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European Association of Urology

Review – Prostate Cancer

Sentinel Node Procedure in Prostate Cancer: A Systematic Review to Assess Diagnostic Accuracy

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Article info

Article history:
Accepted September 2, 2016

Associate Editor:
Giacomo Novara

Keywords:
Prostate cancer
Sentinel node
Targeted lymph node biopsy
Pelvic lymph node dissection
Diagnostic accuracy
Systematic review

Abstract

Context: Extended pelvic lymph node dissection (ePLND) is the gold standard for detecting lymph node (LN) metastases in prostate cancer (PCa). The benefit of sentinel node biopsy (SNB), which is the first draining LN as assessed by imaging of locally injected tracers, remains controversial.
Objective: To assess the diagnostic accuracy of SNB in PCa.
Evidence acquisition: A systematic literature search of Medline, Embase, and the Cochrane Library (1999–2016) was undertaken using PRISMA guidelines. All studies of SNB in men with PCa using PLND as reference standard were included. The primary outcomes were the nondiagnostic rate (NDR), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and false positive (FP) and false negative (FN) rates. Relevant sensitivity analyses based on SN definitions, ePLND as reference standard, and disease risk were undertaken, including a risk of bias (RoB) assessment.
Evidence synthesis: Of 373 articles identified, 21 studies recruiting a total of 2509 patients were eligible for inclusion. Median cumulative percentage (interquartile range) results were 4.1% (1.5–10.7%) for NDR, 95.2% (81.8–100%) for sensitivity, 100% (95.0–100%) for specificity, 100% (87.0–100%) for PPV, 98.0% (94.3–100%) for NPV, 0% (0–5.0%) for the FP rate, and 4.8% (0–18.2%) for the FN rate. The findings did not change significantly on sensitivity analyses. Most studies (17/22) had low RoB for index test and reference standard domains.
Conclusions: SNB appears to have diagnostic accuracy comparable to ePLND, with high sensitivity, specificity, PPV and NPV, and a low FN rate. With a low FP rate (rate of detecting positive nodes outside the ePLND template), SNB may not have any additional diagnostic value over and above ePLND, although SNB appears to increase nodal yield by increasing the number of affected nodes when combined with ePLND. Thus, in high-risk disease it may be prudent to combine ePLND with SNB.
Patient summary: This literature review showed a high diagnostic accuracy for sentinel node biopsy in detecting positive lymph nodes in prostate cancer, but further studies are needed to explore the effect of sentinel node biopsy on complications and oncologic outcome.

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http://dx.doi.org/10.1016/j.eururo.2016.09.007
0302-2838/

1. Introduction

According to European Association of Urology guidelines, the risk of nodal metastases in prostate cancer (PCa) is 20–45% if any biopsy core has predominant Gleason 4 pattern or more than three cores have any Gleason 4 pattern. For detection of lymph node (LN) metastases via imaging, the sensitivity of abdominal computed tomography (CT) and multiparametric magnetic resonance imaging (mpMRI) is <40% [1]. In addition, ^{11}C- or ^{18}F- choline- and ^{68}Ga–prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/CT provide low estimated sensitivity of 49–66% in detection of LN metastases before treatment of PCa [2,3]. For this reason, patients with intermediate- and high-risk disease with a risk of nodal metastases >5% (Briganti nomogram or Memorial Sloan Kettering Cancer Center nomogram), extended pelvic lymph node dissection (ePLND) is the preferred staging tool [1,4]. Unfortunately, ePLND is also associated with intraoperative and postoperative complications [5].

