA relapse rate of 23% in the lPLND group compared with 8% in the ePLND group.

In contrast, other studies could not define the therapeutic role of PLND in prostate cancer. Bhatta-Dhar et al did not show any benefit of PLND. They retrospectively reviewed 336 patients with favorable tumor characteristics such as PSA levels of 10 ng/ml or less, biopsy Gleason scores ≤ 6, and clinical stage of T1 or T2 [60]. They determined that the 6-year biochemical relapse-free rate was not significantly different between patients who underwent PLND and those who did not. However, this study had some limitations including an absence of randomization, the lack of removal of internal iliac nodes (which is crucial in PLND), and the fact that the cohort was confined to only patients with a low risk for LN metastasis. DiMarco et al did not find improvement in prostate cancer outcomes with increasing LN yield between lPLND and ePLND in an adjuvant therapy-free cohort of 7,036 pN0 patients [74]. More recent data from Murphy et al corroborated that LN yield was not a predictor of biochemical recurrence in pN0 patients, even when the patients were stratified into high-

and low-risk groups [75]. The Weight et al study of low-risk patients suggested that there was no difference in the 10-year actuarial biochemical recurrence-free outcomes between a low-risk cohort at the Cleveland Clinic and those who underwent lPLND and no PLND based on surgeon preference [76]. Berglund et al searched the Cancer of the Prostate Strategic Urologic Research Endeavor (CapSURE) observational database to find evidence that lPLND might impact biochemical recurrence after 5 years compared with no PLND [77]. Multivariate analysis demonstrated that performance of lPLND was not a predictor of biochemical recurrence in low-risk, intermediate-risk, or high-risk groups.

Although many studies have examined the therapeutic role of PLND in treating prostate cancer, the question of whether low-risk patients benefit from PLND is still open. In contrast, men with intermediate- to high-risk prostate cancer appear more likely to benefit from ePLND, prognostically and perhaps even therapeutically. Greater nodal removal may also impact patient survival by the therapeutic effect of superior disease clearance, especially in patients with low-volume LN invasion or even in pN0 patients. In addition, removing as many nodes as possible should be the main objective of PLND for improving outcomes as well as detecting metastatic LNs.

COMPLICATIONS OF PLND

Complications of PLND include lymphocele, deep vein thrombosis, hematoma, pulmonary edema, ureteral injury, and obturator nerve injury. Complication rates for PLND range from 2% to 51% in different series [41]. The most commonly described complication is lymphocele [34,55]. Briganti et al compared the complication rates of extended (n=767) and limited (n=196) dissection and found that the lymphocele formation rates were 10.3% and 4.6%, respectively [41]. Lymphocele formation and prolonged length of stay were the only complications that were significantly higher in patients who underwent ePLND. Clark et al compared complication rates by randomly assigning 123 patients undergoing open radical prostatectomy to have ePLND on one side of the pelvis and lPLND on the other [30]. They showed that a complication rate of 10% was attributable to PLND, with complications occurring three times more often with ePLND than with lPLND. In contrast, Heidenreich et al demonstrated that the overall incidence of intra- and perioperative complications was similar for limited and extended PLND [31,78]. To avoid PLND-associated morbidity, the following suggestions have been made: (1) instead of using clips, which are often torn away during subsequent surgery, all lymphatics coming from the lower limb should be ligated; (2) all lymphatics lateral to the external artery should be saved; and (3) two drains should be placed on each side of the pelvis that are not removed until the total volume of secretion is <50 ml per day. In addition, injection of low molecular weight heparin into the arm and not the lower limb may help to reduce the incidence of lymphocele formation [79].

CONCLUSIONS

Currently, PLND is the most accurate and reliable staging procedure for detecting LNI in prostate cancer. We believe that an extended template might be appropriate for PLND in cases of prostate cancer due to higher LN yield, increased removal of positive nodes, and fewer missed positive nodes. Existing data suggest that it may be possible to refrain from performing PLND in low-risk patients with PSA levels <10 ng/ml and biopsy Gleason scores ≤ 6, but the risk of biopsy-related understaging should be noted. The therapeutic role of PLND in prostate cancer is still an open question, especially in low-risk cases. Patients with intermediate- to high-risk disease are likely to benefit from ePLND, even therapeutically.

Conflicts of Interest

The authors have nothing to disclose.

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