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Reconsideration on Clinical Benefit of Pelvic Lymph Node Dissection during Radical Prostatectomy for Clinically Localized Prostate Cancer

Keywords
Lymph node prostate cancer · Prostatectomy · Prognosis · Complication

Abstract
We conducted a review of the literature to identify the clinical benefits of pelvic lymph node dissection (PLND) during radical prostatectomy for clinically localized prostate cancer. The most recent guidelines recommend PLND, particularly extended PLND, during radical prostatectomy for localized prostate cancer. PLND is undoubtedly the most accurate method for nodal staging, and most patients, particularly those with high-risk cancer, are likely to undergo PLND during radical prostatectomy. Although many retrospective studies have assessed oncologic outcomes after PLND, its therapeutic benefit remains controversial. Patients with positive node(s) often have other more common unfavorable prognostic factors, such as seminal vesicle invasion, extraprostatic extension, and positive surgical margins. Oncologic outcomes in patients who have not undergone PLND and those who have undergone PLND are almost identical. If an effective standard adjuvant therapy after prostatectomy is defined, the nodal status may be important and valuable. However, adjuvant treatment strategies for patients with a positive node have not been identified thus far. Therefore, determining the nodal status at surgery may not provide therapeutic benefit. PLND requires additional surgical time and is associated with several complications. Therefore, the indication for PLND should be considered carefully until well-designed prospective randomized trials establish high-quality clinical evidence.

Introduction

Lymph node dissection (LND) is routinely performed during surgical procedures for various cancers, with the aim of accurate staging and direct therapeutic effect. LND also offers cosmetic benefit for patients with some cancers, such as breast and penile cancers. Recent systematic

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reviews of LND during radical surgery for patients with advanced-stage renal pelvic tumors [1] and invasive bladder cancer [2] have indicated possible benefits. LND has been shown to improve survival and provide useful information for the indication of adjuvant chemotherapy in patients with testicular and retroperitoneal cancers [3]. Nevertheless, systematic reviews have been unable to demonstrate the oncologic benefits of LND for renal cell carcinoma [4] and ureteral cancer [1].

The clinical benefit and necessity of pelvic LND (PLND) during radical prostatectomy for prostate cancer has been a topic of debate for quite a few years. The number of patients undergoing PLND is probably increasing as the anatomic template for LND widens. A study investigating outcomes in high-volume European surgical centers determined that 34.5, 64.9, and 91.2% of patients with low-, intermediate-, and high-risk cancer, respectively, underwent PLND during radical prostatectomy; however, positive nodal involvement was detected in only 6.9% (122 patients) of the cohort [5]. The EAU guidelines recommend PLND, particularly extended PLND (ePLND), for patients with intermediate- or high-risk cancers when the risk of positive nodal extension risk may exceed 5% [6]. These guidelines state that ePLND provides important information for staging and prognosis; however, its oncologic benefit is not evident based on a systematic review [7]. Fossati et al. [7] performed a detailed review of PLND during radical prostatectomy in 66 studies, which involved a total of 275,269 subjects. They concluded that although PLND was the most accurate staging procedure for prostate cancer, no therapeutic benefit or improved outcomes were observed for PLND. The AUA/ASTRO/SUO guidelines encourage the consideration of PLND for any patient with localized prostate cancer who is undergoing radical prostatectomy and for those patients with unfavorable intermediate- or high-risk prostatic disease. The guidelines also explain that evidence is lacking as to whether the removal of lymph nodes containing metastatic prostate cancer has therapeutic benefits [8]. Although these guidelines recommend PLND for the diagnosis of nodal metastasis, clinical benefit may not be provided.

Most of the published research regarding PLND has been retrospective and non-randomized in nature, yielding a low quality of evidence with a high probability of introduction of bias. The oncologic outcome in many studies has been defined as the rate of biochemical recurrence (BCR), which is not a critical condition [9–11]. Improvements in surgical techniques and supportive care measures or stage migration may affect survival data in retrospective studies (the so-called Will Rogers phenomenon) [12]. Finally, and perhaps most importantly, PLND is a time-consuming surgical procedure that is associated with lymphocele, lower leg edema, blood loss, iliac vessel injury, ureteral injury, longer operative time, and risk of extended hospital stay risk [7, 13]. These concerns and a lack of proven benefit from PLND during radical prostatectomy may mean that a substantial number of patients have an increased risk of developing complications from an unnecessary surgical procedure.

