Pelvic lymphadenectomy for localized prostate cancer

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In the era of prostate specific antigen, there is increasing proportion of patients with localized prostate cancer. Accurate preoperative determination of lymph node status is important for adequate selection of treatment option, monitoring of response to treatment and early detection of recurrence. Lymph node invasion (LNI) is crucial prognostic parameter for patients who underwent curative treatment.

Despite of continuous improvements of radiological armamentarium, CT, MRI and PET scans are not absolutely reliable in lymph node staging. Many nomograms have been developed for prediction of lymph node status, but accuracy of these statistical models is not better than 78%. Surgery, either open or laparoscopic pelvic lymphadenectmy (PLND), remains a cornerstone in lymph node staging. However, there are several controversies regarding PLND: 1) necessity for routine performing in each patient, 2) anatomic boundaries for PLND, 3) morbidity of PLND, and 4) diagnostic and therapeutic value.

Key words: Surgery, Pelvic lymphadenectomy, ePLND,

A precise diagnosis of lymph node metastasis status is essential for staging of disease, selection of the appropriate treatment procedure, monitoring of the response to treatment, and early detection of recurrence. Therefore lymph node staging seems to be mandatory for patients who are candidates for curative treatment.

Clinical preoperative staging is based on radiological procedures or nomograms. Pelvic lymphadenectomy (PLND) is as an essential staging procedure for patients treated with radical prostatectomy (RP) for localized prostate cancer. It should provide an adequate specimen for histopathological lymph node evaluation. However, there are several controversial issues regarding PLND:

1) is it necessary to perform PLND in each patient;
2) which anatomical boundaries are required for PLND in high-risk patients;
3) morbidity of PLND;
4) diagnostic and therapeutic value of PLND.

RADIOLOGICAL PROCEDURES IN LYMPH NODE STAGING

Computed tomography (CT) has been used for the detection of nodal metastases in patients with prostate cancer. Diagnosis of lymph node metastases is based on size criteria where 1.0 cm is upper border of normal value. Sensitivities as high as 33% to 50% in detecting nodal metastases have been reported in some studies. High sensitivity has been limited to series in which patients have had advanced local stage disease and markedly elevated tumor markers and often have not undergone surgical staging to verify results.

In more contemporary series routinely performing CT before surgery, sensitivity has been diminished due to lower proportion of patients with advanced stages. In a recent study of 861 consecutive patients with newly diagnosed prostate cancer, routinely performed CT scans had a very limited value in detection of lymph node metastases. 13 (1.5%) out of 861 patients, all with PSA levels greater than 20 ng/mL, had nodal metastases diagnosed by CT scan. In the remaining 848 patients, the CT scan was normal, and the result did not influence management. On subsequent surgical staging of 409 patients, 15 patients with normal CT scans were found to have nodal metastases, 13 of whom had microscopic disease only.

These data indicate that CT should not be considered an obligatory component of prostate cancer staging. To decrease the probability of CT being performed useless, CT should be reserved for patients (a) at increased risk of having nodal metastases based on available nomogram data, (b) willing to undergo percutaneous aspiration of enlarged nodes, and (c) unlikely to undergo surgical staging.
MRI detection of lymph node metastases is also based on same size criteria and reported sensitivity of MRI in detecting nodal metastases ranges from 0–33%. Among the 274 patients evaluated by MRI in these three studies, MRI detected nodal metastases in 3 of 31 patients found to have pathologically positive nodes, for a combined sensitivity of 9.6%. Positive MRI findings of nodal metastases had a predictive value of 27.2%.

Recent improvements with contrast-enhanced MRI and rapid imaging sequences, as well as combining CT with fine-needle aspiration and lowering cutoff values for pathologic lymph nodes have led to an increased sensitivity of 75%–78%.

