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Platinum Opinion

Pelvic Lymph Node Dissection in Prostate Cancer: Evidence and Implications

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1. Why perform pelvic lymph node dissection?

Pelvic lymph node dissection (PLND) performed during radical prostatectomy (RP) has been recommended for many years by international guidelines, including previous editions of the EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines, for staging purposes and a potential oncological benefit. An extended PLND (ePLND) template detects more metastases than a standard template and so is recommended by the guidelines when PLND is deemed necessary. ePLND staging information can ideally assist with postoperative counselling, as the presence of lymph node metastases is one of the strongest predictors of adverse oncological outcomes, and prognostic insights from ePLND histopathology can help in guiding patient selection for adjuvant therapies, which may improve survival [1]. However, an oncological benefit of ePLND has not been supported by results from randomised controlled trials. Lestingi et al [2] showed that ePLND detected six times more lymph node (LN) metastases than limited PLND (lPLND), but there was no therapeutic benefit, with similar rates of biochemical recurrence (BCR) and a higher rate of complications. The LN yield with lPLND was low (median 3) in comparison to ePLND (median 17), and the incidence of salvage therapies was numerically higher in the lPLND group, representing limitations to consider. A European multi-institutional retrospective study by Preisser et al [3] suggested no benefit for patients who received PLND in comparison to those who did not. In addition, the extent of PLND did not seem to make a difference in terms of cancer-specific or overall survival, in contrast to smaller retrospective studies that suggested that a higher LN yield and adjuvant radiotherapy were associated with lower cancer-specific mortality. Touijer et al [4] found no difference in BCR rates between lPLND and ePLND groups, and the number of LNs removed only differed by two between the groups. A recent update revealed a lower rate of distant metastases in the ePLND group [5]. However, interpretation of this secondary outcome in a trial that failed to meet its primary outcome and its relevance are uncertain for many reasons as discussed in a separate publication a separate publication [6].

There are limitations of ePLND. First, the perioperative risks and harms are well established, including complications (in up to 20% of patients), a longer operating time (with associated anaesthetic and positional risks), thromboembolic disease (6–10-fold increase), lymphocele formation, and potentially a longer hospital stay [6]. Morbidity in the long term includes a sixfold higher risk

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of severe lower-limb and genital lymphoedema at 3 mo (13.7%). Significantly worse quality of life (adjusted for incontinence and erectile dysfunction) ensues out to 24 mo (4–5% for ePLND vs 0.5–1.5% for no ePLND). Furthermore, patients who receive both ePLND and postoperative pelvic radiotherapy (a common scenario in high-risk disease) are more likely to suffer lower-limb or genital lymphoedema in comparison to either treatment modality in isolation [6]. Finally, prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT) scans have revealed greater incidence of positive LNs outside the classical templates than previously realised [7]. Development of novel metastases and persistence of in-field pelvic LN metastases after ePLND have also been reported [8]. This continuum can affect ePLND outcomes, as shown by Meijer et al: among patients with preoperative PSMA PET suggestive of nodal disease (miN1) and postoperative PSMA PET indicating biochemical persistence, 81% had postoperative miN1 disease, comprising persistent (present on both preoperative and postoperative PSMA PET; 57%) and new (24%) metastases. Similar cases were observed in the prospective trial by Hope et al [8]. Strategies to limit these "technical failures" are under investigation, including radioguided surgery, but the curative potential of local therapies may be limited, as recurrence rates are high and presence outside templates indicates nonlocalised, systemic status of node-positive disease at diagnosis.

