A narrative review of pelvic lymph node dissection in prostate cancer

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Abstract: Pelvic lymph node dissection (PLND) is an important component in the staging and prognostication of prostate cancer. We performed a narrative review to assess the literature surrounding PLND: (I) the current guideline recommendations and contemporary utilization, (II) the calculation of patient-specific risk to perform PLND using available nomograms, (III) to review the extent of dissection, and its associated outcomes and complications. Due to the improved lymph node yield, better staging, and theoretical improvement in the control of micro-metastatic disease, guidelines have supported the use of (extended-) PLND in patients deemed to be at intermediate or high risk of lymph node involvement (often at a threshold of 5% on modern risk nomograms). However, in practice, real-world utilization of PLND varies considerably due to multiple reasons. Conflicting evidence persists with no clear oncological benefit to PLND, and a small, but important, risk of morbidity. Complications are rare, but include lymphoceles; thromboembolic events; and more rarely, obturator nerve, vascular, and ureteric injury. Furthermore, changing disease incidence and stage migration in the context of earlier detection overall have led to a decreased risk of nodal disease. The trade-offs between the benefits, harms, and risk tolerance/threshold must be carefully considered between each patient and their clinician.

Keywords: Pelvic lymph node dissection (PLND); pelvic lymphadenectomy; prostate cancer; staging; treatment

Introduction

Pelvic lymph node dissection (PLND) is an important component in the staging and prognostication of prostate cancer (1,2). Although its utilization was critical in historical series where rates of nodal metastases approached upwards of 25% (3,4), the introduction of improved screening and the earlier detection of prostate cancer has led to a dramatic stage migration and decline in the incidence of nodal involvement (5). Contemporary series now range from less than 5% to approximately 10% depending on the population (6,7). Furthermore, evidence for its therapeutic benefit has been controversial, and may be further reflective of the changing patient population with prostate cancer (1,8,9).

As a result, the benefits, harms, and utilization of PLND have evolved and must be adapted to the modern setting. The aim of this narrative review is to assess the literature surrounding PLND: (I) the current guideline recommendations and contemporary utilization, (II) the calculation of patient-specific risk to perform PLND using available nomograms, (III) to review the extent of dissection, and its associated outcomes and complications.

Indications: guidelines and real-world utilization

Currently, guidelines recommend PLND in the staging and

treatment of intermediate to high risk localized patients for the detection of nodal metastases. The European Association of Urology (EAU), European Society for Radiotherapy and Oncology (ESTRO), EAU Section of Urological Research (ESUR), and International Society of Geriatric Oncology (SIOG) guideline (10) recommends an extended pelvic lymph node dissection (e-PLND) in patients with a greater than 5% risk of nodal involvement (11-13). The American Urological Association (AUA), American Society for Radiation Oncology (ASTRO), and Society of Urologic Oncology (SUO) guideline (14) similarly recommends PLND for all intermediate to high risk patients, although consideration of PLND may be offered to any localized patient. Finally, in the National Comprehensive Cancer Network (NCCN) guideline, e-PLND is recommended at a cut-off of greater than 2% risk of nodal metastases (15,16).

Despite these recommendations however, large scale studies using administrative datasets across the United States [Surveillance, Epidemiology, and End Results (SEER); and National Cancer Database (NCDB)] indicate that practice patterns and utilization are varied, and may have further room for improvement (17). Nocera *et al.* reported that 43% of low risk patients, 75% of intermediate risk patients, and 88% of high risk patients receive PLND (18). Similarly, an analysis by Chen *et al.* found that 79% of patients with a greater than 5% risk of nodal involvement (a composite of intermediate and high risk patients) were receiving PLND with radical prostatectomy (19). Taken together, these suggest that utilization may potentially be slightly under-utilized in a small proportion of intermediate and high risk individuals, but equally importantly, potentially over-utilized in a larger proportion of low risk individuals (20). For these low risk individuals in particular, PLND may be unnecessary, comprising avoidable morbidity (21,22) in the context of no clear difference in prostate cancer specific mortality (1,23). This differential utilization in the real world compared to guideline recommendations evidences a clear gap between the identification of those who may benefit from PLND and those who ultimately receive it.