The use of positron emission tomography scans in prostate cancer lymph node staging has been explored with a plentitude of tracers. Only carbon-11 choline or acetate appears to have emerged as a suitable tracer for the assessment of lymph nodes. de Jong et al. examined 67 histopathologically proven lymph node metastasis cases with carbon-11-choline positron emission tomography. They demonstrated a sensitivity of 80% and specificity of 96% with this modality. Although these results are promising, more trials with larger number of patients are needed to confirm and validate these findings.

**NOMOGRAMS**

A nomogram is currently the most accurate model used to predict a given event that will occur for an individual patient based on collected information about other patients. It does not mean that it is accurate enough to have clinical applicability for a specific patient.

**BOTTOM OF FORM**

Studies have shown that nomograms predict more accurately than clinicians. Thus, it appears that nomograms have a better ability to predict the outcome of interest than even expert clinicians. It is conceivable that the advantage related to the use of nomogram predictions may be even more important if clinical ratings were obtained from less expert clinicians.

Cagiannos et al. provided a limited PLND nomogram that accounts for different institutions. The authors developed two internally validated nomograms that were, respectively, 76% and 78% accurate.

Recently, Briganti et al. published an extended PLND (ePLND) nomogram. ePLND might be necessary to detect occult lymph node metastases because LNI prevalence appears to be directly related to the extent of PLND. More extensive PLND identifies LNI that would not otherwise be detected by a limited PLND because prostate cancer nodal metastases do not follow a predefined pathway of metastatic spread. Presence and extension of LNI predict disease progression and long-term survival. Thus, Briganti et al. developed an ePLND nomogram which was internally validated and was 76% accurate.

**HISTOPATHOLOGICAL STAGING**

Epstein et al. reviewed 310 patients, who underwent frozen section analysis. The detection rates of positive lymph nodes were 67% and 100% for macroscopically normal and involved nodes, respectively. These investigators estimated the cost of metastatic cancer detection to be £7516. respecting the cost and the false-negative rate, they concluded that frozen section analysis was not warranted as a routine practice.

Beissner et al. found an even higher false negative rate of 70%, but the sensitivity was improved by stratifying patients into low, intermediate, and high-risk groups according to the nomograms. They concluded that low-risk patients (Stage 3, PSA level ng/mL, and Gleason score 7) gained no benefit from frozen section analysis. Also, the intermediate group (Stage 3 and Gleason score 7 and/or PSA level 10.1 - 20 ng/mL) gained minimal benefit.

The routine use of frozen section analysis to detect lymph node micrometastasis is unnecessary, because canceling the radical prostatectomy in the presence of micrometastasis is questionable, as such patients may still gain long-term survival benefit from radical prostatectomy.

Wawroschek et al. showed that by examining lymph nodes at several levels, combined with immunohistochemistry, the node positive rate in low-risk patients increased from 5% to 11%. However, the increase was smaller in the intermediate-risk patients (from 34% to 37%). The cautionary note about using immunohistochemistry to detect micrometastasis is that the prognostic significance is uncertain.

**TABLE 1**

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients enrolled</th>
<th>% complications PLND extent</th>
<th>Mean No of LN removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Briganti et al</td>
<td>963</td>
<td>18.9% vs 7.3%</td>
<td>Extended vs limited open 11.7 vs 6.7</td>
</tr>
<tr>
<td>Bader et al</td>
<td>365</td>
<td>2.1%</td>
<td>Extended open 21</td>
</tr>
<tr>
<td>Heidenreich et al</td>
<td>203</td>
<td>8.7% vs 9%</td>
<td>Extended vs modified open 28 vs 11</td>
</tr>
<tr>
<td>Stone</td>
<td>189</td>
<td>35.6% vs 2%</td>
<td>Extended vs modified laparoscopic 17.8 vs 9.3</td>
</tr>
</tbody>
</table>

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Prostate lymphatics drain by way of three routes: ascending ducts, which drain into the external iliac lymph nodes; lateral ducts, which drain into the hypogastric lymph nodes; and posterior ducts, which drain into the sacral lymph nodes.

