



Sentinel node biopsy in combination with extended pelvic lymph node dissection for men with prostate cancer at risk of nodal involvement

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Initial diffusion of prostate cancer (PCa) occurs in the regional lymph node (LN) stations. Positive LNs represent a significant adverse prognostic factor in PCa and can be associated with systemic metastases (1,2). Several anatomic studies with extensive lymphadenectomy have demonstrated that the obturator fossa is not always the primary site for LNs metastasis: therefore, pelvic LN dissection (LND) limited to the obturator fossa can miss about 50% of LN metastases. Therefore, an extended pelvic LN dissection (ePLND) should be performed in all intermediate-high-risk PCa, while a limited LND should be avoided, for the high risk of missing at least half the nodes involved (3).

An ePLND provides several prognostic data, including the number of positive LNs, the volume of metastasis within the LN and the penetration of the capsule of the node, which cannot be achieved with other techniques. ePLND for PCa should include not only the external and obturator regions as well as the portions medial and lateral to the internal iliac vessels, but also the common iliac LNs at least up to the ureteric crossing, thus removing approximately 75% of all nodes potentially harboring metastasis (4). The assessment of an extended lymphadenectomy is performed in relation to the template and the number of LNs removed (5). The ePLND needs of surgical skills and is time consuming.

The benefits of ePLND are accompanied by the potential intraoperative and postoperative complications. Intraoperative complications inherent to ePLND include ureteral, major vascular, and obturator nerve (sensory or motor neuropraxia) injury. Postoperative complications include symptomatic pelvic lymphocele, development

of lymphoedema, ileus, deep venous thrombosis, and pulmonary embolism. The most common complication is the pelvic lymphocele. It is frequently asymptomatic and usually remains undetected. However, in some cases it is necessary to place drainage, in particular for compression phenomena on the vessels or for infections (6).

With the development of minimally invasive surgery, a simple sentinel LN biopsy (SNB) has been proposed as a novel promising technique to reduce the risk of complication, improve the staging efficacy and limit operative time. The sentinel LN is the first node that receives lymphatic drainage from the primary tumor: the concept of the SNB is based on the observation that metastases do not occur in downstream nodes if sentinel LNs are free of tumors. Sentinel guided lymphadenectomy has replaced extended lymphadenectomy in several neoplasms: in particular, for tumor such as breast cancer, penile cancer, and melanoma, SNB has become routine for nodal staging.

In 1999, Wawroschek *et al.* (7) started to transfer techniques and concepts of sentinel node identification to PCa. ^{99m}technetium nanocolloid was transrectally injected directly into the two lobe of the prostate under ultrasound guidance 1 day before pelvic lymphadenectomy. Thereafter a dynamic lymphoscintigraphy and an intraoperative identification with a gamma probe were done. Lymphatic drainage for the prostate gland is highly variable and complex, so different techniques and tracers have been tested to mark the sentinel LN in PCa. Moreover, in the last years, several methodologic improvements have been proposed, including SPECT-CT, intraoperative SN

identification with a minimally invasive/robotic approach, the use of fluorescence imaging guided surgery, and hybrid tracers combining ^{99m}Tc labeled colloid and indocyanine green for guidance (8).

Wit *et al.* has recently published a systematic review with the aim to assess the diagnostic accuracy of SNB in PCa (9). The authors have identified more than 300 articles and selected 21 studies identified from January 1, 1999 to May 31, 2016, recruiting a total of 2,509 patients. They concluded that SNB, as a diagnostic tool, was almost equivalent to ePLND with a low non diagnostic rate (4.1), high overall sensitivity (95.2) and specificity (100.0), no false positive cases (0) and low false negative rates (4.8). Moreover, the rate of detecting positive nodes outside the ePLND template was low: therefore, SNB provided no additional diagnostic value over ePLND, although SNB appeared to increase nodal yield by increasing the number of affected nodes when combined with ePLND. The conclusion of this review was that combining SNB with ePLND could be considered as a valid option for men with high risk disease.

The strength of the review of Wit *et al.* is the systematic approach taken to assess and appraise the evidence base, including use of the standard methods recommended by the Cochrane Methods Group for Systematic Review of Screening and Diagnostic Tests (10), adherence to Preferred Reporting Items for Systematic Reviews (PRISMA) (11), and Standards for Reporting Diagnostic Accuracy Studies (STARD) (12) guidelines and assessment of risk of bias (RoB) using QUADAS-2. Moreover, the studies included in the review were very recent: all articles have been published within the last ten years and the majority within the last 3–5 years. The tracer used was ^{99m}Tc nanocolloid in almost all cases and the referral template of LND was the ePLND.

However, the review has also several limitations. Only in five studies' authors reported data from more than 100 patients, that should be considered as a minimal population to reduce the RoBs related with characteristics of both patient (age, BMI, comorbidity, prostate and lymphatic drainage characteristics) and center (urologists and pathologists). Moreover, half of the patients included in this review were not limited to intermediate/high risk or only high risk PCa according to the D'Amico risk group classification. As reported in *EAU Guidelines*, LND should be avoided for low risk PCa (3): the extreme rare cases of positive LNs in this very favorable group of patients may affect the results on the whole population. Finally, regarding the median number of LNs removed, 3 articles did not report the data, while for 7 the median number was

below 14. As reported by Abdollah *et al.* (5) 14 LNs should be considered as a prognostic relevant cut-off point in order to define an extended lymphadenectomy: in particular, in patients with LN involvement the removal of at least 14 LNs during radical prostatectomy was associated with a significant improvement in cancer-specific survival rate (5).

Nevertheless, the interesting review from Wit *et al.* confirms an urgent need to standardize the definition and the technique of SNB: unifocal *vs.* multifocal PCa, intratumoral *vs.* peritumoral injection, monolateral *vs.* bilateral inoculation can strongly affect the definition of primary lymphatic landing sites (13). Therefore, patients with high risk of nodal involvement should undergo an extended PLND, based on a template including common iliac arteries up to the cross with ureter obturator region and LNs medial and lateral of the internal iliac vessels. As suggested by the authors, SNB in combination with ePLND seems to provide a better nodal removal by increasing the number of affected nodes in 5% of cases in high risk PCa (9).

Despite the recent methodologic advances in SNB techniques, a prospective well designed trial comparing SN dissection in addition to or alternatively to ePLND has not yet been performed. Many clinicians claim against SN detection in PCa mainly due to the multifocality of this specific neoplasm, the lack of a single positive sentinel node, the difficulty of peritumoral tracer inoculation and the lack of a reliable technique for intraoperative detection of the sentinel node. Future studies are strongly recommended to define if SNB with ePLND could allow improving the oncologic outcomes, in addition to the hypothetic role in staging of PCa.

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