Thus, this study aimed to review published research in this area focusing on the oncologic benefit and clinical significance of PLND during radical prostatectomy. Standard nomenclature has not yet been established for PLND; therefore, we categorized the extent of PLND in this review as follows: (1) limited PLND (lPLND): obturator nodes, (2) standard PLND (sPLND): obturator and external iliac nodes, and (3) ePLND: obturator, external iliac, internal iliac, and/or other additional nodes.

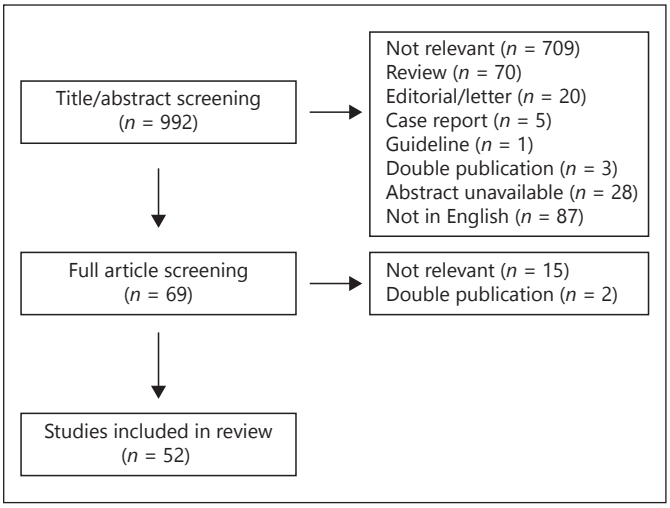

Fig. 1. Study selection flow diagram.

Materials and Methods

A PubMed search was performed to find original articles describing PLND during radical prostatectomy for prostate cancer. The keywords used were "prostate cancer," "radical prostatectomy," and "LND." Representative articles published after 2000 and essential to the aim of our review were included along with other relevant articles in reference lists. Previous reviews, duplicate publications, editorial comments, letters, single case reports, and guidelines were excluded. The language was restricted to English (Fig. 1).

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Sentinel Nodes and Anatomic Template of PLND

A pathologic examination of sentinel lymph nodes provides useful information for accurate nodal staging and aids in treatment decision-making. Further, LND could be avoided once sentinel nodes were negative for metastasis. Lymphatic drainage and the landing sites of cancer cells from the breast in patients with breast cancer were studied extensively. Thus, a sentinel node biopsy is considered the standard of care to assess the metastatic spread of breast cancer to the surrounding lymph nodes [14]. Conversely, lymphatic drainage from the prostate gland is rather complex making the identification of sentinel nodes quite difficult. Although the obturator, internal iliac, external iliac, and common iliac nodes are the most commonly identified sentinel nodes in patients with prostate cancer, lymph nodes in other anatomic sites, such as those within the presacral, pararectal, and para-aortic regions, may also serve as sentinel nodes [13].

Standard sentinel nodes and an optimal anatomic template for PLND in patients with prostate cancer are yet to be defined. Planar and single-photon emission computed tomography and magnetic resonance imaging by intraprostatic injection of Tc-99 m-nanocoloid followed by LND have shown that the primary lymphatic landing sites were often found outside the dissection area that is defined as the template for PLND [15]. Mattei et al. [16] in their study reported that only 63% of lymph nodes associated with the prostate were located within the ePLND. Other lymphatic landing sites were found in the presacral and perirectal (8%), common iliac (16%), para-aortic or caval (12%), and inguinal regions (1%) regions. Similarly, Joniau et al. [17] also identified sentinel nodes located outside the regions of the ePLND template, such as the common iliac, presacral, pararectal, para-aortic, and mesenteric fat chains. They concluded that 13% of positive nodes may have been missed by ePLND.

Diagnostic Value of PLND

Prevalence of Positive Nodes

Table 1 summarizes the prevalence of positive nodes in patients after PLND and radical prostatectomy without neoadjuvant therapy [18–44]. Positive nodes were detected in 0–37% of patients. The prevalence differed based on the risk category and extent of LND. Briganti et al. [30] reported the lymph node status obtained by ePLND in a large number of patients, regardless of prostate cancer characteristics. Of the 588 patients studied, 539 (91.6%) and 49 (8.3%) patients had no lymph node metastasis (pN0) and pN1 respectively. Among men with stage T1–2 disease, only 5.9% (33/557) had pN1. Therefore, only a small subset with low-stage cancer benefit from PLND. Among patients with stage T3 cancer or those with a primary Gleason grade >4, 51.6% (16/31) and 27% (27/100), respectively, had pN1.

