# Radical Prostatectomy with Extended Pelvic Lymphadenectomy: Impact of Separate Vs. En Bloc Lymph Node Submission on Pathohistological Analysis

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Original Scientific Paper



# RADICAL PROSTATECTOMY WITH EXTENDED PELVIC LYMPHADENECTOMY: IMPACT OF SEPARATE VS. *EN BLOC* LYMPH NODE SUBMISSION ON PATHOHISTOLOGICAL ANALYSIS

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SUMMARY – **Introduction:** In prostate cancer (PC), it is well established that the wider the anatomical template of dissection, the higher the number of lymph nodes (LNs) retrieved, and the higher the nodal yield, the better the detection of metastasis[1,2].
**Objectives:** The objectives of this study were to evaluate if the change in submission methodology (*en bloc* vs. separate) had an impact on the number of total LNs identified per patient and the number of positive LNs found, and to determine the impact of individual pathologists on the number of total LNs and positive LNs.
**Patients and methods:** We performed a retrospective analysis of hospital records of patients with PC in whom radical prostatectomy (RP) with pelvic lymphadenectomy (PLND) was done in the period from November 2012 to December 2018. We used only a single-surgeon series in order to avoid performance bias in the lymphadenectomy template. Pathohistological examinations were performed by our hospital's two dedicated urogenital pathologists. Patients were divided into high and intermediate risk groups according to the European Association of Urology (EAU) guidelines, based on submission methodology of the lymphadenectomy tissue and by the pathologist performing the examinations. The number of LNs and number of positive LNs acquired were then compared using the Mann-Whitney test.
**Results:** Patients who underwent separate submission of lymphadenectomy tissue had a significantly higher nodal yield, but there was no difference in the number of positive LNs. There was no significant difference in the total number of LNs acquired and LN metastases detected between our two pathologists when comparing them by submission technique.
**Conclusions:** Separate submission of lymphadenectomy tissue resulted in a higher nodal yield, but it did not translate to a higher number of positive LNs found.

Key words: *prostate cancer; lymphadenectomy; nodal count; separate; en bloc*

## Introduction

Prostate cancer (PC) is currently one of the biggest public health issues in the European Union, as it is a cancer with increasing incidence and mortality[3]. In Croatia, it is the most frequently diagnosed cancer with a high mortality rate.

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In the last few decades, there have been many new technological and medical developments with new concepts for the treatment of PC. As a result of these developments, patients can be offered different treatment modalities. For patients with organ-confined disease, RP still remains one of the basic treatment options. RP was introduced to oncologic surgery more than 100 years ago and has established itself as a valid treatment option. During this period, RP has evolved in several different aspects. In addition to technological developments such as the introduction of robot-assisted laparoscopic surgery, it has also evolved as a concept with the introduction of nerve-sparing surgery as a basis for functional recovery of patients. However, a favorable oncologic outcome remains an indispensable prerequisite, so oncologic treatment principles continue to form the basis of any treatment modality. In this context, lymphadenectomy (LND) has become a standard component of surgery. Lymph node removal is a well-established concept in oncology with proven benefits in terms of staging and its therapeutic role in certain types of cancer. The role of LND in patients with prostate cancer is still under debate. The current literature supports LND as the most accurate staging procedure, whereas we can still only hypothesize about the therapeutic role of LND[2,4-7]. The European Association of Urology (EAU) PC guidelines suggest pelvic lymphadenectomy (PLND) in patients in whom lymphadenectomy is indicated. PLND in patients with prostate cancer is currently defined as removal of nodes overlying the external iliac artery and external iliac vein, nodes in the obturator fossa located cranially and caudally to the obturator nerve, and the nodes medial and lateral to the internal iliac artery. There is no definitive conclusion on whether the different submission technique of the LND tissue have an impact on the detection of lymph node metastases.

We had three main research objectives to achieve in this study. Firstly, derermining whether submission of the LND tissue in separate containers result in a higher number of lymph nodes (LNs) found on pathohistological examination than submission of tissue *en bloc*. Secondly, determining whether the submission technique has an effect on the number of lymph node metastases found. And thirdly, investigating what influence individual pathologists had on the total number of LNs found and the number of lymph node metastases found.

## Patients and methods

In this retrospective study, we evaluated the medical records of patients who underwent RP with extended PLND at the Clinical Hospital Centre Rijeka between November 2012 and December 2018. To avoid performance bias, we used data only from patients who had the same senior surgeon. Pathohistological analysis of the tissue obtained by surgery was performed by the hospital's two dedicated genitourinary pathologists.

The LND tissue was immersed in a formaldehyde solution after surgery. It was then first examined macroscopically in the pathology laboratory, and palpable lymph nodes were excised and placed in cassettes. The cassettes were then prepared in a series of ethanol solutions of increasing concentration (70-99%) and then immersed in xylol before being immersed in paraffin, sectioned, and stained using a standard hematoxylin and eosin stain.

