ACI/ STRUČNI RAD

616.65-006.04-06:616.423 -089.894

Pelvic lymphadenectomy for localized prostate cancer

J. Bogdanovic, J. Djozic
Klinika za urologiju, KC Vojvodine, Novi Sad

rezime

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 improvments 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 perfoming 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[1]. 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[2]. 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 1.0 cm 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[3].

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 detecton of lymph node metastases[4]. 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[4].

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.

TABLE 1

COMPLICATION RATES RELATED TO PELVIC LYMPH NODE DISSECTIONS

Study	No of patients enroled	% complications PLND extent	Mean No of	LN removed
Briganti et al	963	18.9% vs 7.3%	Extended vs limited open	11.7 vs 6.7
Bader et al	365	2.1%	Extended open	21
Heidenreich et al	203	8.7% vs 9%	Extended vs modified open	28 vs 11
Stone	189	35.6% vs 2%	Extended vs modified laparoscopic	17.8 vs 9.3

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%[5-7]. 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[8], 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%[9,10].

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[11]. 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 clinicians12. 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[13].

Recently, Briganti et al. published an extended PLND (ePLND) nomogram[14]. 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[24,14].

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[15]. 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[16].

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[17].

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[18].

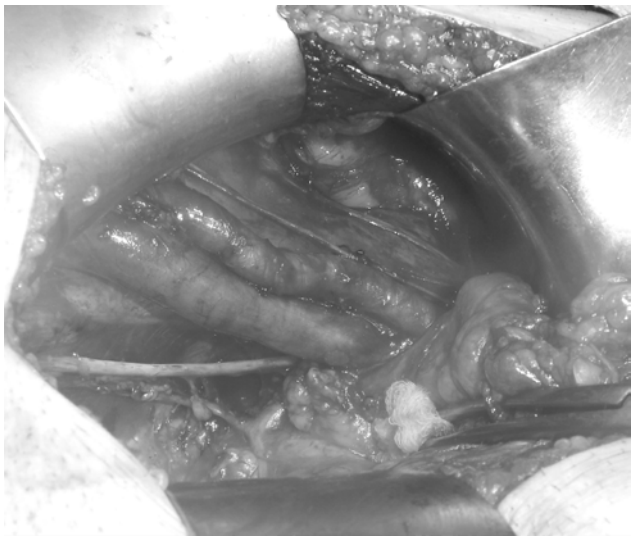

FIGURE 1.
LIMITED PELVIC LYMPHADENECTOMY

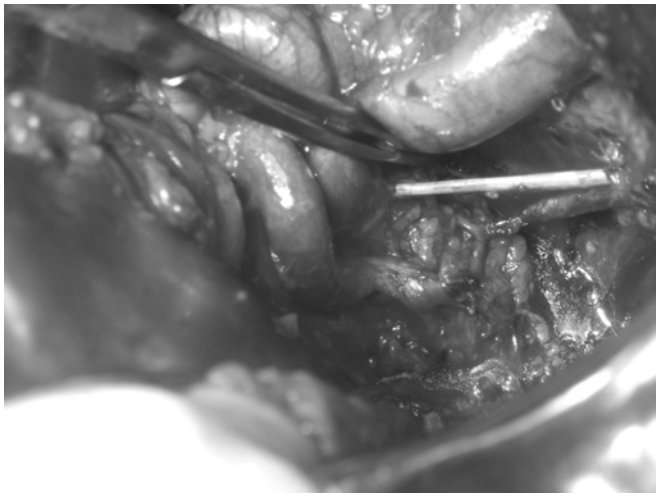

FIGURE 2.
EXTENDED PELVIC LYMPHADENECTOMY

SURGICAL PROCEDURES

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[19].

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 removedWith a limited PLND, 38% of LNs are at best removed, whereas with an extended PLND approximately 63% are removedWith a limited PLND, 38% of LNs are at best removed, whereas with an extended PLND approximately 63% are removedBottom of Form

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[20]. 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[21]. 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[22].

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 rtner*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[23].

Matei et all 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[24].