Diagnostic Value

LND may provide accurate pathological information to select patients for an adjuvant therapy, for enrollment in a clinical trial, and for determination of the postoperative follow-up schedule. Nodal status would indeed be valuable if positive nodes were utilized to determine appropriate postoperative management. Messing et al. [45] demonstrated that immediate androgen deprivation therapy (ADT) after radical prostatectomy for men with lymph node-positive prostate cancer improved overall survival (OS), cancer-specific survival (CSS), and progression-free survival. Abdollah et al. [46] identified a subset of patients with pN1 who could benefit from adjuvant radiation therapy combined with ADT. This subset included men with ≤2 positive nodes, with intermediate to high-risk cancer, with disease not confined to the specimen, and with 3–4 positive nodes. Similarly, several other studies have also suggested the benefit of adjuvant radiation and ADT after radical prostatectomy [47].

Conversely, it is also important to examine the prognosis of patients with prostate cancer and known lymph node metastases and who did not undergo any adjuvant therapy. This was investigated in a study by Touijer et al. [48] who followed 369 patients with pN1 and who did not undergo any adjuvant treatment. Although the 5- and 10-year BCR-free rates were low (35 and 28%, respectively), the prognosis of these patients was good. The 5- and 10-year metastasis-free rates were 79 and 65% respectively. The 5- and 10-year OS and CCS rates were 91 and 94%, and 60 and 72% respectively. These results suggest that the most patients do not require any adjuvant therapy, even with positive lymph node metastasis detected via PLND. Other pathologic characteristics, such as grade, stage, and resection margin status, are associated with oncologic outcomes and survival statistics. Somatic genomic testing is also a powerful tool to determine prognostic markers [49]. Finally, the development of imaging studies such as prostate-specific membrane antigen positron emission tomography may improve the accuracy of lymph node metastasis [50]. Therefore, the diagnostic value of PLND may be limited and the risk may outweigh the potential benefit of procedure.

Table 1. Studies reporting PLND at radical prostatectomy without neoadjuvant therapy for clinically localized prostate caner

