



Open to Debate – Referee

Pelvic Lymph Node Dissection at the Time of Radical Prostatectomy: Extended or Not. The Referee Point of View

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1. Introduction

Performance of pelvic lymph node dissection (PLND) and the appropriate extent of dissection during prostatectomy remains a point of controversy in contemporary clinical practice. Although PLND provides valuable staging and prognostic information that may inform further treatment decisions, the therapeutic benefit remains unproven. Guidelines published by both the European Association of Urology [1] and the National Comprehensive Cancer Network [2] recommend an extended PLND (ePLND). However, the American Urological Association (AUA) guidelines do not recommend one PLND template over the other and balance the risks and benefits of each approach [3]. This discordance is clearly reflected by the wide variability in practice patterns seen among uro-oncologists in North America [4] and the UK. In this Open To Debate series, our aim is to objectively balance the pertinent arguments presented in favor of ePLND by Gandaglia et al. [5] and against it by Sooriakumaran et al. [6].

2. Staging

The value of prognostication and expedient diagnosis of postprostatectomy early nodal invasion was addressed by both groups, and both agree that PLND is the most reliable staging procedure [5,6]. Several studies have demonstrated that the quality of nodal staging is closely associated with the anatomical extent of PLND, with an almost linear relationship between the number of nodes removed and the probability of detecting nodal metastasis [7–10].

This accumulated knowledge was developed on the basis of conventional preoperative imaging. In this debate, both sides accept the limitations of cross-sectional imaging and agree that the advent of molecular imaging will force a paradigm change. Prostate-specific membrane antigen (PSMA) positron emission tomography (PET) has superior diagnostic utility for primary staging in comparison to conventional imaging, allowing detection of nodal metastases before development of the morphological changes required for diagnosis via conventional imaging [11,12]. However, in the micrometastatic disease setting, the sensitivity of PSMA is poor, particularly when nodal disease is <5 mm [13]. Gandaglia and colleagues [5] see this as a factor limiting the substitution of PSMA-based staging with PLND. Sooriakumaran et al. [6] cast doubt on the prognostic significance of micrometastatic nodal metastasis. They propose omission of PLND when PSMA imaging is negative and patient treatment with salvage radiation therapy if they experience recurrence.

Given the increasing utilization of active surveillance in the setting of low-risk disease and the fact that the median size of nodal metastatic focus is 3 mm (interquartile range 2–6) in modern series [14], it is clear that the low sensitivity

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of PSMA imaging in detecting smaller nodal metastases will hinder its use as a substitute to PLND. Currently, this question has yet to be addressed in a prospective clinical trial. In the meantime, as suggested in the debate, the integration of PSMA findings might improve the predictive accuracy of preoperative nomograms. The high specificity of PSMA imaging and, most importantly, its ability to detect nodal metastasis outside of the limits of ePLND will in fact push for an even wider anatomical limit of ePLND and is likely to usher in an era of image-guided PLND or PSMA-based theranostics for detection of nodal metastases. The value of these innovative approaches is currently under investigation [15,16].

3. Therapeutic benefit

Regarding the oncological benefit of PLND, Sooriakumaran et al. [6] suggest that missed micrometastatic disease, particularly in the era of PSMA imaging, is of little consequence, as these patients may receive salvage whole-pelvis radiotherapy should recurrence occur. This is an interesting strategy, but this hypothesis has not yet been tested. To this effect, Gandaglia et al. [5] argue that ascertainment of pathological nodal status can prompt adjuvant therapy and they suggest that the results from the RADICALS-RT, GETUG-AFU 17, and RAVES trials, testing the role of adjuvant versus early salvage radiotherapy, may not be applicable to patients with pN1 disease, as such patients were not included according to the inclusion criteria for these trials. However, it should be noted that PLND for staging was not mandated in these trials. For example, patients staged as pNx were eligible for the GETUG-AFU 17 trial and indeed accounted for 27% of patients in the adjuvant group and 29% in the early salvage group [17]. Similarly, in the RADICALS-RT trial, 44% of the cohort did not undergo PLND. Adjuvant hormonal and radiation therapy prolonged survival over observation or hormonal therapy alone. However, this observation has not been confirmed prospectively.

Two randomized clinical trials comparing ePLND to limited PLND [18,19] recently failed to show any benefit in terms of biochemical recurrence (hazard ratio [HR] 1.044, 95% confidence interval [CI] 0.93–1.15; $p = 0.5$ [18]; HR 0.91, 95% CI 0.63–1.32; $p = 0.6$ [19]). Gandaglia et al. [5] suggest that the oncological benefit might not have been demonstrated owing to the inclusion of lower-risk disease, short follow-up, and the variability of the anatomic extent of ePLND. We do agree that across various specialties randomized trials comparing limited PLND to ePLND are challenging and suffer from lack of blinding, lack of statistical power, or lack of precision for the therapy delivered. We do not consider the results of the above-mentioned trials as a moratorium on ePLND but rather a demonstration that comparison of PLND versus no PLND is a better design to answer the elusive question of therapeutic benefit of lymphadenectomy in prostate cancer. Such a trial is under way at Memorial Sloan Kettering Cancer Center (MSK) [20,21].

4. Morbidity

As with any increasingly extensive resection, ePLND is associated with higher costs and morbidity. Both Sooriaku-

maran et al. [6] and Gandaglia et al. [5] appropriately acknowledge this issue, citing a longer operative time and a higher risk of complications in up to 15% of patients, including lymphocele, lymphorrhea, lower limb lymphedema, thromboembolism, and ureteral injury [22,23]. Indeed, data from studies comparing the extent of nodal dissection at MSK suggest that performance of PLND versus no PLND is associated with higher rates of the aforementioned complications [24]. However, this analysis did not show that morbidity would be improved by limiting the extent of PLND, with rates Clavien Dindo grade ≥ 3 complications of 4% in the limited group versus 4.5% in the ePLND group. Similarly, data from randomized trials did not reveal a clinically significant difference between PLND templates [18].

5. Conclusions

ePLND is the most reliable staging procedure. The information obtained from nodal staging can help in guiding further therapy. However, ePLND is associated with a higher risk of complications. The risk/benefit trade-off is unclear, since the therapeutic benefits of ePLND remain unproven. Clinical trials comparing ePLND versus no lymphadenectomy are under way. PSMA PET imaging will impact the indication for and extent of PLND. This impact needs to be carefully investigated.

Conflicts of interest: Karim A. Touijer is co-inventor of intellectual property focused on tumor imaging nanoparticle technology licensed to Elucida Oncology. Marlon Perera has nothing to disclose.

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