Who gets PLND: calculating patient-specific risk for nodal involvement

To this aim, numerous nomograms and/or clinical risk algorithms using clinically relevant characteristics have been developed to quantify the risk of nodal involvement and

standardize the identification of high risk individuals (24). This was first pioneered with Partin's work to establish prostate cancer staging nomogram tables beginning in the 1990s (25,26). Since then, the updated Briganti and MSK nomograms are currently recommended within the guideline statements for use (6,15,16,27-29). These nomograms demonstrate good discrimination in calibration and validation studies, with area under the curve (AUC) estimates consistently between 0.80 and 0.90 in their cohort data (27,30,31).

In practice, using Gleason grade, clinical stage, PSA, and core involvement in the updated 2017 Briganti nomogram, approximately 1% of patients with lymph node involvement would be missed while sparing 66% patients from the morbidity of e-PLND at the predominant guideline threshold of 5% predicted risk (27). However, despite their robust utility in the traditional setting and across different levels of predicted risk, these nomograms were primarily created in the era preceding routine MRI assessment and cancers detected via targeted biopsy. These contemporary patients, thus, likely have differing risk profiles relative to those identified by traditional biopsy, and question has been raised to the generalizability of these nomograms to predict patient risk following MRI detection (32). Consequently, a recent update to the Briganti nomogram has now been adapted for this setting. For these patients, at the predominant guideline threshold of 5% predicted risk, approximately 2% of patients with lymph node involvement would be missed while sparing 51% patients from the morbidity of e-PLND (7). Finally, it is important to note that different patients may exhibit different levels of risk tolerance relative to the trade-off between PLND positivity and treatment morbidity (and that different nomograms may yield different predictions of risk). In this light, any clinical decision must be made in conjunction with the patient's preferences and their own disease characteristics.

Role for imaging in risk assessment

In addition to these risk nomograms, modern imaging modalities have also been of interest for their predictive value for lymph node involvement (33). Particularly in the case of patients with a lower predicted risk (<5%) using conventional nomograms, imaging has been proposed to play a role in identifying patients who may still benefit from PLND and harbor nodal disease (34).

Here, conventional imaging traditionally has had relatively poor diagnostic accuracy: CT has a sensitivity

of 0.42 and specificity of 0.82, and MRI has a sensitivity of 0.39 and specificity of 0.82, even when assessed against an imperfect gold standard of limited-PLND (l-PLND; where the number of positive reference lesions may be understated) (23,35-37). However, novel contrast agents and molecular imaging have recently upended this paradigm, and have led to substantial interest in MRI- and PET-based imaging for lymph node staging (14,38).

In particular, superparamagnetic iron oxide (SPIO) MRI has greatly improved the detection over conventional MRI, and PSMA-based PET tracers have demonstrated promising results amongst existing ligands (35,39,40). The recent proPSMA study by Hofman *et al.* demonstrated the superior diagnostic accuracy of PSMA PET-CT scan in high risk patients with an overall sensitivity of 85% and specificity of 98% (83% and 99% in pelvic nodal disease, respectively) (41). Although a direct comparison cannot be drawn, these imaging techniques may yield even greater sensitivity than PLND alone, in addition to the benefits of detecting distant metastases outside of the treatment field. Moreover, when these imaging tests are combined with emerging techniques for sentinel node biopsy and radio-guided targeting (e.g., indocyanine green), small scale studies have suggested that almost all patients are correctly identified versus e-PLND management: 100% sensitivity, 94% accuracy (42). Taken together and with appropriate patient selection, these may represent less-invasive staging options in the future.

However, at the current time, the majority of the evidence for these remains limited with substantial heterogeneity amongst the diagnostic accuracy and predictive value with these techniques, often ranging by up to an order of magnitude in retrospective and small scale studies (2,43). Furthermore, the clinical significance of nodal deposits detected on novel imaging at time of staging remains to be elucidated, and its ultimate impact, if any, on prognosis is unknown. As a result, these have yet to be formally incorporated into widescale practice and guideline adoption.

Extent of dissection

Differing limits to the extent of dissection in PLND have been described, ranging from l-PLND (obturator nodes only) to standard PLND (s-PLND; obturator, and external iliac nodes), e-PLND (obturator; external and internal iliac nodes), and super-extended PLND (se-PLND; obturator; external, internal, and common iliac; pre-sacral; other)

(1,44). Where available, limited randomized comparisons have been reported. However, differing definitions/ terminology are often used interchangeably across the study literature (e.g., substituting e-PLND with se-PLND) or are not documented, and significant heterogeneity limit their direct comparison in outcomes assessment. Additionally, studies are mostly retrospective, and from a single institution/single operator, further limiting their generalizability and must be taken with a grain of salt (1).

