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Standard versus extended pelvic lymphadenectomy in the patients with clinically localized prostate cancer

Standardna u odnosu na proširenu karličnu limfadenektomiju kod bolesnika sa klinički lokalizovanim karcinomom prostate

Jovo Bogdanović*†, Vuk Sekulić*†, Sandra Trivunić-Dajko†‡, Ranko Herin*, Senjin Djozić*†

Clinical Center of Vojvodina, *Clinic of Urology, ‡Center for Pathology and Histology, Novi Sad, Serbia; University of Novi Sad, †Faculty of Medicine, Novi Sad, Serbia

Abstract

Background/Aim. Pelvic lymph node dissection (PLND) is the most accurate staging procedure in the diagnosis of lymph node involvement by prostate cancer. However, the therapeutic value of this procedure is still unclear. The objective of the study was to compare diagnostic and therapeutic values of extended and standard PLND as an adjunct of radical prostatectomy. **Methods.** The patients who underwent surgical treatment for clinically localized prostate cancer (n = 157) were enrolled in this open nonrandomized prospective study. In the standard PLND (sPLND) group 109 patients were enrolled while the extended PLND (ePLND) group involved 48 patients. Both groups were compared regarding age, prostate-specific antigen (PSA) level, a percentage of positive biopsies, preoperative and postoperative Gleason score, number of retrieved and positive lymph nodes, duration of surgery, blood loss, amount of lymphorrhea and biochemical recurrence-free survival. **Results.** The average number of retrieved lymph nodes was 17.27 and 24.46 in the sPLND and ePLND group, respectively ($p = 0.001$). The rate of positive lymph nodes was 9/109 (8.3%) and 8/48 (16.7%) in the sPLND and ePLND groups, respectively. Biochemical recurrence was noted in 38/109 (31.2%) and 7/48 (14.6%) patients in the sPLND and ePLND group, respectively ($p = 0.003$). **Conclusion.** Comparison of sPLND to ePLND led to the following conclusions: nodal yield was significantly higher in the ePLND group; the ePLND template was associated with a much higher rate of lymph node metastases; the biochemical recurrence-free survival rate was significantly more favorable in the ePLND group comparing to the sPLND group.

Key words:
lymph node excision; pelvis; prostatic neoplasms; prostatectomy; surgical procedures, operative.

Apstrakt

Uvod/Cilj. Karlična limfadenektomija predstavlja najpreciznu proceduru u dijagnostici metastaza karcinoma prostate u limfne čvorove. Međutim, njena terapijska vrednost još uvek nije jasna. Cilj ove studije je bio da uporedi dijagnostičku i terapijsku vrednost proširene i standardne karlične limfadenektomije u sklopu radikalne prostatektomije. **Metode.** Ukupno 157 bolesnika koji su hirurški lečeni radi klinički lokalizovanog raka prostate bili su uključeni u otvorenu nerandomizovanu prospektivnu studiju. U grupu standardne karlične limfadenektomije (sPLND) bilo je uključeno 109 bolesnika, a u grupu proširene karlične limfadenektomije (ePLND) 48 bolesnika. Obe grupe su bile upoređene prema starosti, koncentraciji prostate specifičnog antigena (PSA), procentu pozitivnih bioptata, Gleason skoru, broju odstranjenih i pozitivnih limfnih čvorova, trajanju operacije, procenjenoj količini gubitka krvi, količini limforeje i preživljavanju bez biohemijskog recidiva. **Rezultati.** Prosečan broj odstranjenih limfnih čvorova bio je 17,3 u sPLND grupi i 24,5 u ePLND grupi ($p = 0.001$). U sPLND grupi 9/109 (8,3%) bolesnika imalo je pozitivne limfne čvorove, a u ePLND grupi 8/48 (16,7%). Biohemijski recidiv ustanovljen je kod 31/109 (31,2%) bolesnika u sPLND grupi odnosno 7/48 (14,6%) bolesnika u ePLND grupi ($p = 0.003$). **Zaključak.** Upoređivanje sPLND i ePLND grupa dovelo je do sledećih zaključaka: proširenom karličnom limfadenektomijom se odstrani značajno više limfnih čvorova; prošenom karličnom limfadenektomijom dijagnostikuje se mnogo više metastaza u limfnim čvorovima; značajno je povoljnije preživljavanje bez biohemijskog recidiva u grupi proširene karlične limfadenektomije.