Study [ref.], year	Recruitment period, year	Number	Risk category	Extent of LND	Number of LN yield, median	Positive nodes, %	SV+ (or pT3b), %	ECE (or pT3a), %	PSM, %
Fergany et al. [18], 2000	1986–1999	575	Low	NR	NR	2	4	41	NR
Heidenreich et al. [19], 2002	1999–2000	103	Any	s, e	e: 28, s: 11 (mean)	e: 26.2, s: 12	NR	NR	NR
Bader et al. [20], 2003	1989–1999	367	Any	e	21	25	26.4 (pT3b)	16.3 (pT3a)	NR
Allaf et al. [21], 2004	1992–2003	4,000	Any	l, e	l: 8.9 e:11.6 (mean)	l: 1.1, e: 3.2	l: 16.9, e: 30.6	NR	l: 4.1, e: 10.6
Bhatta-Dhar et al. [22], 2004	1995–1999	140	Low	s	NR	1	4	34	NR
Schumacher et al. [23], 2006	1989–2004	231	PSA <10 ng/mL	e	NR	11	10 (pT3b)	10 (pT3a)	NR
Berglund et al. [24], 2007	NR	3,961	Any	l	Low: 5 IM: 7, H: 13	Low: 0 IM: 0.8, H: 11	NR	NR	Low: 5.7 IM: 7.4, H: 12
Schiavina et al. [25], 2011	1995–2009	567	Any	s, e	10.9 (mean)	L: 2.2% IM-H: 11.6%	Low: 5.7 IM, H: 17.5 (pT3b)	Low: 22.2 IM, H: 36.8 (pT3a)	Low: 26.9 IM, H: 26.9
Ku et al. [26], 2011	1997–2009	111	Any	s	7	3.6	22.5	57.7	45.9
Dorin et al. [27], 2012	1988–2008	2,487	Any	e	16	6	44.3	17.9	11.6
Daimon et al. [28], 2012	2002–2006	85	Low	s	NR	0	1.2	32.9	NR
Jung et al. [29], 2012	2005–2010	200	H	s, e	s: 15, e: 24	s: 5.2%, e: 22.2%	s: 9, e: 8.9	s: 38.1, e: 53.3 (pT3a)	s: 37.4, e: 55.6
Briganti et al. [30], 2012	2006–2010	588	Any	e	19	8.3	9.9 (pT3b)	NR	NR
van der Poel et al. [31], 2012	2006–2011	325	>10% LN+	s, e	9	8.3	11.0 (pT3b)	23.7 (pT3a)	NR
Sagalovich et al. [32], 2013	2010–2011		Any	l, e	Low: 5, IM: 7, H: 13	L: 0, IM: 0.8, H: 13.4	NR	NR	NR
Mitsuzuka et al. [33], 2013	2000–2009	147	Low	s	NR	0.7	1.4	NR	19
Kim et al. [34], 2013	2006–2011	464	IM, H	s, e	s: 12, e: 21	s: 3.4, e: 13.5	s: 9.2, l: 14.7 (pT3b)	s: 28.6, l: 28.8 (pT3a)	NR
Yuh et al. [35], 2013	2008–2012	406	IM, H	l, e	l: 7, e: 21.5	l: 3.9, e: 11.9	l: 11.3, e: 10.4 (pT3b)	l: 23.5, e: 16.8 (pT3a)	l: 24.5, e: 20.8
Moris et al. [36], 2016	1989–2011	1,249	H	NR	5	36.1	39.2 (pT3b)	30.7 (pT3a)	54
Furubayashi et al. [37], 2017	1998–2013	467	Any	s, e	s: 13, e: 19	s: 2.3, e: 3.6	s: 6.6, e: 4.2	s: 30.9, e: 30.1	s: 20.6, e: 15.7
Albisinni et al. [38], 2017	2004–2014	140	IM, H	e	18	15	50 (>pT3)	NR	31.4
Gandaglia et al. [39], 2017	2011–2015	94	>T3	e	16	37.2	42.6 (pT3b)	33.0 (pT3a)	32.3
Mistretta et al. [40], 2017	2009–2015	184	IM, H	s, e	s: 11 e: 21	s: 12.8, e: 29.3	s: 13, e: 21.3 (pT3b)	s: 21.3, e: 26.7 (pT3a)	NR

Table 1. (continued)

Study [ref.], year	Recruitment period, year	Number	Risk category	Extent of LND	Number of LN yield, median	Positive nodes, %	SV+ (or pT3b), %	ECE (or pT3a), %	PSM, %
Parcaro et al. [41], 2017	2013–2016	102	H	e	25	27.5	NR	NR	NR
Maderthaner et al. [42], 2018	2010–2015	754	Any	s, e	s: 23, e: 34	s: 16, e: 27	s: 30, e: 46 (pT3+4)	NR	NR
Chenam et al. [43], 2018	2008–2012	584	IM, H	l, e	l: 6, e: 20	l: 3.4, e: 15.1	NR	NR	l: 28.5, e: 20.5
Roscigno et al. [44], 2018	2009–2016	630	IM, H	e	21	21.1	NR	NR	NR

LND, lymph node dissection; SV+, seminal vesicle invasion; ECE, extra-capsular extension; PSM, positive surgical margin; IM, intermediate risk; H, high risk; l, limited; s, standard; e, extended; NR, not reported; PLND, pelvic lymph node dissection.

Table 2. Comparison of oncologic outcome

a. No PLND vs. any extent of PLND

Study [ref.], year	Outcome measure	*p* value (log-rank, *MVA)
Fergany et al. [18], 2000	BCR	0.16
Bhatta-Dhar et al. [22], 2004	BCR	0.28
Berglund et al. [24], 2007	BCR	0.11
Weight et al. [51], 2008	BCR	0.33
Porter et al. [52], 2010	CSM	0.6
Ku et al. [26], 2011	BCR	0.36
Daimon et al. [28], 2012	BCR	0.28
Mitsuzuka et al. [33], 2013	MFS	0.65
Liss et al. [53], 2013	BCR	0.294*
Gandaglia et al. [54], 2015	BCR	0.3
Karl et al. [55], 2015	BCR	0.12*
Koo et al. [56], 2015	BCR	0.08
Boehm et al. [57], 2015 (pNx vs. pN0)	BCR	<0.05
	MFS	<0.05
	OS	0.46

