HHS Public Access

Author manuscript

J Urol. Author manuscript; available in PMC 2024 August 01.

Published in final edited form as:

J Urol. 2023 August ; 210(2): 244–246. doi:10.1097/JU.0000000000003494.

Point: Radioisotope-guided lymphadenectomy for pelvic node staging – The SENTINELLE study

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Keywords

PSMA; PLND; prostate cancer

Pelvic lymph node dissection (PLND) at the time of radical prostatectomy remains the most accurate procedure for lymph node staging in prostate cancer. However, the question about its therapeutic benefit remains unanswered and a point of controversy in contemporary clinical practice. Two recently published randomized clinical trials failed to demonstrate a benefit in terms of biochemical recurrence when comparing extended to limited PLND templates (HR 1.044, 95% CI 0.93-1.15, p=0.5) and (HR 0.91. 95% CI 0.63-1.32, p=0.6)[1, 2]. A third more definitive trial comparing PLND to no PLND is currently underway[3, 4].

Determining the status of the pelvic lymph nodes informs therapeutic decision-making, such as initiation of adjuvant hormone and radiation therapy, a strategy shown to improve survival in men with node-positive prostate cancer[5]. However, this potential benefit must be weighed against the potential for a higher risk of PLND associated complications such as symptomatic lymphocoeles, venous thromboembolic events, ureteral injury or to a lesser degree lower limb lymphedema[6, 7]. Investigations aimed at optimizing locoregional staging for prostate cancer, while limiting the potential morbidity are important.

We read with interest the results of the SENTINELLE study, published by Lannes et al, a single-arm, open-label study assessing the diagnostic utility of sentinel lymph node biopsy against the gold-standard of extended template PLND (ePLND). The investigators recruited 162 patients with intermediate- and high-risk prostate cancer, with no evidence of metastatic disease based on conventional imaging (computerized tomography and bone scan). Intraprostatic administration of ^{99m}Tc-nanocolloid was performed, followed by SPECT-CT to define the relevant sentinel node. Intra-operative gamma probe was utilized to locate the sentinel node, which was identified in 142/162 (94.4%) patients. A mean of 5 sentinel nodes per-patient were identified. these were primarily located in the obturator fossa (21.5%), internal iliac (20.8%), external iliac (13.45) or common iliac regions (17.9%). Compared to ePLND, 141/142 patients were correctly staged with sentinel node biopsy, and one patient was classified as a false negative. Resulting sensitivity, specificity, negative

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predictive value and positive predictive value were 95.4% (95% CI 75.1-99.7), 100% (95%CI 96.6-100), 99.2% (95%CI 95.5-99.2) and 100% (95%CI 80.7-100). Given all patients received sentinel node biopsy and ePLND, the morbidity of the sentinel node biopsy could not be discerned.

The SENTINELLE study reports favorable diagnostic utility for nodal staging, when compared to the reference of ePLND. However, unlike other malignancies, lymph node mapping studies in prostate cancer have failed to identify a specific “gatekeeper” sentinel node for the metastatic spread of prostate cancer. In the study by Jeshke et al using technetium-99 and indocyanine green (ICG) as tracers, a median of 10 sentinel lymph nodes per patient were identified[8]. Other studies using ICG only have shown different frequencies of distributions of the lymph node mapping, with dominant sites varying from the external iliac and common iliac to the obturator fossa and external iliac.[9, 10]. Using a non-cancer targeting tracer merely shows the lymphatic drainage of the prostate rather than the patterns of metastatic spread to the lymph nodes. Often the distribution of technetium-99 is affected by the injection technique and the size of the associated colloid in the mix.

Prostate-specific membrane antigen (PSMA) Positron Emission Tomography (PET) has superior diagnostic yield for primary staging compared to conventional imaging. It enables the detection of nodal metastatic disease prior to the development of the morphologic changes required for diagnosis on conventional imaging[11, 12]. Maurer et al provided an early report of the diagnostic performance of ^{68}Ga-PSMA PET compared to PLND [13]. On per-nodal analysis, the resulting sensitivity, specificity, negative predictive value and positive predictive value were 65.9%, 98.9%, 86.3% and 96.4%, respectively. A subsequent systematic review and meta-analysis of ^{68}Ga-PSMA PET by Perera et al reported a sensitivity and specificity of 77% (95%CI 46-93) and 97% (95%CI 91-99) on pooled analysis[12, 14]. Similar analyses have been performed with alternate PSMA-based tracers including ^{18}F-DCFPyL-PSMA PET, as reported in the OSPREY trial which reported a sensitivity, specificity, negative and positive predictive value of 40.3%, 97.9%, 83.2% and 86.7%, respectively[15]. Despite the superiority of PSMA PET over conventional cross-sectional imaging, several limitations exist regarding its diagnostic performance. For example, in the setting of micrometastatic disease the sensitivity of PSMA is poor – particularly when the metastatic node is <5mm[15]. Specifically, in the aforementioned OSPREY trial, when metastases <5mm were excluded, sensitivity improved from 40.3% (95%CI 28.1-52.5) to 60.0% (43.8-76.2) and specificity was preserved at 97.9% (95% CI 94.5-99.4). It must also be recognized that the interpretation and analysis of PSMA PET is non-uniform due to the variations in the definitions of ‘positive’ PSMA avid lesions that exist. While in other modes of PET, such as fluorodeoxyglucose (FDG), a threshold of SUV is frequently utilized, this measure has not been validated in the setting of PSMA PET. Current recommendations published in the aPROMISE system recommends comparison SUV uptake of a lesion in reference to liver or parotid uptake to classify as positive. With the accumulated experience, we will likely see more standardization and further improvement in the diagnostic characteristics of PSMA PET[16, 17].

Given the aforementioned PSMA imaging characteristics, the low sensitivity will hinder the possibility of foregoing a PLND when the PSMA is negative. As a number of patients

with nodal micrometastatic disease will go undiagnosed. In such a scenario, the possibility of salvage whole-pelvis radiotherapy should recurrence occur, is an interesting strategy that has yet to be tested. 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 even wider anatomical limit of ePLND and likely usher us in an era of image-guided PLND or PSMA-based theranostics of nodal metastases. The value of these innovative approaches is currently under investigation [18, 19]. Using a predetermined anatomical template for all patients undergoing a radical prostatectomy and establishing the ePLND as the gold standard is now shown to be a flawed concept as the PSMA PET shows that up to 40% of the nodal metastasis fall outside of the ePLND limits[20]. The value of Preoperative PSMA PET imaging is a better understanding of the metastatic spread of prostate cancer and providing a roadmap to a more thorough pelvic lymph node dissection tailored to the specifics of each prostate cancer patient.

Funding:

This work was supported by the Sidney Kimmel Center for Prostate and Urologic Cancers at MSK, NIH/NCI grant P50 CA092629, and the NIH/NCI Cancer Center Support Grant to Memorial Sloan Kettering Cancer Center (P30 CA008748). Marlon Perera is sponsored by the Australian-America Fulbright Commission administered through a 2021–2022 Fulbright Future Scholarship funded by The Kinghorn Foundation.

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