Ključne reči:
limfadenektomija; karlica; prostata, neoplazme; prostatektomija; hirurgija, operativne procedure.

Correspondence to: Jovo Bogdanović, Clinical Center of Vojvodina, Clinic of Urology, Hajduk Veljkova Str 1-9, 21 000 Novi Sad, Serbia. E-mail: jovo.bogdanovic@mf.uns.ac.rs

Introduction

The incidence of lymph node metastases reported in the contemporary series of radical prostatectomies ranges between 2% and 57% [1, 2]. These differences may be a consequence of the extent of pelvic lymph node dissection (PLND) and inconsistent patient selection criteria. However, a lymph node involvement is an unfavorable prognostic factor for patients with prostate cancer.

Radical prostatectomy with, or without a PLND is a surgical procedure aimed to cure the patients with localized, or locally advanced prostate cancer. Despite the recent improvements of radiological imaging modalities, PLND is still the most accurate procedure for the diagnosis of lymph node metastases in the patients with prostate cancer [2]. Regardless of a surgical approach, either open or minimally invasive, PLND should provide an adequate surgical specimen of lymph nodes for the histopathological analysis. Retrieval of over 20 lymph nodes was considered as an adequate specimen for satisfying staging [3]. However, an autopsy study reported by Weingärtner et al. [4] showed the significant interpersonal variations in the pelvic lymph node count, even in the standard template of PLND. Therefore, a meticulous dissection in an anatomically defined template seems to be more important than the retrieval of certain number of lymph nodes. Unfortunately, there is still no consensus regarding the optimal PLND template. On the other hand, there are significant interpersonal variations among surgeons performing PLND with doubtful adherence to the proposed template [5]. Some authors suggested that the patients who underwent minimally invasive surgery had a lower yield comparing to those receiving an open surgical procedure [6].

The therapeutic value of extended PLND (ePLND) is controversial. However, several authors reported a long-term biochemical recurrence-free survival in the patients with the minimally invaded lymph nodes even without the androgen-deprivation therapy [7].

This prospective study was aimed to analyze the diagnostic and therapeutic value of two different templates of PLND used in our institution.

Methods

During the period from January 2007 to December 2011, a total of 309 patients underwent the radical retropubic prostatectomy at the tertiary institution. The open nonrandomized prospective study was aimed to compare the diagnostic and therapeutic value of two templates of PLND that were used as an adjunct of radical prostatectomy.

The inclusion criteria were as follows: age up to 75 years, the preoperative prostate- specific antigen (PSA) level up to 25 ng/mL, 12-cores transrectal ultrasound (TRUS)-guided prostate biopsy with a complete histopathological report including the number of positive cores and primary and secondary Gleason grades, and completed clinical staging.

The non-inclusion criterion was the administration of neoadjuvant hormonal therapy.

The exclusion criterion was poor compliance with the follow-up schedule.

A total of 157 patients who fulfilled the inclusion criteria were included in the study. According to the template of performed PLND, the patients were enrolled into the standard PLND (sPLND) group (n = 109), or ePLND group (n = 48). The template of PLND was selected upon discussion between a surgeon and a patient.

Both groups were compared regarding age, the PSA level, a percentage of positive biopsies, the Gleason score, the number of retrieved and positive lymph nodes, the duration of surgery, blood loss and the amount of lymphorrhea and biochemical-free survival. Also, a total count of retrieved and lymph nodes as well as those bearing metastases within the sPLND and ePLND templates were analyzed in the ePLND group.