The study patients were classified according to their initial prostate specific antigen (PSA) level, biopsy results, and clinical staging data (MSCT of the abdomen and pelvis; mpMR of the pelvis; bone scintigraphy). We defined the intermediate and high risk groups according to the EAU PC guidelines. Patients were also divided according to the submission technique of the lymphadenectomy tissue into *en bloc* and separate submission groups. We also divided patients according to the pathologist who performed the pathohistological examination. The total number of LNs removed and the number of positive LNs found were analysed, and the distribution of the data was examined for normality of distribution using the Shapiro-Wilk test; the difference in distribution was then analysed using the Mann-Whitney test in Stata 14 software.

We identified a total of 71 patients with a median age of 76 years of age, ranging from 59 to 83 years. Of these, 40 patients were in the high-risk group and 31 were in the intermediate-risk group.

Of the 40 patients in the high-risk group, lymphadenectomy tissue was submitted *en bloc* in 13 patients and in separate containers in 27 patients. Of the 13 patients with *en bloc* submission, pathohistological examinations were performed by pathologist A in 9 cases and by pathologist B in 4 cases. Of the 27 patients in the separate submission technique group, pathohistological examinations were performed by pathologist A in 14 cases and by pathologist B in 13 cases.

Of the 31 patients in the intermediate-risk group, lymphadenectomy tissues were submitted *en bloc* in 13

patients and in separate containers in 18 patients. Of the 13 in the *en bloc* submission group, lymphadenectomy tissue was examined by pathologist A in 10 cases and by pathologist B in 3 cases. In the separate submission group, of the total 18 patients, 5 lymphadenectomy tissues were examined by pathologist A and 13 by pathologist B.

## Results

Analysis of lymph node yield and positive (metastatic) lymph nodes by prostate cancer risk group **(Table 1)**

High-risk group

In the high-risk PC group, the median of number of LNs found in the separate submission group was 16 and ranged from 9 to 38.

In the *en bloc* submission group, the median number of LNs found was 12, ranging from 8 to 17. The difference in the distribution of the data was statistically significant with a p value of 0.0033.

In the high-risk PC group, the median number of positive LNs found was 0, while it ranged from 0 to 3 in the separate submission group. In the *en bloc* submission group, the median positive LNs found was also 0, ranging from 0 to 10. The difference in the distribution of the data was not statistically significant, with a p value of 0.7082.

Intermediate-risk group

In the intermediate-risk PC group, the median number of LNs found was 19 and ranged from 8 to 28 in the separate submission technique group. In the *en bloc* submission group, the median number of LNs found was 13, ranging from 6 to 22. The difference in the distribution of the data was statistically significant with a p value of 0.0286.

In the group of patients with intermediate-risk prostate cancer who underwent RP with extended PLND, no positive LNs were found regardless of the submission technique.

Table 1. Number of LN and positive LN by submission type

| | **Total** | | **En bloc** | | **Separate** | | |
|---|---|---|---|---|---|---|---|
| | N | Median (min-max) | N | Median (min-max) | N | Median (min-max) | p value |
| **HIGH RISK** | | | | | | | |
| Total LN | 40 | 14.5 (8-38) | 13 | 12 (8-17) | 27 | 16 (9-38) | **0.0033** |
| Positive LN | 40 | 0 (0-10) | 13 | 0 (0-10) | 27 | 0 (0-3) | 0.7082 |
| **INTERMEDIATE RISK** | | | | | | | |
| Total LN | 31 | 15 (6-28) | 13 | 13 (6-22) | 18 | 19 (8-28) | **0.0286** |
| Positive LN | 31 | 0 (0-0) | 13 | 0 (0-0) | 18 | 0 (0-0) | N/A |

LN=lymph nodes, N/A=not available. Data are presented as medians and minimal to maximal value range. N denotes number of patients. Significant values are denoted in bold (p<0.05).

Table 2 Number of LN and positive LN by pathologist and submission type – high risk PC

| | **Total** | | **Pathologist A** | | **Pathologist B** | | |
|---|---|---|---|---|---|---|---|
| | N | Median (min-max) | N | Median (min-max) | N | Median (min-max) | p value |
| **EN BLOC** | | | | | | | |
| Total LN | 13 | 12 (8-17) | 9 | 12 (8-17) | 4 | 11 (10-16) | 1.0000 |
| Positive LN | 13 | 0 (0-10) | 9 | 0 (0-10) | 4 | 0 (0-0) | 0.1308 |
| **SEPARATE** | | | | | | | |
| Total LN | 27 | 16 (9-38) | 14 | 14 (9-32) | 13 | 21 (10-38) | 0.0794 |
| Positive LN | 27 | 0 (0-3) | 14 | 0.5 (0-3) | 13 | 0 (0-3) | 0.2057 |

LN=lymph nodes, N/A=not available. Data are presented as medians and minimal to maximal value range. N denotes number of patients. Significant values are denoted in bold (p<0.05).

