How Many Prostate Cancer–bearing Lymph Nodes Did We Miss in the Past?

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Despite recent advances in imaging techniques, pelvic lymph node dissection (PLND) remains the most accurate and reliable staging procedure for detection of lymph node (LN) invasion in prostate cancer (PCa) patients [1]. Tables and nomograms to identify candidates for PLND have been developed and validated. Two points need to be discussed concerning these prediction models. First, as already pointed out by many authors—in particular, by the authors of an important collaborative review [2]—most of the models are based on results derived from limited PLND and, consequently, may underestimate the real incidence of LN invasion. Second, the widespread use of standard histopathologic examinations, which can miss small-volume or “occult” nodal metastases, may also lead to an underestimation of the real incidence of LN invasion.

Although it has long been known that micrometastatic PCa cells in LNs can be detected by reverse transcriptase polymerase chain reaction (RT-PCR) [3], this technique has been somewhat neglected in recent decades and has not been used in the development of nomograms for identifying candidates for PLND. In a prospective study, Heck et al. [4] apply RT-PCR to map the topography of LN metastasis in intermediate- and high-risk PCa patients undergoing radical prostatectomy and extended PLND (ePLND). Of particular interest are the results of combining molecular (ie, RT-PCR) and standard histopathologic examinations of nodes removed during ePLND to avoid understaging the cancer.

How significant is this understaging using standard histopathology if the total LN count is considered apart from the number of patients and, conversely, the number of patients is considered apart from the LN count? And how does understaging affect the clinical outcome in patients undergoing radical prostatectomy for intermediate- and high-risk PCa?

Let us look at the data of Heck et al. from a slightly different point of view. Of the 1186 LNs from 52 patients examined using both standard histopathology and RT-PCR, 127 LNs were positive on molecular examination (molN1). It is interesting to note that only 32 of these 127 molecularly positive LNs (25%) were simultaneously positive on standard histopathologic examination (pN1 and molN1), while 95 LNs (75%) were histopathologically negative although molecularly positive (pN0 and molN1). This finding leads to the conclusion that LN examination by standard histopathology, as applied by Heck et al. (one tissue section per LN \(\times 5\) mm thick and \(x\) tissue sections per LN with a size of \(x\times x\) mm), may miss up to three-quarters of all LN (micro)metastases.

Looked at from another vantage point, 27 of the 52 patients studied were LN metastasis–positive on molecular examination (molN1). Of these 27 patients, only 12 (44%) were simultaneously positive on standard histopathologic examination (pN1 and molN1), while 15 patients (56%) were histopathologically negative and molecularly positive (pN0 and molN1). It can be concluded, therefore, that almost one-third of this specific group of patients (15 of 52 patients, or 29%) would have been understaged as pN0 if they had undergone standard histopathologic examination alone.

But what of the localization of the LN metastasis? Using combined molecular and standard histopathologic examination of the nodes removed during the ePLND, Heck et al. produce—as could be expected—a template similar to that proposed by the Berne group [5] and newly confirmed and slightly enlarged by the Leuven group [6].
Concerning outcomes in patients undergoing radical prostatectomy for intermediate- and high-risk PCa, Bastian et al. document a trend confirming good outcomes, especially when the surgery is combined with adjuvant treatments [7]. Heck et al. further reinforce the importance of ePLND in these categories of patients by showing that it removes a generous number of occult LN metastases, thus positively influencing the subsequent course of the PCa. In fact, the beneficial effect of ePLND was recently demonstrated in a prospective randomized study by a Chinese group: In patients with intermediate- and high-risk PCa, ePLND positively affected biochemical progression–free survival over a median of 6 yr [8].

What can we learn from this study? First, in the past, ePLND performed during radical prostatectomy in patients with intermediate- and high-risk PCa probably resulted in resection of many more PCa-bearing LNs than previously thought. This idea could partially explain the acceptable outcome after radical prostatectomy, even in patients with high-risk PCa. Second, the template of PLND must encompass iliac external and obturator regions and the areas lateral and medial to the internal iliac vessels, as well as the common iliac LNs. Clearly, the templates for PCa and bladder cancer are becoming increasingly superpositionable.

Looking to the future, I would recommend that Heck et al. compare the long-term course of PCa (eg, the PSA course and the development of systemic disease) in patients with LN metastases detected by both standard histopathologic and molecular examination (pN1 and molN1) with the long-term course in patients with micrometastasis alone (pN0 and molN1) and in patients who are LN-negative (pN0 and molN1). This comparison may help us to further understand the potential curative effect of metastases resection.

Conflicts of interest: The author has nothing to disclose.

References