The sPLND template was bordered laterally by the genitofemoral nerve, distally with the inguinal ligament, proximally with the bifurcation of the common iliac artery, medially with the lateral bladder wall, and the internal iliac artery including obturator fossa with the completely skeletonized obturator nerve and the external iliac artery and vein (Figure 1a). The ePLND template was defined proximally with the common iliac vein, medially with perirectal and perivesical fat tissue, laterally with the genitofemoral nerve and lateral pelvic wall and distally with the inguinal ligament, with the completely skeletonized common iliac vein, the internal iliac artery and vein, the external iliac artery and vein as well as the obturator nerve (Figure 1b). The procedure was completed with the removal of the prostate within the prostatic capsule and seminal vesicles and creation of vesicourethral anastomosis over 18 Fr three-way Foley catheter leaving the drains bilaterally.

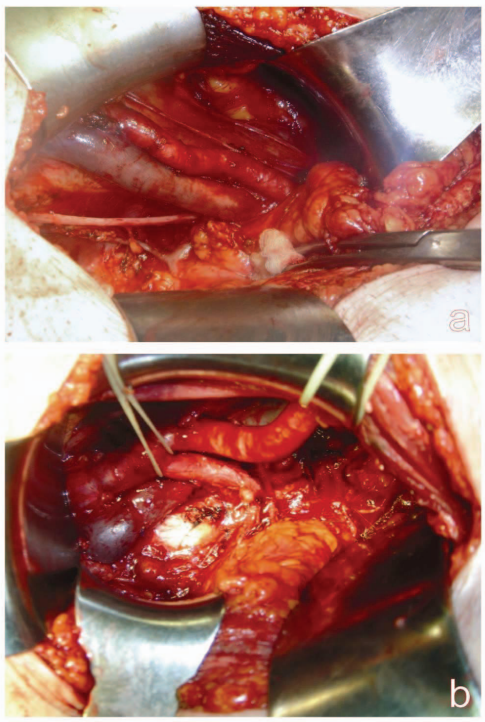

Fig. 1 – a) Standard pelvic lymph node dissection (PLND) template; b) extended PLND template.

Prostate cancer was confirmed by the histopathological examination of 12-core transrectal ultrasound-guided prostate biopsy specimen. The Gleason score was determined by different pathologists according to the International Society of Urological Pathology (ISUP) criteria [8]. A percentage of positive biopsies was calculated as the ratio of the number of positive biopsies/total number of biopsies.

All patients were staged by the digital rectal examination, computed tomography (CT) of abdomen and pelvis, and bone scan. All patients underwent surgery under the general anesthesia. A radical prostatectomy specimen was handled according to the recommendation by Montironi et al. [9]. Two dedicated uropathologists analyzed the surgical specimen for the lymph node count, lymph node metastases, extraprostatic extension, seminal vesicle invasion, status of surgical margins and Gleason score. Immunohistochemistry was not available during the observed period, and only the haematoxylin and eosin (H&E) staining was used.

The digital rectal examination and determination of PSA level were used for the routine follow-up at six weeks after surgery, every three months during the first year, and thereafter twice annually until July 2012. Biochemical recurrence was defined as the presence of two consecutive and rising PSA values above 0.2 ng/mL. Time to the biochemical recurrence was recorded prospectively during the outpatient visits.

The statistical analysis was performed using "Smart line agency" packet of statistical programs. The parametric data were analyzed using the Student's *t*-test and ANOVA. The categorical data were analyzed by using Pearson's χ^2 test. Biochemical recurrence-free survivals were shown as the Kaplan–Meier estimates and overall group differences were evaluated by the log-rank statistics.

The study was conducted according to the principles of the Helsinki declaration and it was approved by the Ethics Committee of our Institution. An informed consent was obtained from all individual participants included in the study.

