

The role of lymphadenectomy in high risk prostate cancer

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Abstract Historically, patients with high risk prostate cancer were considered poor candidates for radical prostatectomy (RP) due to the likelihood of positive pelvic lymph nodes and decreased long term survival. Although there is still no consensus on the optimal therapy for this group of patients, there is increasing evidence that surgery could play a role. Cancer specific survival (CSS) rates after RP for locally advanced disease at 10 year follow up range from 29 to 72%, depending on tumor differentiation. The role of pelvic lymph node dissection (PLND) in prostate cancer remains a controversial topic. Nonetheless, in conjunction with RRP extended PLND (ePLND) should be performed as extended lymph node dissection in lieu of standard PLND may increase staging accuracy, influence decision making with respect to adjuvant therapy and possibly impact outcome. High risk patients with organ confined prostate cancer and low volume (micro)metastatic disease may be the ones to profit most from this approach.

Keywords High risk prostate cancer · Lymphadenectomy · Nodal metastases · Radical prostatectomy

Introduction

Historically, patients with high risk prostate cancer were considered poor candidates for radical prostatectomy (RP) due to the likelihood of positive pelvic lymph nodes and decreased long term survival [1, 2]. Although there is still no consensus on the optimal therapy for this group of

patients, there is increasing evidence that surgery could play a role. The initiation of PSA screening, has led to stage migration and improved outcome after RP rekindling the interest in surgery as an option for patients with high risk prostate cancer. In locally advanced disease (cT3) the cancer specific survival (CSS) rate after RP at 10 year follow up is 57–72% [1, 3, 4]. Tumor differentiation is an important confounding factor and in well differentiated and moderately differentiated cT3 tumors CSS rates at 10 years range from 67–85%, however in poorly differentiated tumors CSS rates sink to approx. 29% [1, 4].

The role of pelvic lymph node dissection (PLND) in prostate cancer 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 it's prognosis. It's 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) [5].

Definition of high risk prostate cancer

The definition of high risk prostate cancer varies throughout the literature. Where some consider a PSA >20 ng/ml or a Gleason sum >7 or primary Gleason pattern of four or five or clinical stage T3a to be high risk, others consider a PSA \geq 15 ng/ml, \geq cT3 or biopsy Gleason score >7 high risk prostate cancer [6, 7]. The AUA clinical guidelines define high risk as a PSA >20 ng/mL or a Gleason score of 8–10 or clinical stage \geq T2c [8]. Using eight different definitions of high risk prostate cancer Yossepowitch et al.

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[9] assessed a study population of 4,708 men treated by RRP and concluded that: “patients diagnosed with high risk prostate cancer by currently available definitions do not have a uniformly poor prognosis after radical prostatectomy”. Of the high risk tumors 22–63% proved to be confined to the prostate, 7–23% had lymph node metastasis and the 5 year relapse free probability after RP was 49%. The conclusion was that in high risk prostate cancer, RP monotherapy may be an acceptable treatment option and that many cancers in this group are confined to the prostate.

PSA values are not specific for prostate cancer, however PSA dynamics may be. Both a short PSA doubling time and an increased PSA velocity have been associated with poor prognosis, however clear cut definitions are still lacking [10, 11]. Although PSA dynamics may well prove to be one of the most important factors to help predict patients at risk of death from prostate cancer, they are not likely to reflect the actual course of disease in all patients. PSA changes may only provide useful information in a few patients at a time when the disease is still localized and the patient will truly profit from treatment. Indeed many patients without an accelerated PSA doubling time or velocity at the time of local therapy with curative intent will later progress [12]. In addition PSA negative tumors may have misleading PSA values. To summarize, the definition of high risk prostate cancer has yet to be standardized and future efforts need to be focused on developing methods to discriminate between patients at high risk for relapse who may benefit from local therapy alone and those requiring an aggressive combination therapy.

Clinical staging

Accurate staging defines the extent and location of disease, helps predict malignant potential, influences decision making with respect to therapeutic options and possibly has an impact on outcome. Efforts are being made to improve pre-operative diagnosis of lymph node metastasis and so minimize surgical risks and costs. Predictive nomograms that help estimate the likelihood of positive nodes for each individual patient by assigning points for specific risk factors have been developed. However, most of these nomograms are based on limited PLND and therefore their applicability is questionable. They may be adequate to estimate the incidence of positive nodes in a limited field of resection, they do not however reflect the true probability of lymph node metastases.

