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REVIEW

Regional lymph node staging in prostate cancer: Prognostic and therapeutic implications

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Abstract
The role of pelvic lymph node dissection (PLND) in prostate cancer, in which patients and to what extent it should be performed, remains a controversial topic. Preoperative diagnostic methods are more or less unreliable for lymph node staging and PLND remains the most reliable and accurate method. PLND is indicated in all patients with a PSA value >10 ng/ml and in those with a PSA <10 ng/ml if the Gleason score is ≥7. If PLND is performed then it should always include the tissue along the external iliac vein, in the obturator fossa and on either side of the internal iliac vessels, up to where the ureter crosses the common iliac vessels. In conjunction with RRP extended PLND may increase staging accuracy, influence decision making with respect to adjuvant therapy and possibly impact outcome.

Contents

Introduction

The role of pelvic lymph node dissection (PLND) in prostate cancer, in which patients and to what extent it should be

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performed, remains a controversial topic. There is no doubt that an adequate PLND improves staging and as a consequence allows better assessment of the disease and its prognosis. Its beneficial effect on disease progression and survival, however, can be questioned, especially in patients with low-risk prostate cancer. Patients with high-risk prostate cancer may be the ones most likely to profit from ePLND, especially those with micrometastatic disease. Patients with more extensive lymph node metastases may benefit from androgen deprivation therapy (ADT) [1].

This review therefore critically analyses past and more contemporary literature pertaining to indications, anatomic extent as well as diagnostic and therapeutic benefit of ePLND.

Clinical staging options for lymph node metastases

In continued efforts to tailor treatment options to individual patient circumstances and minimize morbidity, nomograms that estimate the likelihood of positive nodes for an individual by assigning points for specific risk factors have been developed. Heidenreich et al. analysed the predictive accuracy of Partin tables and CART analysis in patients undergoing RP and ePLND [2]. Overall both nomograms predicted a significantly lower rate of positive nodes than detected after ePLND. This underscores the limitations of nomograms based on a limited area of dissection where a large number of potentially positive nodes remain undetected.

It has been shown that the risk of harbouring positive nodes in men undergoing RP increases linearly in proportion to the number of lymph nodes (LN) removed [3,4]. Briganti and coworkers attempted to develop and validate a nomogram that, based on clinical parameters (PSA level, clinical stage, biopsy Gleason score sum) and the number of nodes removed during PLND, estimates the optimal number of nodes that should be removed [5]. However, its reliability may be impeded by the fact that the majority of patients included qualify as low-risk patients and only 9% (total 71 patients) were lymph node positive. In addition, ePLND was performed only in 23% of patients. The rather limited number of positive patients, combined with the knowledge that primary lymphatic drainage sites go as far up as the inferior mesenteric artery, which was not accounted for in this nomogram, limits its reliability [6]. With knowledge of the inter-individual variability of LN distribution, it appears easier to either perform an ePLND including most known areas of prostatic drainage or to omit PLND altogether. In addition, nomograms can only attempt to predict the probability of finding positive nodes in an individual patient based on collected information about other patients with a ''most likely inadequate'' area of lymph node dissection and their accuracy for a specific patient remains questionable.

Despite advances in radiological technology, CT and MRI, owing to their low sensitivity (0–30%) in detecting lymph node metastases, are not recommended for routine evaluation of prostate cancer within the pelvis [7–9].

High-resolution MRI used in tandem with the intravenous administration of lymphotropic superpara-magnetic nanoparticles potentially enables detection of small and otherwise undetectable LN disease. An issue of concern is that nanoparticles do not, as yet, adequately identify nodes with micrometastases, in patients who are most likely to benefit from PLND. Such novel imaging techniques are as yet not available for routine application and require further clinical evaluation and validation before widespread use [10].

Monoclonal antibody radioimmunoscintigraphy has shown limited accuracy in the detection of lymph node metastasis because the antibody targets an intracellular epitope that is only exposed in dying or dead cells [11]. The ProstaScint Scan (Indium In 111 capromab pendetide) showed a very low positive predictive value (11%) and sensitivity (17%) in predicting lymph node involvement [12]. Although initially promising, molecular techniques using reverse transcription polymerase chain reaction (RT-PCR) have demonstrated varying sensitivities in detecting circulating cancer cells and positive PCR assays have been found in men with negative nodes [13]. Thus, the significance of a positive assay remains unknown and for the time being this method cannot determine patients at risk for lymph node metastasis.

The sentinel lymph node concept has in recent years been applied in prostate cancer and was first introduced by Wawroschek and coworkers [14]. One of the first applications of this concept was introduced by Cabanas for penile cancer and is based on the idea that lymphogenic spread of cancer is a gradual process and usually is first encountered in the first node reached by the lymphatic outflow from the diseased organ [15]. Therefore if the first lymph node is negative lymphadenectomy can be avoided. In prostate cancer the apparent sensitivity was 96% for detecting lymphatic spread in node positive patients [16]. However, this technique has its setbacks. Only nodes in close contact with the collimator are detected. If these are not directly accessible there is a large chance of them being missed. As it has been shown that a significant number of nodes are found outside the area explored, e.g. along the internal iliac vessels, the common iliac vessels and in the presacral and aortic tissue, some positive nodes may have been missed resulting in incomplete sampling [6,17,18]. Indeed after applying preoperative fusion imaging of SPECT (single-photon emission computed tomography) and CT scans following intraprostatic injection of Technetium-99m-nanocolloid multiple primary landing sites (prostatic SLN) were identified with 30–40% of these landing sites being found outside the common area of PLND [6]. Although this appears to be a reliable imaging technique, it is time consuming, expensive and dependent on the skills of the nuclear medicine specialist [19]. Another shortcoming of the technique is that in bulky nodal disease approximately one-third of positive nodes may remain unrecognized due to compromised uptake of Technetium [20].

In summary, preoperative diagnostic methods are more or less unreliable for lymph node staging and PLND remains the most reliable and accurate method.

When discussing the role of PLND, three issues have to be taken into account. One is the extent of PLND; the next is, in which patients it is necessary; and the third is what are the true advantages.