Results

The patient demographics and biopsy characteristics of prostate cancer are shown in Table 1. The patients' age in both groups was similar and differences were not statistically significant ($p = 0.865$, Student's *t*-test). The mean PSA level was 10.30 ng/mL and 12.44 ng/mL in the sPLND group and the ePLND group, respectively. Although the mean values were close within the intermediate-risk group range, the difference was statistically significant ($p = 0.012$, Student's *t*-test). Also, the patients who received ePLND had a higher percentage of positive biopsies than those receiving sPLND, but the difference was not statistically significant. The distribution of biopsy Gleason scores was similar in both groups.

The variables that characterized surgery are shown in Table 2. The mean duration of surgery was 218.5 minutes and 204.5 minutes in the ePLND and sPLND group, respectively. The difference was statistically significant ($p = 0.043$, Student's *t*-test). The mean blood loss was significantly higher in sPLND than in ePLND ($p = 0.009$, Student's *t*-test). The average postoperative drainage was 1491.50 mL and 1158 mL in the ePLND and sPLND group respectively. However, the differences in the total amount and duration of postoperative drainage were not statistically significant.

Table 1
Preoperative characteristics of the study population

Variable	sPLND	ePLND	*p*
Age (years)[a]	65.14 ± 5.78	65.27 ± 6.02	0.865*
PSA level[a] (ng/mL)	10.30 ± 5.08	12.44 ± 4.41	0.012*
Percent of positive biopsies[a]	37.03 ± 24.35	43.68 ± 29.41	0.138*
Biopsy, Gleason score (n)			0.364**
4 and 5	38	9	
6	32	17	
7	35	19	
8 to 10	4	3	
Total	109	48	

[a]results are given as mean ± standard deviation.
sPLND – standard pelvic lymph node dissection;
ePLNS – extended pelvic lymph node dissection;
PSA – prostate specific antigen;
n – number of patients; *Student's *t*-test; **χ^2 test.

The postoperative pathological staging and Gleason scores are shown in Table 3. The patients in the ePLND group had more commonly the locally advanced disease and lymph node metastases than those in the sPLND group. Although the lymph node metastases (pN1) were diagnosed more frequently following ePLND, this difference was not statistically significant ($p = 0.119$). Also, there was no association between the distribution of postoperative Gleason score in the investigated groups.

Table 2
Surgery-related features in the investigated groups

Variable	sPLND mean ± SD	ePLND mean ± SD	*p*
Number of lymph nodes	17.27 ± 5.66	24.46 ± 10.98	0.001*
Duration of surgery (min)	204.5 ± 38.33	218.54 ± 43.45	0.043*
Average blood loss (mL)	826.84 ± 549.07	590.96 ± 444.84	0.009*
Drainage (mL)	1158.13 ± 1517.77	1491.50 ± 1570.77	0.081*
Drainage (days)	12.89 ± 4.34	14.29 ± 5.48	0.084*

Abbreviation under Table 1.
SD – standard deviation; *Student's *t*-test.

Table 3

Distribution of pathological stages and the Gleason score in the investigated groups.

Parameters	sPLND n (%)	ePLND n (%)	*P* (χ^2 test)
Pathological stage			0.004
pT0	3 (2.75)	0	
pT2	82 (75.23)	30 (62.50)	
pT3a	8 (7.34)	9 (18.75)	
pT3b and 4a	16 (14.68)	9 (18.75)	
pN1	9 (8.25)	8 (16.67)	0.119
Postoperative Gleason score			0.065
not available (pT0)	3 (2.75)	0	
4 and 5	20 (18.35)	5 (10.42)	
6	40 (36.70)	13 (27.08)	
7	36 (33.03)	21 (43.75)	
8–10	10 (9.17)	9 (18.75)	

Abbreviation under Table 1.
n (%) – number (percentage) of patients.