Pelvic lymphadenectomy are classified as minimal including only obturatorial fossa LN, standard or limited including external iliac and obturatorial LN (Figure 1) and extended including above mentioned with internal iliac and presacral LN (Figure 2). The extent of lymph node dissection during radical prostatectomy has been a source of recent controversies.

With a limited PLND, 38% of LNs are at best removed, whereas with an extended PLND approximately 63% are removed. With a limited PLND, 38% of LNs are at best removed, whereas with an extended PLND approximately 63% are removed.

Bader et al. showed that the anatomic boundaries of lymphadenectomy influence the accuracy of lymph node detection. In their study, 88 of the 365 patients had positive lymph nodes. Of the 88 patients, 51 (58%) had positive internal iliac lymph nodes. Heidenreich et al. also showed that significant lymph node metastasis (42%) occurred outside the external iliac and obturator lymph node distribution in the 103 patients who underwent extended lymph node dissection during prostatectomy. The report by Wawroschek et al. on sentinel lymph node (SLN) mapping in prostate cancer concluded that most of the histopathologically proven metastatic lymph nodes occurred in the external and internal iliac node packets. If pelvic lymphadenectomy was confined to the obturator fossa, it would miss approximately 60% of the metastases.

The total number of lymph nodes removed during lymphadenectomy is of importance to maintain the accuracy of the staging procedure. This is based on the results by Weing et al. from cadaveric dissections showing that approximately 20 lymph nodes must be present in the histopathologic specimen to ensure an adequate and representative pelvic lymphadenectomy.

Matei et al. reported results of mapping study of distribution of 317 lymph nodes found on SPECT/CT/MRI fusion imaging as follows: external iliac and obturator fossa (38%), internal iliac (25%), presacral and pararectal (8%), common iliac (16%), para-aortic/paracaval (12%), and inguinal (1%). Only 38% of the lymph nodes were located within the area of the commonly performed limited PLND area, dorsal to and along the external iliac vein and along the obturator nerve. Only 63% were located in the region of extended PLND, which also includes the LNs both medial and lateral to the internal iliac vessels.

Several studies suggest that more extensive PLND might be associated with higher incidence of positive nodes. ePLND with a mean 17.8 lymph node count was associated with a 3-fold higher LNI rate vs. modified PLND (mean: 9.3 removed lymph nodes) (23% vs 7%; p=0.02). This was confirmed by Heidenreich et al. who found twice as many positive nodes using the extended vs. modified technique (26% vs 12%; p). These findings were further corroborated in a European cohort where 24% of patients treated with ePLND (median 21 nodes), had LNI.

No consensus has been reached regarding PLND extent or the number of lymph nodes that should be removed and examined to maximize the yield of locoregional lymph node staging.

Briganti et al. have indicated that the nodal yield at PLND is directly related to the LNI rate. A greater nodal yield is associated with superior staging accuracy. PLNDs in which fewer than 10 nodes are obtained should probably be omitted, because the probability of finding positive lymph nodes is very limited.
The practical application of more accurate LNI diagnosis in patients with prostate cancer may allow more timely administration of systemic therapy and may result in better survival.\(^\text{168}\)

There is an increasing interest in determining the value of a meticulous pelvic lymph node dissection in prostate cancer patients undergoing radical prostatectomy. Every extended surgical procedure carries additional risks for complications that must be weighed against the potential benefits.

Complication rate increases virtually in direct proportion to the number of nodes removed\(^\text{29}\). (Table 1)

In comparison of complication rates of extended vs limited PLND, Briganti et al found statistically significant difference only for lymphorrhoea and acute urinary retention.