Advantages of targeted dissection of tumor-associated LNs include tailoring of the surgical procedure to the individual patient, with potentially more accurate staging and lower morbidity [6,7]. For malignancies such as breast cancer, penile cancer, and melanoma, sentinel node biopsy (SNB) has become routine for nodal staging as it helps in distinguishing patients who need extensive nodal dissection from those who would not gain an oncologic benefit from such dissection. SNB in PCa is still considered experimental, as the lymphatic drainage for the prostate gland is highly variable and complex. Knowledge about lymphatic drainage is crucial for detection of sites of LN metastases. There are four pelvic lymphatic drainage pathways known for PCa. The main route of drainage is the lateral route to the medial chain of the external iliac nodal group (ie, obturator nodes), spreading from there to the middle and lateral chains of the external iliac nodes. The second route of drainage is the internal iliac route, via LNs positioned along the visceral branches of the internal iliac vessels. Some lymphatic drainage occurs along an anterior route, via LNs located anterior to the urinary bladder. The last possible drainage pathway is a presacral route anterior to the sacrum, coccyx, and perirectal lymphatic plexus, subsequently ascending to the lateral sacral nodes and those at the sacral promontory (ie, medial chain of common iliac nodes) [8].

Since 1999, when the first SNB for PCa was performed by Wawroschek et al [9], various techniques have been developed to identify SN in PCa. A separate review performed by our team revealed significant heterogeneity of definitions regarding SN, radiotracers, size and radioactivity dose of the tracer, tracer administration, use of preoperative imaging, and intraoperative detection of SNs [10]. So far, there is no consensus on the definition and optimal SN technique, or on the diagnostic role of SN in PCa patients.

The aim of this systematic review was to assess the diagnostic accuracy of SNB in PCa as reported in the literature. The results will be used to develop consensus statements on how to optimally perform SNB in PCa in order to guide clinical practice and further research.

2. Evidence acquisition

2.1. Search strategy

The protocol for the review has been published elsewhere (www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016037679). We used standard methods recommended by the Cochrane Methods Group for Systematic Review of Screening and Diagnostic Tests [11], Preferred Reporting Items for Systematic Reviews (PRISMA) [12], and Standards for Reporting Diagnostic Accuracy Studies (STARD) [13]. Databases including Medline, Embase, and the Cochrane Central Register of Controlled Trials were searched systematically from January 1, 1999 to May 31, 2016. The search was complemented by additional sources including reference lists from the studies included. Only English language articles were included. The search terms were *prostatic neoplasms*, *prostate*, *carcinoma*, *sentinel lymph node biopsy*, and *lymph node excision/dissection*. The full search strategy is outlined in the Supplementary material.

All abstracts and full-text articles were independently screened by two reviewers (EW and CA). Disagreement was resolved by discussion or with an independent arbiter (HvdP or TBL). Exclusion criteria were animal studies, reviews, historical overviews, editorials, SNB in other cancers, analysis of SNB techniques in different types of cancer, studies on the effectiveness of SPECT/CT and/or radiotherapy treatment without obtaining pathology, and studies with ten or fewer patients.

2.2. Study types

All retrospective and prospective studies on SNB in PCa with PLND as reference standard were included. We excluded studies without a reference standard (ie, when only SNB was done) or when PLND was performed after frozen sections obtained from SNs were positive. Conference abstracts were also included.

2.3. Type of intervention (index test and reference standard)

For inclusion, studies had to assess SNB as the index test using PLND as the reference standard, with positive or negative nodal disease as determined by histopathologic examination. To maintain external validity, any form of PLND, including limited, standard, extended, or super-extended PLND, was included. The ePLND template was defined as removal of nodes from the obturator fossa, internal, and external iliac vessels up to the ureteric crossing. All definitions, routes, and approaches for SNB were included. The procedure could be performed via an open operation, laparoscopic approach, or with robot assistance. Treatment of the primary tumor was either radical prostatectomy or radiotherapy. For SNB, tracers were administered into the prostate via the transrectal or transperineal route under ultrasound guidance and

Please cite this article in press as: Wit EMK, et al. Sentinel Node Procedure in Prostate Cancer: A Systematic Review to Assess Diagnostic Accuracy. Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2016.09.007