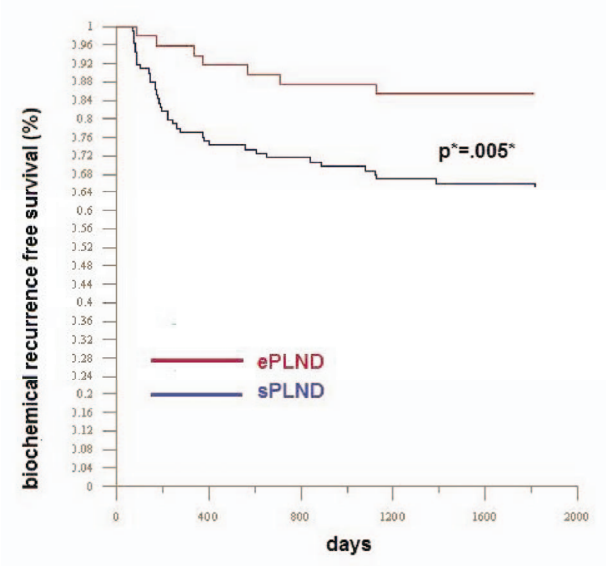

Fig. 2 – Kaplan-Meier plots of biochemical recurrence-free survival in the sPLND and ePLND groups. Abbreviations under Table 1.

There was a statistically significant difference in the lymph node yield among the sPLND and ePLND groups ($p = 0.003$, Student *t*-test). A total of 1,882 lymph nodes was removed in the sPLND group; the average number of lymph nodes was 17.27 ± 5.66 (range 8 to 34). The total of 1,174 lymph nodes was retrieved in the ePLND group; the mean number was 24.46 ± 10.98 (range 9 to 73). This nodal yield consisted of 861 and 313 lymph nodes removed within the sPLND template and hypogastric and presacral regions, respectively. The average number of retrieved nodes was 17.94 ±7.59 within the sPLND template and an additional 6.53 ± 4.35 in the hypogastric and presacral region.

In the sPLND group 9 (8.25%) patients were found to have the lymph node metastases. Eight (16.67%) patients in the ePLND group were diagnosed to have the nodal metastases. The lymph node metastases were found exclusively within the sPLND template in 2 (25%) patients. The lymph node metastases were detected exclusively in the hypogastric and presacral region in 3 (37.5%) patients. Another three patients had positive nodes within both templates. Therefore, increasing of nodal yield for 24.46% led to increased detection of lymph node involvement by 37.5%.

However, 40% of patients with sPLND group retrieved less than 15 lymph nodes, while 26.61% had 22 or more lymph nodes. Only 16% of surgical specimens contained less than 15 lymph nodes in the ePLND group, and 50% had 22 or more lymph nodes. There was also a statistically significant difference ($p = 0.006$; χ^2 test).

The biochemical recurrence-free survival was more favorable in the ePLND group. Figure 2 represents the Kaplan-Meier plots for biochemical recurrence-free survival in both groups.

Discussion

Radical prostatectomy with PLND is the treatment option for the patients with high-risk prostate cancer as well as a substantial proportion of those with intermediate-risk disease. Nowadays, the ePLND is recommended whenever a lymph node dissection has to be performed in these patients [10]. However, the limits of ePLND are still controversial. Currently, there are a few suggested templates of ePLND. The original, extended PLND template included a dissection of lymph nodes within the obturator fossa, external and internal iliac region. Recently, it was suggested that the presacral lymph nodes should be included in the ePLND template, too. The super-extended PLND means an additional dissection of lymph nodes in the common iliac region [11].

The clinicians dealing with the surgical treatment of prostate cancer are truly lacking a reliable radiological tool for the detection of positive lymph nodes. It is not expected that radiological imaging will be improved to the extent of detecting lymph node micrometastases in the near future. Therefore, we still need to adhere to meticulous PLND within extended templates. Generally, there are significant interpersonal and inter-institutional variations in the performance of this procedure. A surgeon seems to be the most important risk factor for a lymph node yield. Obviously, few surgeons who were performing radical prostatectomy in this study did not adhere to the recommended ePLND template.