Recently, Briganti et al. found that the risk of positive nodes in men undergoing RRP increases linearly in proportion to the number of lymph nodes removed, hereby confirming previous observations by other authors [13, 14]. They then proceeded to develop and validate a nomogram

that predicts the probability of lymph node invasion based on clinical parameters (PSA level, clinical stage, biopsy Gleason score sum) and the number of nodes removed during PLND [15]. The aim of this nomogram is to estimate the optimal number of nodes that should be removed. As with all other nomograms its accuracy depends on the cohort used for its development. For one the majority of patients included qualify as low risk patients and 9% (total 71 patients) were lymph node positive, this rather small number limiting the significance. In addition, true ePLND was performed only in 23% of patients and this combined with the knowledge that primary lymphatic drainage sites may go up to the inferior mesenteric artery which was not accounted for in the nomogram may again limit its reliability [16]. In knowledge of the interindividual variability of lymph node distribution, it appears easier to either perform an ePLND including the known areas of prostatic drainage or to omit PLND. Furthermore, the aim of PLND should not only be to determine if a patient has positive nodes, but also to remove as many nodes as possible. Nomograms can only attempt to predict the probability of finding positive nodes in a large series of patients and their value for the individual patient remains questionable. The use of CT scans or MRI to evaluate lymph node involvement is not routinely recommended as the low sensitivity of 10–30% for imaging pelvic lymph node metastases is not acceptable in high risk patients [17].

The sentinel lymph node (SLN) concept has been applied to various malignant tumors. The SLN a term introduced by Cabanas [18] is the node where lymphatic flow from the tumor first arrives. Wawroschek et al. [19] introduced the radioisotope method for detection of SLN in prostate cancer. In their study the SLN method and the consecutive lymphadenectomy showed an apparently high sensitivity rate of 96%. However the study had certain weaknesses. The gamma probe needs to be in very close contact with the tissue to get a good signal and lymph nodes outside the area explored or with a weak signal may be missed. Since it is known that a significant number of positive nodes are also found along the internal iliac vessels, the common iliac vessels, in the presacral and paraaortic tissue, areas which were not all explored, some could have been missed with the possibility of incomplete sampling [16, 20, 21]. Takashima et al. [22] using the SLN technique were only able to detect in vivo 40% of the hot nodes detected ex vivo after extended PLND. Anatomic localization of prostatic sentinel nodes with fusion imaging of single photon emission computed tomography (SPECT) and CT scans after intraprostatic injection of Technetium-99m-Nanocolloid may be a more reliable imaging technique but is time consuming, costly and is dependent on the skills of the nuclear medicine specialist [23]. In addition in significant nodal disease technetium uptake can be compromised so

over 1/3 of positive nodes remain unidentified [24]. Other new and potentially promising techniques such as high resolution MRI with lymphotropic superpara-magnetic nanoparticles are being developed and evaluated, however detection of micrometastasis remains limited and these techniques are as yet not available [25]. The inability to accurately diagnose minor lymph node metastasis preoperatively and the important prognostic information gained by identifying nodal disease emphasizes the role of extended PLND during radical retropubic prostatectomy (RRP).

Where to look for the nodes in high risk prostate cancer

A standardized universal definition of limited/ extended PLND for prostate cancer does not exist. The minimal template only includes lymphatic tissue from the obturator fossa, the standard variant also includes lymphatic tissue along external iliac vein. Extended PLND additionally includes lymphatic tissue along the internal iliac vessels both medially and laterally and in some cases along the common iliac vessels. The next question is where to look for the positive nodes. Evidence suggests that increased lymph node sampling outside the obturator fossa may increase the detection of metastatic disease. Heidenreich et al. [26] reported on 103 patients who had an extended PLND comprising the external iliac, internal iliac, obturator, and common iliac lymph nodes bilaterally and the presacral nodes. They compared this group of patients with 100 men who received only standard PLND. Lymph node metastases were diagnosed in 26% in the extended group and in only 12% in the standard PLND group. Despite negative obturator LN, positive LN were identified in the internal iliac and presacral regions. Forty-two percent of all LN metastases were detected outside the regions of standard PLND. Wawroschek et al. by extending the region of lymphadenectomy to include not only the tissue in the external iliac region and fossa obturatoria but also the tissue along the internal iliac vessels, in the paravesical, presacral and pararectal tissue they detected an additional 35% of lymph node positive patients [27]. Our group reported the results following meticulous PLND along the external iliac vein, the obturator nerve, and the internal iliac (hypogastric) vessels in men with clinically organ-confined disease. Eighty-eight of 365 men (24%) had positive LN. Internal iliac LN were positive in 58% and internal iliac LN alone were positive in 19% of the men [20]. Similar results have been reported using the laparoscopic approach [28]. Stone et al. [28] reported twice as many LN removed via extended than limited laparoscopic PLND (mean 17:8 vs. 9.3), and three times as many patients with LN metastasis in the extended group [23.1 vs. 7.3% ($p = 0.02$)]. However, the link between the extent and the yield of PLND was not always