Several studies suggest that more extensive PLND might be associated with higher incidence of positive nodes [21,25-27] 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[28].

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[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 lPLND. 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 need to 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[30]. 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[21]. 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[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, whilepelvic 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 prostata specifičnog antigena, raste proporcija bolesnika sa lokalizovanim rakom prostate. Precizno odredjivanje preoperativnog statusa limfnih žlezda važno je za odgovarajući izbor terapijske opcije, praćenje rezultata lečenja i ranu detekciju recidiva. Invazija limfnih žlezda 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 stagingu limfnih žlezda. Razvijeno je više nomograma za predikciju stanja limfnih žlezda ali tačnost ovih modela nije veća od 78%.

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

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

Ključne reči: hirurgija, pelvična limfadenektomija, ePLND,

BIBLIOGRAPHY

1. Israel O, Keider Z, Iosilevsky G, Bettman L, Sachs J, Frenkel A. The fusion of anatomic and physiologic imaging in the management of patients with cancer. *Semin Nucl Med*. 2001;31:191–205

2. Aus G, Abbou CC, Bolla M, et al.. EAU guidelines on prostate cancer. Eur Urol. 2005; 48:546–551

3. Flanigan RC, Mohler JL, King CT, *et al:* Preoperative lymph node evaluation in prostatic cancer patients who are surgical candidates: the role of lymphangiography and computerized tomographic scanning with directed fine needle aspiration. J Urol 1985;134**:** 84–87

4. Levran Z, Gonzalez JA, Diokno AC, *et al:* Are computed tomography, bone scan and pelvic lymphadenectomy necessary in the staging of prostatic cancer? Br J Urol 1995; 75**:** 778–781

5. Harris RD, Schned AR, and Heaney JA: Staging of prostate cancer with endorectal MR imaging: lessons from a learning curve. RadioGraphics 1995; 15: 813–829

6. Rifkin MD, Zerhouni EA, Gatsonis CA, *et al:* Comparison of magnetic resonance imaging and ultrasonography in staging early prostate cancer. N Engl J Med 1990; 23: 621–626

7. Vapnek JM, Hricak H, Shinohara K, *et al:* Staging accuracy of magnetic resonance imaging versus transrectal ultrasound in stages A and B prostatic cancer. Urol Int 1994; 53: 191–195

8. Jager GJ, Barentsz JO, Oosterhof GO, Witjes JA, Ruijs SJH. Pelvic adenopathy in prostatic and bladder cancer: MR imaging with a three-dimensional T1-weighted magnetization-prepared-rapid gradient-echo sequence. AJR. 1996; 167: 1503–1507

9. Oyen RH, Van Poppel HP, Ameye FE, Van de Voorde WA, Baert AL, Baert LV. Lymph node staging of localised prostate carcinoma with CT and CT guided fine needle aspiration biopsy: prospective study of 285 patients. Radiology. 1991; 190: 315–322.

10. Wolf JS, Cher M, dalla'Era M, Presti JC, Hricak H, Carrol PR. The use and accuracy of cross-sectional imaging and fine needle aspiration cytology for detection of pelvic lymph node metastases before radical prostatectomy. J Urol. 1995; 153: 993–999

11. de Jong IJ, Pruim J, Elsinga PH, Vaalburg W, Mensink HJ. Preoperative Staging of Pelvic Lymph Nodes in Prostate Cancer by ^{11}C-Choline PET Journal of Nuclear Medicine 2003; 44; 331-335

12.Ross PL, Gerigk C, Gonen M, et al.. Comparisons of nomograms and urologists' predictions in prostate cancer. *Semin Urol Oncol*. 2002;20:82–88.