Our data clearly showed that sPLND provides significantly fewer lymph nodes than ePLND. Also, this study showed that a substantial proportion of patients who received ePLND had a lower nodal yield than some patients receiving sPLND. This phenomenon can be explained by the inter-individual variations of pelvic lymph node count. Weingärtner et al. [4] analyzed a lymph node count on 30 cases in an autopsy study within the standard template only. They found significant interpersonal variations of lymph nodes count in the range from 8 to 56.

Although the rate of lymph node metastases was twice as higher in the ePLND group, the difference was not statistically significant. A lower percentage of diagnosed lymph node metastases in the ePLND group may be a result of restrictive inclusion criteria with the upper PSA level < 25 ng/mL.

The nodal yield of 20 lymph nodes was considered adequate for the reliable pathological staging [3]. Although the lymph node count is suitable for statistical analysis, it may represent a problem in clinical practice because a substantial proportion of patients receiving ePLND do not have 20 lymph nodes in their surgical specimen. In our opinion, there are five anatomical regions of pelvic lymph nodes: external iliac, obturator, hypogastric (internal iliac), presacral, and common iliac group. With an increasing number of these anatomical regions within the PLND template, there is also increasing the probability of accurate staging and complete dissection of involved nodes. Duration of surgery was increased significantly by more extensive lymph node dissection. Studer and Collette [12] reported that extended PLND increased the duration of surgery for 30 minutes approximately. The smaller difference was found in this study, probably because less experienced surgeons who required more time for prostate removal performeds PLND. It was also reflected in the amount of intraoperative blood loss. The amount of drainage was higher in the ePLND group, but this difference was not statistically significant. Capitanio et al. [13] reported a positive association between the amount of lymphorrhea with the number of removed lymph nodes and patients'age. The surgeons in both groups have used different techniques for lymph vessels control such as ligation, electrocautery, and harmonic scalpels. The influence of dissection techniques on the severity and duration of lymphorrhoea was not investigated in this study.

Lymph node metastases are an unfavorable prognostic factor in prostate cancer patients. However, many authors have reported a possible therapeutic role of PLND, particularly in patients with 1 or 2 positive nodes. Schumacher et al. [14] and Seiler et al. [15] reported that 20% of patients with one positive node have a chance to remain free of recurrence even without adjuvant hormonal treatment. Also, ePLND provided superior treatment outcome in terms of biochemical recurrence-free survival than sPLND even if the pN0 stage was confirmed. This treatment effect may be based on two facts: s PLND cannotremove positive nodes outside of the used template, and ePLND may remove more nodes with the unrecognized micrometastases. The patients who have experienced early biochemical recurrence after the radical prostatectomy with sPLND were diagnosed with the Gleason score ≥ 7, or PSA level > 10 ng/ml. Therefore, all patients with a high-risk prostate cancer (Gleason score ≥ 8, and/or clinical stage ≥ T3a, and/or PSA level >20 ng/mL) and a substantial proportion of patients with intermediate-risk disease (Gleason score 7, and/or clinical stage T2b, of T2c, and/or PSA level 10–20 ng/mL), particularly those with the primary Gleason grade 4 in the prostate biopsy, had a clear indication for PLND. It is recommended to perform an ePLND when it deemed necessary. The patients with low-risk prostate cancer (Gleason score < 7, PSA < 10 ng/mL, and clinical stage ≤ T2a) are not candidates for PLND [10, 16].

This study has certain limitations. Inapplicability of randomization is a potential limitation of the study design. Also, the heterogeneity of study groups may be another limitation of the survey. However, this problem is common in the majority of single-center studies. Further concerns are related to possible selection bias and the interpersonal variations in the experience and the expertise level in performance of PLND among different surgeons in the study.

Conclusion

The extended pelvic lymph node dissection was clearly superior to the standard pelvic lymph node dissection in terms of nodal yield. Detection of metastatic lymph nodes was much higher following the extended pelvic lymph node dissection.

Biochemical recurrence-free survival was significantly less favorable following the standard pelvic lymph node dissection. However, the therapeutic value of extended pelvic lymph node dissection has to be confirmed in further investigations.

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