confirmed. The only randomized study on extended versus limited PLND was reported by Clark et al. [29], who found no difference in the yield of positive nodes with more extended dissection (extended: 3.2% vs. limited: 2.4%). The two types of dissection were conducted in the same patient on contralateral sides, however, the majority of patients had a low probability of LN metastases and therefore would not have required a PLND. Comparing these two techniques in a cohort who are unlikely to have positive LN obviously limits the power of the trial. Even without this limitation, the number of patients examined was inadequate for an equivalence study. In addition, 90% of their patients had T1c or T2a disease, which is mostly a unilateral disease, and therefore randomly assigning them to extended PLND on only one side carries a substantial risk that the extended PLND was performed on the non tumor bearing side. Also, neither the number of nodes removed, nor the histopathological work-up were defined. Therefore, the study design renders it hard to compare their data with those of other previous studies or draw any conclusions for high risk patients.

A consensus on terminology of PLND is desperately needed. In addition as a result of new insights the optimal extent of PLND is continually being redefined. Recent data using intraprostatic technetium injections and fused single-photon emission tomography (SPECT) combined with either CT or MRI to map lymphatic drainage from the prostate showed that the prostate has multiple landing sites and that the extended template may need modification as potentially 30–40% of the lymphatic landing sites are not included if PLND is limited to the iliac vessels distal the bifurcation of the common iliac artery [16]. By extending the dissection along common iliac vessels at least up to the ureteric crossing approximately 75% of all nodes potentially harbouring metastasis can be removed (Fig. 1).

Taken together, the above data shows that, in general, extended PLND yields higher rates of positive LN. Importantly, several studies demonstrated that up to two thirds of all patients with LN metastasis have positive nodes along the internal iliac vessels, an area not included in a limited PLND. A PLND, should therefore always include at least the internal iliac tissue on both sides, so identifying LN invasion that would remain undetected following limited PLND. By extending the template to include the tissue along the common iliac vessels up to the ureteric crossing 75% of all nodes potentially harbouring metastases are removed.

Therapeutic consequences of extended PLND

While a therapeutic benefit of PLND has been questioned by some authors, the possibility of a therapeutic benefit for PLND in prostate cancer has been suggested by others.

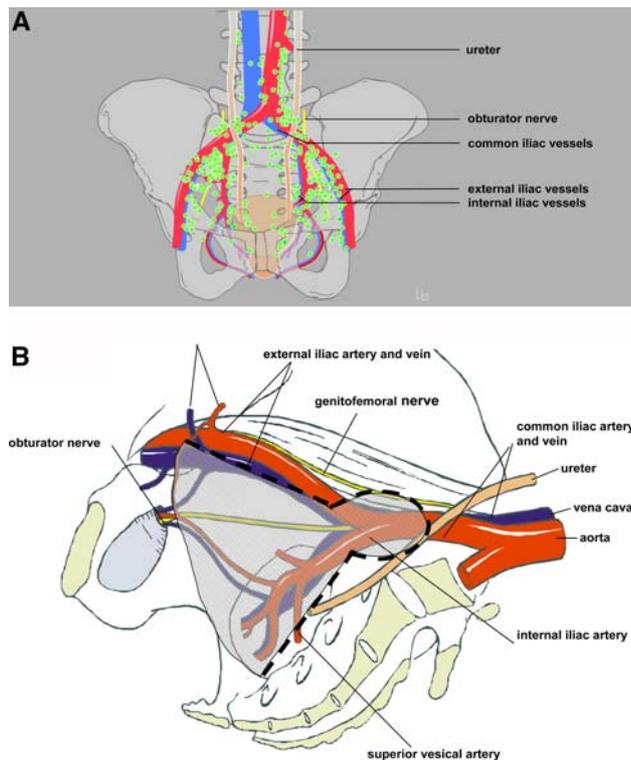


Fig. 1 **a** Primary landing sites of the prostate determined by intraprostatic technetium injections and fused single-photon emission tomography (SPECT) combined with either CT or MRI. **b** Proposed template including tissue along the common iliac vessels up to the crossing of the ureter