13.Cagiannos I, Krakiewicz P, Eastham JA, et al. A preoperative nomogram identifying decreased risk of positive pelvic lymph nodes in patients with prostate cancer. J Urol 2003;170:1798-1803

14. Briganti A, Chun FK, Salonia A, et al.. Validation of a nomogram predicting the probability of lymph node invasion among patients undergoing radical prostatectomy and an extended pelvic lymphadenectomy. *Eur Urol*. 2006; 49: 1019–1027

15. Epstein JI, Oesterling JE, Eggleston JC, *et al:* Frozen section detection of lymph-node metastases in prostatic carcinoma: accuracy in grossly uninvolved pelvic lymphadenectomy specimens. J Urol 1986; 136:1234–1237

16. Beissner RS, Stricker JB, Speights VO, *et al:* Frozen section diagnosis of metastatic prostate adenocarcinoma in pelvic lymphadenectomy compared with nomogram prediction of metastasis. Urology 2002: 59: 721–725

17. Han M, Partin AW, Pound CR, *et al:* Long-term biochemical disease free and cancer specific survival following anatomic radical retropubic prostatectomy: the 15 year Johns Hopkins experience. Urol Clin North Am 2001;28:555–565

18. Wawroschek F, Wagner T, Hamm M, *et al:* The influence of serial sections, immunohistochemistry and extension of pelvic lymphnode dissection on the lymph-node status in clinically localized prostate cancer. Eur Urol 2003: 43: 132–137

19. Gil-Vernet JM: Prostate cancer: anatomical and surgical considerations. Br J Urol 1996; 78:161–168

20. Bader P, Burkhard FC, Markwalder R, *et al:* Is limited lymph-node dissection an adequate staging procedure for prostate cancer? J Urol 2002; 168: 514–518

21. Heidenreich A, Varga Z, and Knobloch RV: Extended pelvic lymphadenectomy in patients undergoing radical prostatectomy: high incidence of lymph-node metastasis. J Urol 2002:167:1681–1686

22. Wawroschek F, Hamm M, Weckermann D, *et al:* Lymph-node staging in clinically localised prostate cancer. Urol Int 2003; 71:129– 135

23. Weing rtner K, Ramaswamy A, Bittinger A,*et al:* Anatomical basis for pelvic lymphadenectomy in prostate cancer: results of an autopsy study and implications for the clinic. J Urol 1996; 156:1969–1971

24. Matei A, Fuechsel FG, Bhatta Dhar N, Warncke SH, Thalmann GN, Krause T, Studer U. The Template of the Primary Lymphatic Landing Sites of the Prostate Should Be Revisited: Results of a Multimodality Mapping Study. Eur Urol in press.

25. Bader P, Burkhard FC, Markwalder R, Studer UE. Is a limited lymph node dissection an adequate staging procedure for prostate cancer?. J Urol. 2002;168:514–518

26. Allaf ME, Palapattu GS, Trock BJ, Carter HB, Walsh PC. Anatomical extent of lymph node dissection: impact on men with clinically localized prostate cancer. J Urol. 2004;172:1840–1844.

27. Stone NN, Stock R, Unger P. Laparoscopic pelvic lymph node dissection for prostate cancer: compariсon of the extended and modified technique. J Urol. 1997;158:1891–1894

28. Briganti A, Chun F, Salonia A, Gallina A, Zanni G, Scattoni V, Valiquette L, Rigatti P, Montorsi F, and Karakiewicz P. Critical assessment of ideal nodal yield at pelvic lymphadenectomy to accurately diagnose prostate cancer nodal metastasis in patients undergoing radical retropubic prostatectomy. Urology 2007; 69: 147-151

29. Briganti A, Chun FKH, Salonia A, et al.. Complications and other surgical outcomes associated with extended pelvic lymphadenectomy in men with localized prostate cancer. Eur Urol. 2006;50:1006–1013

30. Schumacher M, Burchard F, Thakmann G, Fleischman A, Studer U. Is Pelvic Lymph Node Dissection Necessary in Patients with a Serum PSAng/ml Undergoing Radical Prostatectomy for prostate cancer ?, Eur Urol 2006; 50: 272-279

31. Bhatta-Dhar N, Reuther AM, Zippe C, Klein EA. No difference in six-year biochemical failure rates with or without pelvic lymph node dissection during radical prostatectomy in low-risk patients with localized prostate cancer. Urology2004;63: 528-531