b. Limited/standard PLND vs. extended PLND

Study [ref], year	Outcome measure	*p* value (log-rank)
Allaf et al. [21], 2004	BCR	0.07 (pN+)
Jung et al. [29], 2012	BCR	NS
Kim et al. [34], 2013	BCR	0.497
Bivalacqua et al. [58], 2013	BCR	0.018 (pN+)
	MFS	0.035 (pN+)
	CCS	0.199 (pN+)
Hatzichristodoulou et al. [59], 2016	BCR	0.011 (pT2)
		0.3 (pT3)
Chenam et al. [43], 2018	BCR	0.1

PLND, pelvic lymph node dissection; MVA, multivariate analysis; BCR, biochemical recurrence; NS, not significant; MFS, metastasis-free survival; OS, overall survival; CCS, cancer-specific survival.

Therapeutic Value of PLND

Extent of Dissection and Oncologic Outcomes

Table 2 shows the comparison of oncologic outcomes between the different extents of PLND. In most studies, BCR-free survival rates were not improved for patients across risk groups who underwent PLND compared with BCR-free survival rates for patients who did not undergo any PNLD [18, 21, 22, 24, 26, 29, 33, 34, 43, 48–59]. Choo et al. [60] compared the oncologic outcomes between ePLND and sPLND during radical prostatectomy in patients with moderate-to-high-risk prostate cancer across 9 studies between 2004 and 2014, including >1,500 patients. The BCR-free survival rates favored patients who underwent ePLND (hazard ratio 0.71, 95% CI 0.56–0.09, $p = 0.005$). The study by Bivalacqua et al. [58] found better oncologic outcomes in patients who underwent ePLND than in those patients who underwent lPLND. At a median follow-up of 10.5 years, the 5-year BCR-free survival rates were 30.1 and 7.1% for the ePLND and lPLND groups respectively ($p < 0.018$). However, this study was limited by the decision to analyze outcomes only for the 92 patients with positive nodes, rather than for the entire cohort of 4,265 patients. Thus, this oncologic benefit was lost when analyzed using Cox proportional hazards. No statistical difference was found in CSS between the ePLND and the lPLND groups. Recent studies focusing on LND via robotic-assisted surgical procedures also failed to show favorable oncologic outcomes when compared with lPLND and sPLND [34, 51]. Most of the reviewed studies utilized BCR-free intervals rather than OS rates to determine oncologic outcomes; thus, outcomes may be less significant. No evidence to date has proven that ePLND results in better oncologic outcomes than less or no LND. Ongoing prospective clinical trials (NCT01812902 and NCT01555086) are comparing ePLND and lPLND during radical prostatectomy in patients with intermediate- and high-risk prostate cancer. These trials may identify the clinical significance of the extent of PLND during radical prostatectomy.

Number of Lymph Nodes Removed

Several studies have reported an association between the number of lymph nodes removed and oncologic outcomes. Schiavina et al. [25] reported that patients with >10 lymph nodes removed had better BCR-free survival ($p = 0.021$). The numbers of both removed lymph nodes and positive nodes were significant independent predictors of BCR in patients with intermediate- and high-risk lymph node involvement. Other studies have also found better BCR-free survival [61] or CSS [62] in patients with more lymph nodes removed.

Joslyn et al. [63] reported that when at least 4 lymph nodes (positive/negative) were removed or >10 negative nodes were removed, patients had a lower risk for prostate cancer-specific death risk at 10 years postoperatively than patients who did not undergo PLND. Although they suggested that more extensive PLND provided clinical benefit, these data should be interpreted carefully because they were obtained between 1988 and 1991 from the Surveillance, Epidemiology, and End Results Program. Furthermore, 16.2 and 64.3% of patients were classified with Gleason scores 2–4 and 5–6 respectively. These data lacked other important information, such as margin status and neoadjuvant or adjuvant therapies.