DiMarco et al. [30] did not observe an inter-relation between the extent of PLND and prostate cancer outcome in LN negative men, nor did they find a survival difference when comparing the results of extended PLND (14 nodes removed) between 1987 and 1989 with those of a more limited PLND (5 nodes removed) from 1999 to 2000. However, possible T-stage migration, with higher tumor stages in the earlier period, was not taken into account. Because an extended PLND in the earlier period led to similar results for disease progression and survival as removing fewer nodes in the later period, their results may ultimately imply that the extended PLND had a therapeutic role for the earlier cohort. Recently, Masterson et al. [31] examined the association between the number of LNs removed, the number of positive LNs and disease progression in patients with clinically localized prostate cancer. They found that in men without nodal involvement an increased number of nodes removed correlated significantly with freedom from biochemical recurrence. Similarly, Joslyn and colleagues, using the SEER database, concluded that patients with LN involvement had a significantly greater number of nodes removed compared with those with no LN involvement and that extended PLND reduces the long-term risk of prostate cancer related death, even in patients with negative nodes

compared to patients without PLND [14]. Recently Bader et al. [13] demonstrated that the rate of tumor progression is higher in pN0 patients with few nodes removed than in patients with a larger number of negative nodes removed. A potential explanation for these observations is that a thorough nodal resection eliminated micrometastases that were not detected by routine histologic examination. This hypothesis is reported by recent studies applying special assays to determine occult metastasis in pathologically lymph node negative patients [32–34]. These investigators found occult metastasis in up to 30% of patients and concluded that a significant benefit in biochemical recurrence-free survival might exist for patients with micrometastases in a few nodes undergoing an extended dissection. It seems therefore that not only detection of diseased nodes but removal of as many primary lymphatic landing sites as possible should be the main objective for PLND to improve outcome.

This is supported by further evidence indicating that patients with minimal LN metastases will have better prognosis by removing the diseased nodes. Golimbu and coworkers [35] retrospectively analyzed 42 patients with nodal disease who underwent PLND and RRP. In this series, patients with low tumor bulk and one positive LN had survival rates comparable to those of matched controls after a mean follow-up of 5 years. Catalona suggested that treatment may be curative even in LN positive disease, however the 6 year follow up may be too short to allow a definite statement. In a small series of 12 patients with LN involvement and no adjuvant therapy, 75% remained recurrence free at 5 years and 58% at 7 years [36]. The results reported by Pound et al. [37] for patients with LN micrometastasis, revealed a 10-year metastasis-free survival rate of 68%, again without adjuvant therapy. In 2003, Bader et al. reported on 92 men followed with histologically proven LN metastases who received no adjuvant therapy. After 45 months (median), 15 of 39 patients with only one positive node remained without signs of progression [38]. Recently Boorjian and colleagues [39] retrospectively reviewed a large series of patients with positive lymph nodes after RRP and PLND, although with a limited number of nodes (median 11) removed. The majority of the node positive patients received androgen deprivation therapy. In their series 56% of the patients had a 10 year BPPS. In Pagliarulo's group of initially node negative high risk patients with immunohistochemically detected occult lymph node metastasis there was an estimated 39% probability of remaining biochemically disease free for 10 years [34]. This did not differ significantly from the group of patients who were pathologically lymph node positive. Interestingly after a median observation time of 12.9 years only half of the patients with PSA relapse also developed clinical recurrence.

Prognosis has also been shown to depend on the number of positive nodes involved. Daneshmand et al. [40] reported that patients who had one or two positive LNs had a clinical recurrence-free survival rate of 70 and 73% at 10 years. In our series 10 and 14% of patients with two or more positive LN remained disease free [38]. By contrast, men with five or more involved nodes had a recurrence-free survival rate of only 49%. Boorjian found that one lymph node metastasis increased the risk of cancer specific death almost 4-fold, which in patients with two or greater positive lymph nodes was increased 2-fold compared to that in patients with one positive node [39].

Opponents of extended PLND argue that performing an extended PLND results in increased morbidity and costs [41]. Morbidity can be minimized if attention is paid to a few details: (1) Ligation of lymphatic vessels coming from the legs, instead of clipping. Hemoclips have a tendency to be torn away during subsequent surgery. (2) Placement of two drains one on each side of the pelvis where PLND was performed. Drains should be removed gradually until the total amount drained is less than 50 ml/24 h. (3) Injection of low molecular heparin into the upper arm instead of the thigh.

Conclusions

There is evidence suggesting that RRP monotherapy is a treatment option in selected high risk patients. In conjunction with RRP extended PLND should be performed as extended lymph node dissection in lieu of limited PLND may increase staging accuracy, influence decision making with respect to adjuvant therapy and possibly impact outcome. High risk patients with localized prostate cancer and low volume (micro)metastatic disease may be the ones to profit most from this approach.

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