Why all prostate cancer surgery should include an adequate lymph node dissection

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The role of a lymph node dissection in most cancer sites portends a benefit from accurate staging and assignment of adjuvant therapy or, possibly, a direct therapeutic effect by local/regional control. The adequacy of this regional dissection has become an important quality of care indicator (i.e., colon, rectal, testes and bladder). The adoption of recommendations to limit lymphadenectomy in other sites has generally followed prospective studies (i.e., uterine) or established predictive tools (i.e., sentinel biopsy in melanoma, breast cancer). This issue is controversial for prostate cancer management given the lack of prospective data and ambiguous retrospective studies[1] and is illustrated in the variation in our clinical practice guidelines (Table 1).[2-5]

Coincident with the decrease of lymph node involvement (LNI) in most prostatectomy series[6,7] there has been remarkable decline in pelvic lymph node dissection (PLND) for low-risk disease,[8] although this trend may be less apparent in Canada.[9] A risk-adapted approach to PLND remains controversial; it has been suggested that other complicating elements are involved in its decline, including changes in surgical approach as well as reimbursement issues.[10] But what is the evidence to abandon this concept of regional control for prostate cancer in patients with perceived low-risk disease? Without prospective randomized data the argument to omit PLND generally revolves around the following three issues: staging, therapeutic benefit and side effects.

Staging issues

Recent mapping studies suggest that a limited PLND (involving only the superficial external iliac-obturator group) and an even more extended PLND will miss a significant number of lymph nodes with metastatic disease.[11] Debate exists on the optimal extent or location of PLND, but it is likely that there is a threshold for the number of nodes (approximately 20) to ensure a representative sampling.[12-14] However, PLND still represents the most accurate and reliable staging procedure for the detection of LNI in prostate cancer. Despite numerous technical advances, including positron emission tomography/computed tomography, lymphotropic nanoparticle-enhanced magnetic resonance imaging and sentinel lymphoscintigraphy, standard lymph node imaging lacks sufficient sensitivity to supplant PLND.[1]

The most common argument to omit PLND at prostatectomy is that prediction of LNI can be determined with preoperative parameters with the aid of prediction models. Multiple prediction tables or nomograms have been published with significant variation in their predictive accuracy.[15-18] Two commonly used tools, an update of the Partin tables[15] and the preoperative nomogram by Cagiannos and colleagues,[16] reported accuracies of only 76% in validation studies. Furthermore, most of these tools were developed in populations with only a limited PLND (with LNI <1%)[19,20] and therefore seriously underestimated the true presence of LNI. Recent series of more extended PLND reveal alarmingly higher rates of LNI including one cohort of patients with a PSA<10 having a LNI of 11%.[21] Other extended PLND series in low-risk patients have confirmed LNI rates up to 7.4%.[22,23] This issue is critical to our understanding and subsequent reliance of predictive tools in the surgical management of prostate cancer.

Therapeutic issues

The putative reasoning for accurate staging in prostate cancer is to appropriately assign patients for adjuvant therapy. Despite some debate to its applicability, there is prospective, randomized evidence for the early addition of androgen deprivation therapy for men with lymph node positive disease.[24] Such adjuvant treatment may affect epithelial-stromal interactions sufficiently to arrest the growth of micrometastases into clinically apparent lesions.[25] Still, the overall impact of PLND on cancer outcomes remains controversial given the lack of prospective data. However, there is a growing body of evidence that PLND may have a direct therapeutic benefit. The long-term outcomes of patients with low burden lymph node metastasis are exceptional, regardless of the administration of adjuvant treatments.[26-28] Reports of 10-year cause-specific survival are as high as 85.8%[27] for men with positive lymph nodes and as high as 94% for those with very low volume nodal disease.[28] Several studies have demonstrated a survival benefit for men treated surgically with PLND compared to ADT alone.[29-31]

Table 1. Overview of clinical practice guidelines on prostate cancer management

	Risk adapted recommendation for PLND	Extent of PLND
CCO	High risk mandatory Intermediate risk recommended Low risk optional	Standard
EUA	High risk and intermediate risk	Extended
AUA	Reserved for higher risk of LNI	Not indicated
NCCN	Exclude PLND if <2% LNI	Extended

PLND = pelvic lymph node dissection; LNI = lymph node involvement; CCO = Cancer Care Ontario; EAU = European Association of Urology; AUA = American Urological Association; NCCN = National Comprehensive Cancer Network

Furthermore, there is growing interest in the concept of "biologically" positive, pathologically negative lymph nodes and that removal of these nodes with micro-metastatic disease may lead to a therapeutic benefit. Studies have reported a significant inverse association between number of removed lymph nodes and PSA-free and cause-specific survival in node-negative patients.[9,26,32] In one of the largest studies, Joslyn and colleagues reported that for N0 patients, those that had greater than 10 nodes removed had a lower risk of prostate cancer death than those who did not undergo PLND.[32] We have demonstrated a similar trend in a population-based study in Ontario men with low to intermediate risk disease,[9] although there is a real possibility that these latter findings are influenced by a "Will Rogers Phenomenon" misclassification bias. However, the evidence would suggest that the presence of LNI in those with lower risk disease is much higher than we intuitively expect and it is possible that these are the very cases that would benefit from an adequate PLND.

Side effects

Performing a PLND at the time of prostatectomy does increase some time and side effects, with reported PLND specific complication rates in contemporary series varying between 2% and 35%.[1,13,33-35] There is some controversy whether a more extended PLND leads to higher complication rates but in these series the higher rates are driven mostly on the development of lymphocoeles.[35] Although PLND is not a completely innocuous procedure, the overall added complications to the prostatectomy itself is likely acceptable, with a low likelihood of serious complications extending hospital stay or long-term morbidity.

There is significant need, yet little likelihood, for a prospective randomized study to determine the appropriateness of a risk-adapted approach to omitting PLND at the time of prostatectomy. In the meantime, given the only modest accuracy of other prediction tools, the possibility of outcome benefits with PLND (especially for those with lower "risk" or volume of nodal disease) and the acceptable added morbidity, it remains essential that all men who truly need surgical treatment of their prostate cancer should also have a PLND.[36]

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