Potential oncologic benefits

To date, randomized data have demonstrated a significant detection benefit for e-PLND/se-PLND over more limited dissections: gross lymph node yield is improved, and detectable lymph node metastases are increased (45-47). In a contemporary cohort from the randomized, phase III trial by Lestingi *et al.*, (s)e-PLND yielded a median of 17 nodes versus 3 from l-PLND, and detected 6 times more nodal metastases (45). Nevertheless, despite the improved performance on staging and prognostication, no therapeutic benefit was garnered with similar rates of biochemical recurrence and increased complications. These findings are echoed in a recent systematic review of 66 studies by Fossati *et al.*: no benefit was seen across biochemical recurrence, progression to distant metastases, cancer specific or overall survival with PLND; in a European multi-institutional retrospective study by Preisser *et al.* demonstrating no difference in oncologic outcomes; and in a large propensity-matched SEER analysis in 2019 by Chen *et al.* where neither those who received versus those who didn't receive PLND, nor the extent of PLND affected cancer specific or overall survival (1,19,48). Notably, many of these studies were confounded by substantial selection bias (in the case of the cohort studies) or with limited follow-up (in the clinical trials). On the other hand, lymph node yield itself, and thereby extent of PLND, has previously been found to predict the risk of 10-year prostate cancer specific mortality since a landmark historic SEER analysis (49), and at least conceptually, the removal of lymph nodes and potential sources of micro-metastatic disease may lead to theoretical benefit. On balance of these conflicting and controversial data however, convincing evidence of therapeutic benefit with PLND has not been demonstrated.

Risk of complications

Despite not demonstrating a clear benefit to oncological

outcomes, morbidity associated with PLND is not uncommon (8,50). The degree of complications are highly variable and correlate to the extent of dissection, remaining a significant consideration when performing PLND (8,51,52). The predominant complications include lymphocele, thromboembolism, obturator injury, ureteric injury, and vascular injury (22).

Lymphoceles are a common complication following PLND, and are positively associated with a greater extent of dissection (52,53). In a contemporary series, Keskin *et al.* noted that 9% of patients experienced a lymphocele after e-PLND (54). However, only 2.5% were symptomatic. This proportion underscores the issue: data series with reflexive post-operative imaging have demonstrated that the post-operative incidence of lymphoceles may be as high as 22% to 54%, yet only a small proportion will ever become symptomatic and cause morbidity (55-58).

Similarly, thromboembolic events remains a fairly rare occurrence: only a small percentage of these (0.3–0.5%) are symptomatic and/or require treatment, although the incidence of subclinical events is higher (59,60). As such, routine pharmacological prophylaxis is not currently recommended in low risk (for thromboembolism) patients with PLND, but may be used for patients at intermediate risk (indicated for e-PLND only) and high risk (indicated for s-PLND and e-PLND) (61,62). For all patients with PLND, mechanical prophylaxis is recommended.

The obturator nerve may be clipped or injured as part of PLND in crush, thermal, and transection injuries (63,64). Although a rare complication, these can lead to significant sensory (medial thigh) and motor (adduction) impairments in the post-operative period, requiring intensive physiotherapy, and if recognized, surgical repair or removal of the offending clip (65,66). In one of the largest consecutive contemporary cohorts of 3,558 laparoscopic and robotic cases, Gozen *et al.* reported 5 cases (0.1%) of obturator nerve injury (67). In 3 cases, clips were removed, and in the other 2 cases, the transected nerve was repaired intra-operatively. Prolonged physiotherapy, pain management, and vitamin B6 were required, but no long-term deficits were noted at follow-up. Finally, ureteric and vascular injuries (<1% each) are extremely rare, but significant complications associated with PLND (50). These are often immediately recognized and repaired at the time of OR (8).

Conclusions

PLND is a common and indicated procedure in patients with intermediate to high risk for nodal involvement of their prostate cancer. For these individuals, e-PLND remains the recommended approach due to the improved lymph node yield, better staging, and theoretical improvement in the control of micro-metastatic disease, although the data surrounding the oncological benefits of PLND and its extent remain controversial. Complications are rare for PLND; however, changing disease incidence and stage migration in the context of earlier detection have led to a decreased risk of nodal disease; and the trade-offs between the benefits, harms, and risk tolerance/threshold must be carefully weighed for each patient.

Footnote

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