Recently, Fossati et al. [64] indicated that an increased number of resected nodes was associated with favorable outcomes following salvage radiation therapy in patients who had experienced an increased prostate-specific antigen (PSA) level after prostatectomy. Multivariate analysis demonstrated that the risk of biochemical and clinical recurrence after salvage radiation therapy was inversely associated with nodal yield at prostatectomy. Nodal yield was an independent predictor of BCR and clinical recurrence. However, the statistical difference was minimal with hazard ratios of 0.98 and 0.97 and p values of 0.049 and 0.042 for BCR and clinical recurrence respectively. The association was even weaker than that for the Gleason score, tumor stage, and PSA level at salvage radiation. The salvage radiation dose was not incorporated as a variable in multivariate analysis, but it was significantly higher ($p < 0.0001$) for patients with more nodal yield (>7) than for those with <7 nodal yield (71 Gy [interquartile range 66–76 Gy] vs. 66 Gy [interquartile range 65–66 Gy]). Conversely, the number of lymph nodes and extent of PLND did not affect oncologic outcomes [65, 66]. DiMarco et al. [66] evaluated the association between the number of dissected lymph nodes and prostate cancer outcomes in 7,036 patients with pTxN0 prostate cancer. The BCR-free, systemic progression-free, and CCS rates at 10-year postprostatectomy were 63, 95, and 98% respectively. Once prognostic factors, such as PSA, Gleason score, stage, margin status, and surgical date, were controlled, the number of lymph nodes obtained was not associated with BCR, systemic progression, and CCS. Therefore, the authors of this study concluded that removal of an increased number of lymph nodes had no clinical advantage. Pierorazio et al. [67] reviewed 505 men with node-positive prostate cancer and concluded

Table 3. Pathological characteristics in patients with node-positive prostate cancer

Study [ref.], year	Number	SV+ (or pT3b), %	ECE (or pT3a), %	PSM, %
Bader et al. [20], 2003	92	51.1 (pT3b)	16.3 (pT3a)	NR
Palapattu et al. [76], 2004	143	57.3	97.9	39.9
Daneshmand et al. [77], 2004	235	9 (pT3b)	89	44
Messing et al. [45], 2006	98	60.2	NR	64.3
Boorjian et al. [78], 2007	507	66.5	85.6 (pT3/4)	62.1
Pierorazio et al. [67], 2013	505	53.3	92.3	41.8
Bivalacqua et al. [58], 2013	94	47.9	94.7	27.7
Dorin et al. [79], 2013	150	60.7	70.6	50.7
Touijer et al. [48], 2014	369	42.8	87.3	37.4
Mandel et al. [80], 2017	706	67.3 (pT3b)	22.7 (pT3a)	50.5

SV+, seminal vesicle invasion; ECE, extra-capsular extension; PSM, positive surgical margin; NR, not reported.

that the total number of dissected lymph node was not a predictor of survival.

Some studies have suggested that PLND was associated with improved survival in patients with pN0. More extensive PLND (lymph node yield ≥11) was associated with a better cancer-specific mortality-free rate in patients without lymph node involvement (99.5 vs. 98.1%; $p = 0.01$) [68]. The survival rate in patients with pN0 was better than that in patients who did not undergo PLND (pNx), although the difference in the 15-year overall mortality was modest (34.5 vs. 35.3%) [69]. The explanation for such data is that removal of lymph nodes containing micrometastases, which are undetectable by routine pathological examination removal, may reduce recurrence and cancer-specific death risk. Miyake et al. [70] examined the micrometastases in lymph nodes dissected during radical prostatectomy by quantitative real-time RT-PCR for PSA and prostate-specific membrane antigen levels and found micrometastases in 143/619 (23.1%) of pathologically negative lymph nodes. BCR-free survival in patients with micrometastases was significantly less than in those without micrometastases. Nevertheless, not all micrometastases will progress to life-threatening cancer. The clinical significance of lymph node micrometastasis and the therapeutic benefit of negative node removal in prostate cancer, as in other types of cancer, remains under investigation [71–73].