PSMA PET/CT is noninvasive with high specificity (95%) for detection of LN metastases (per molecular imaging; miN1) in intermediate- and high-risk disease [9]. In addition, miN1 status on PSMA PET/CT often indicates which patients harbour a greater total number of LN metastases (median 2; interquartile range [IQR 1–3] vs 1, IQR 1–2; $p = 0.005$) and larger metastatic LN size (median 6 mm, IQR 4–10 vs 3 mm, IQR 2–5; $p < 0.001$) according to ePLND histology in comparison to patients with miN0 PSMA PET/CT results [10,11]. The extent of miN1 disease on PSMA PET may be prognostic. Meijer et al [12] found that both two or more LN metastases (odds ratio [OR] 5.7, 95% confidence interval [CI] 3.6–9.0; $p < 0.001$) and one LN metastasis (OR 3.06, 95% CI 1.9–4.9; $p < 0.001$) resulted in worse biochemical progression–free survival in comparison to none (miN0). In addition, the group with two or more LN metastases had a shorter median time to biochemical progression than the group with one LN metastasis (4.1 vs 12.0 mo; p = 0.05). However, despite better detection of LN metastases, PSMA PET/CT still misses small-volume deposits below the spatial resolution of the scanner (approx. 5 mm) [9]. As a consequence, it is clear that PSMA PET/CT scans provide additional information to guide patient management, but may be limited by sensitivity, costs, and availability.

2. Patient selection for PLND

Validated nomograms based on preoperative information have been used to individualise patient selection for ePLND for more than 20 yr to overcome the limitations of conventional imaging (CT, magnetic resonance imaging [MRI]) in terms of sensitivity. Different nomogram cutoffs have been proposed to maximise capture of patients who are likely to have pN1 disease while trying to avoid routine PLND in all patients. Historically, nomogram cutoff ranges of 5–7% were proposed and could result in avoidance of up to 80% of ePLND procedures for similar numbers of patients with pN1 status (up to 30% after ePLND; ~6% overall). Novel nomograms that incorporate imaging (MRI, PSMA PET/CT) serve to further improve patient selection and can significantly reduce the number of ePLND procedures [13]. These might be particularly relevant when negative PSMA PET/CT findings mean that clinicians have to weigh up the possible advantage of detecting low-volume nodal disease via ePLND and how this may impact postoperative management against the risks and harms associated with ePLND. PSMA PET/CT is characterised by a high negative predictive value when the risk of LN invasion is low [9]. Therefore, ePLND can be avoided when risk is low and PSMA PET/CT imaging is negative [14]. Surgeons may consider staging ePLND for selected patients with high-risk aggressive disease who might harbour micrometastatic LN invasion.

An alternative option would be to avoid ePLND and accept the possibility of requiring whole-pelvis radiotherapy for men with persistent prostate-specific antigen (PSA) after RP despite no evidence of metastatic disease on recent PSMA PET/CT imaging. Accumulating data from randomised trials support postoperative whole-pelvis radiotherapy with systemic therapy for recurrent disease after RP [15]. Radiotherapy fields encompass wider coverage than ePLND templates, so may treat all potential pelvic metastases. However, intensified postoperative treatment (in comparison to prostate bed–only radiotherapy) can result in higher toxicity. It is unclear whether ePLND first with a subsequent adjuvant/salvage approach, or no ePLND with PSA- or imaging-guided postoperative treatment is superior in terms of oncological outcomes.

3. The 2024 EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines Panel position

The prior "strong" recommendation to perform ePLND because of its ability to accurately stage disease was revisited following review of the available evidence and consideration of risk/benefit ratio. The change in recommendation in 2024 was driven in part by the decision to recommend PSMA PET for staging assessment of patients before treatment. PSMA PET/CT is highly specific but with a negative predictive value of approximately 80% [8,9], where most of missed metastases are low volume (number of affected nodes, size of nodal deposits). However, its ability to identify additional lymph-node deposits beyond conventional imaging reduces the gap between imaging and pathological staging to fundamentally alter the risk/benefit ratio. Despite some staging advantages, it is difficult to define which patients may benefit from ePLND owing to the lack of proof of an oncological benefit, with a significant risk of morbidity. We expect that clinicians will use their discretion and discuss the uncertainty with patients before offering ePLND in accordance with the standard medical principle of "Primum non nocere".

Conflicts of interest: The authors have nothing to disclose.

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