The surgeons could be responsible for difference in the incidence of complication rates. Acute urinary retention and urinary anastomotic leakage occurred significantly or substantially more often in patients in whom a higher number of nodes were removed. This finding is hardly attributable to the pelvic lymph node dissection itself; rather, it would suggest that the cause of these complications were the surgeons whose patients more frequently had lymphorrhoea. Instead of adjusting the multivariate analysis for age, prostate-specific antigen (PSA), or tumour stage, an adjustment for the surgeon, incidence of positive nodes, and length of subcutaneous heparin administered would perhaps have been more helpful.

Other study limitations are related to differences between the number of lymph nodes removed and the number of lymph nodes that are actually examined by the pathologist. Surgical technique variability and differences in patient anatomy, as defined by the number of lymph nodes contained within the fibrofatty tissue specimen, may further contribute to this discrepancy. Moreover, pathologic evaluation of node specimens may account for different number of nodes identified and examined.

With meticulous surgery, serious complications can be avoided, and minor sequelae of short duration, such as a prolonged lymphorrhoea, should not refrain the surgeon from providing patients with the potential benefit of removing lymph nodes harboring micrometastases.

Extended PLND is associated with a threefold increase in the overall rate of complications relative to IPLND. Moreover, the rate of complications increases in a virtually direct proportion to the number of removed nodes. Finally, ePLND also translates into longer hospital stay. These detriments must be taken into account when the staging benefit associated with ePLND is considered.

The incidence of positive lymph nodes was 3% in group of patients having PSA level 10 ng/ml and biopsy Gleason score 7. Studer et al. reported only 3% of positive lymph nodes in surgical specimen of patients with a Gleason score\(^\text{36}\). Heidenreich and coworkers reported that 2.4% of their patients with a PSA 10.5 ng/ml and biopsy Gleason score 7 had positive lymph nodes after extended PLND\(^\text{31}\). Bhatta-Dhar et al. found the risk of positive nodes to be less then 1% in their retrospective series of patients with organ-confined prostate cancer, a preoperative PSA 10 ng/ml, a biopsy Gleason score 7 and with or without PLND\(^\text{31}\). Expectedly, omission of PLND in the low risk group did not negatively affect biochemical relapse rates 6 years after surgery in their series. Therefore, in patients with a PSA 10 ng/ml and a Gleason score it may be reasonable to refrain from performing PLND. However, one must keep in mind that the preoperative decision to do PLND or not is based on biopsies only, which have an inherent 30 to 40% risk of understaging and undergrading.

Current indications for ePLND are PSA level 10 ng/ml, PSA level 10 ng/ml and Gleason score 6, while pelvic lymphadenectomy might be omitted in low risk patients with PSA level 10 ng/ml and Gleason score 7.

**SUMMARY**

**KARLIČNA LIMFADENektomija KOD LOKALIZOVANOG RAKA PROSTATE**

U eri prosta specifičnog antigena, raste proporcija bolesnika sa lokalizovanim rakom prostate. Precizno određivanje preoperativnog statusa limfnih žleza važno je za odgovarajući izbor terapijske opcije, praćenje rezultata lečenja i ranu detekciju recidiva. Invazija limfnih žleza je ključni prognostički parametar za bolesnike koji su podvrgnuti kurativnom tretmanu.

Uprkos kontinuiranim poboljšanjima radiološke opreme, CT, MRI i PET sken nisu apsolutno pouzdani u stajingu limfnih žleza. Razvijeno je više nomograma za predikciju stanja limfnih žleza ali tačnost ovih modela nije veća od 78%.

Hirurgija, bilo otvorena ili laparoskopska karlična limfadenektomija, ostaje temelj stajing-a limfnih žleza. Ipak, postoji više protivrečnosti u vezi karlične limfadenektomije: 1) neophodnost rutinske primene u svih bolesnika, 2) anatomske granice resekcije limfnih žleza, 3) morbiditet limfadenektomije, 4) dijagnostička i terapijska vrednost procedure.

U ovom pregledu literature autori će pokušati da daju odgovore na ova pitanja.

Ključne reči: hirurgija, pelvična limfadenektomija, ePLND.

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