Patients Group with the Greatest Benefit from PLND

PLND may be beneficial in patients with metastases in the pelvic lymph nodes. However, lymph node metastasis is not the only determinant of recurrence and progression. Cancer cells may remain at resection margins, in other sites, and within the lymphatic system. In addition to positive nodes, other pathologic factors, such as stage, seminal vesicle invasion (SV+), extra-capsular extension (ECE), and positive surgical margins (PSM), were associated with a poor prognosis [74, 75]. The prevalence of these unfavorable prognostic factors was more frequent than that of the positive nodal status alone. The prevalence rate of positive nodes was 0–37%. However, SV+, ECE, and PSM was noted in 1.2–51%, 10–57.7%, and 4.1–55.6% of patients, respectively (Table 1). Patients with positive nodes are also more likely to simultaneously have other unfavorable pathologic features. SV+/pT3b, ECE/pT3a, and PSM were noted in 9–67.3%, 16.3–97.9%, and 27.7–62.1% of patients with positive nodes respectively (Table 3) [20, 44, 48, 58, 67, 76–80]. PLND did not reduce BCR risk in patients with SV+ [81]. Even if all positive nodes were dissected, it was unlikely that all cancer lesions were also removed. Moschini et al. [11] analyzed the natural history of 1,011 patients with pN1 at the time of radical prostatectomy. Among them, 255 patients developed clinical recurrence. As a solitary location of recurrence, the bone was the most frequent site (55%), followed by the lymph node (34%). Jackson et al. [82] investigated anatomic patterns of clinical recurrence following salvage radiation therapy after radical prostatectomy and PLND. Salvage radiation was delivered to the prostate bed alone in men with BCR. Of 574 men, 128 developed a clinically detectable recurrence, with recurrence sites in 120 patients. Sixty-two (51.7%) patients had osteotropic disease and 34 (28.3%) patients had multifocal disease, but lymphotrophic disease was noted only in 19 (15.8%) patients. Bone marrow aspiration studies revealed that a substantial number of patients with clinically localized prostate cancer had bone marrow involvement. Köllermann et al. [83] dem-

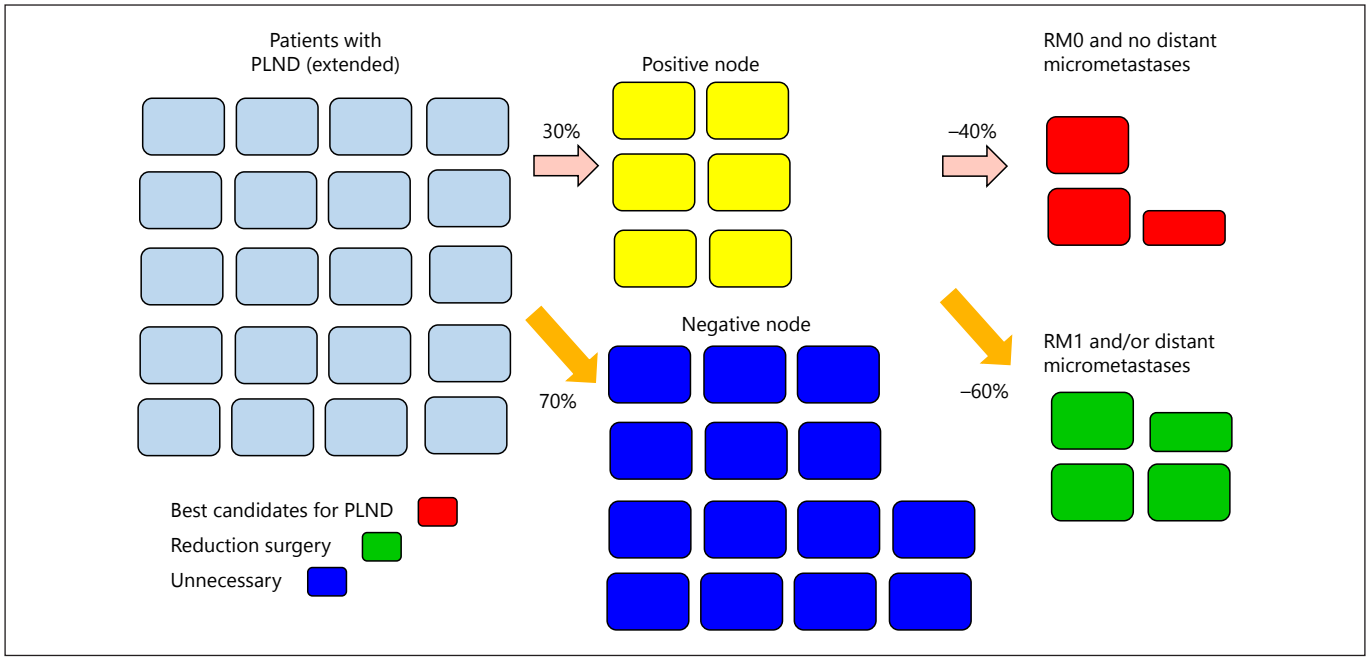

Fig. 2. Subset of patients who benefit from PLND during radical prostatectomy. PLND, pelvic lymph node dissection.

onstrated that 44.6% of patients with localized cancer (cT1-4N0M0) had prostate cancer cells within the bone marrow. Patients with positive bone marrow biopsies had unfavorable clinical outcomes compared with those patients with negative biopsies. Figure 2 shows the estimated number of patients who obtain the greatest benefit from PLND based on the clinical data in the previous reports (Tables 1, 3). Approximately 30% of patients have positive pelvic lymph nodes. Of these patients, 40% are negative for resection margin and distant metastasis. These patients should be the best candidates and obtain the greatest benefit from radical prostatectomy and PLND.

Alternatively, 60% of patients with positive pelvic lymph nodes could have PSM and/or distant micrometastases beyond the pelvic lymph nodes; thus, radical prostatectomy and PLND may not be a curative surgery in these patients.

Approximately 70% of patients who undergo PLND may be negative for pelvic lymph node metastasis. Although radical prostatectomy with PLND may be a curative surgery, PLND is unnecessary and may be harmful for these patients because the lymph nodes do not contain any cancer cells. Taken together, PLND with radical prostatectomy would be considered effective and an ideal surgery in only a small subset (10–20%) of patients with localized prostate cancer.

Local Treatments without PLND

PLND is not performed with perineal prostatectomy and/or brachytherapy or external radiation. Oncologic outcomes following these therapies are not significantly different from those outcomes following radical prostatectomy with PLND. For example, 673 patients, including 128 patients with Gleason scores >7 (19.0%) and 152 patients with stage T3–4 prostate cancer (22.6%), were treated with perineal prostatectomy and only 34 (5.1%) patients underwent PLND. With a mean follow-up of 64 months, 140 (20.8%) patients experienced BCR, with a 5-year BCR-free survival rate of 75.3%, and only 18 (2.7%) died because of prostate cancer [84]. Radiotherapy targeting the prostate ± seminal vesicle without whole pelvis irradiation or PLND achieved favorable results in patients with intermediate to high-risk cancer [85, 86].

Between 2004 and 2011, we performed open retropubic radical prostatectomy without PLND in 108 patients with clinical T1–2 prostate cancer (intermediate risk, 59 patients; high risk, 49 patients) with/without neoadjuvant ADT. None of the patients received any adjuvant therapy postoperatively. At a median follow-up of 78 months, the 5- and 10-year BCR-free survival rates for patients with intermediate- and high-risk prostate cancer were 78.2 and 66.6%, and 58.2 and 58.2% respectively. The 5- and 10-year OS rates for patients with intermediate- and high-risk prostate cancer were 96.3 and 90.3%, and 93.5 and 93.5%

respectively (unpublished data). These results indicate that patients with prostate cancer have favorable survival rates even without PLND during radical prostatectomy.

Limitations of this Review

This review has several limitations. The studies selected for this review had a certain degree of heterogeneity. PLND was performed by different surgical procedures including open, laparoscopic, and robotic-assisted surgery. Clinical and pathological analyses of lymph nodes varied among studies, due to the different imaging studies and microscopic examinations. As the patients included in this review were treated over a long period of time (1986–2015), the diagnostic accuracy of clinical stage and indication of PLND has been changed over the timeframe of this review. A high heterogeneity was also found when assessing oncologic outcomes. Patients with adjuvant hormone therapy or radiation were included in some studies, but not in others. The oncologic outcome was measured using different survivals, such as biochemical-free, metastatic-free, or CCS. OS, the most important endpoint of cancer therapy, was not assessed in any of the reviewed studies. Therefore, it was difficult to obtain evidence of the clinical benefit of PLND during radical prostatectomy.

Conclusions

Although PLND during radical prostatectomy is recommended by clinical guidelines and is undoubtedly the most accurate method for nodal staging, the therapeutic benefit remains unproven. The magnitude of clinical significance may be limited. PLND requires additional surgical time and is associated with a significant risk of complication. Until well-designed prospective randomized trials can establish high-quality clinical evidence, urologists should consider and discuss with patients the risks and benefits of PLND during radical prostatectomy.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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