Table 3 Number of LN and positive LN by pathologist and submission type – intermediate risk PC

| | Total | | Pathologist A | | Pathologist B | | |
|---|---|---|---|---|---|---|---|
| | N | Median (min-max) | N | Median (min-max) | N | Median (min-max) | p value |
| **EN BLOC** | | | | | | | |
| Total LN | 13 | 13 (6-22) | 10 | 12.5 (6-21) | 3 | 14 (7-22) | 0.6116 |
| Positive LN | 13 | 0 (0-0) | 10 | 0 (0-0) | 3 | 0 (0-0) | N/A |
| **SEPARATE** | | | | | | | |
| Total LN | 18 | 19 (8-28) | 5 | 15 (12-19) | 13 | 19 (8-28) | 0.3177 |
| Positive LN | 18 | 0 (0-0) | 5 | 0 (0-0) | 13 | 0 (0-0) | N/A |

LN=lymph nodes, N/A=not available. Data are presented as medians and minimal to maximal value range. N denotes number of patients. Significant values are denoted in bold ($p<0.05$).

Analysis of lymph node yield and positive (metastatic) lymph nodes according to the pathologists

High-risk group (**Table 2**)

When comparing the pathologists who performed the pathohistological examinations in the high-risk PC group with the separate submission technique of LND tissue, pathologist A found a median of 14 LNs, ranging from 9 to 32. In the same group, pathologist B found a median of 21 LNs, with a range of 8 to 38. The difference in the distribution of the data was not statistically significant, with a p value of 0.0794.

When comparing the positive (metastatic) LNs found in the high-risk group by each pathologist in the separate submission group, we found that the median number of LNs found for pathologist A was 0.5, with a range of 0 to 3, while the median number for pathologist B was 0, with a range of 0 to 3. The difference in the distribution of the data was not statistically significant, with a p value of 0.2057.

In the high-risk PC group with the *en bloc* submission technique of the LND tissue, the median number of LNs found by pathologist A was 12, with a range of 8 to 17, while pathologist B found a median of 11 LNs, with a range of 10 to 16. The distribution of the data was not statistically significant, with a p value of 1.0000.

When comparing the positive LNs found in the high-risk PC group with the *en bloc* submission technique by our pathologists, we found that the median number of positive LNs was 0 for pathologist A and ranged from 0 to 10, while pathologist B found no positive LNs. The distribution of data between the pathologists was not statistically significant, with a p value of 0.1308.

Intermediate-risk group (**Table 3**)

In the intermediate-risk prostate cancer group with separate submission of the LND tissue, comparison of the total number of LNs found between our pathologists revealed that the median number of LNs found was 15 for pathologist A, with a range of 12 to 19, and 19 for pathologist B, with a range of 8 to 28. The difference in the distribution of data was not statistically significant, with a p value of 0.3177. In the case of *en bloc* submission, the median number of LNs found was 12.5 for pathologist A, with a range of 6 to 21, while it was 14.0 for pathologist B, with a range of 7 to 22. The difference was not statistically significant, with a p value of 0.6116.

Since no positive LNs were found in the intermediate-risk PC group, it was not evaluated according to the pathologist who performed the pathohistological analysis.

## Discussion

One of the options for patients with intermediate and high-risk PC with good performance status and no metastatic disease in our hospital is RP with extended PLND. The LND tissue is taken *en bloc* as a standard procedure and divided into two containers, separating the left and right groups. This is because that shortens the operating time and also shortens the time for pathohistological analysis. Additionally, it is also more cost-effective because only two specimens are needed for histologic processing, compared with eight specimens when lymph node tissue is submitted in separate containers (four for each side).

Our research has shown that although more LNs were found when LND tissue is submitted in sepa-

rate containers, this did not result in more positive LNs found. We also found that the personal influence of our pathologists did not affect the results of the pathohistological analysis. This indicates a consistent approach to pathohistological analysis that leads to results with high reliability.

Several factors are known to influence the final nodal yield, such as a patient's individual lymph node number, surgical LND template, thoroughness of dissection by the surgeon, and pathologic evaluation. Therefore, the postoperative LN number is highly variable[8]. For example, the limits of LND are still a subject of controversy[2,4,5,7,9]. It is important to note that the surgical technique and the limits of LND remained identical during the study period.

In the present study, the number of LNs identified changed according to the change in the submission technique, while the number of positive LNs did not change, confirming the role of pathologists in evaluation of the LNs. Differences in pathology practice and methods of lymph node counting are known to affect nodal yield[8,10]. Since all specimens were examined by two dedicated genitourinary pathologists during the study period, we consider this a factor which limited inter-pathologist variability.

Accurate staging is of utmost importance in oncology, as it has a major impact on treatment options and decisions. Examining our results, we can see that there was no difference in positive LNs between patients, regardless of the submission technique. To the best of our knowledge, there is no published randomized series on this topic in PC. Current literature data supports separate submission, but our results put this into question. Similar studies have been performed in patients with bladder cancer, with the same results as our study: submission of LND tissues in separate containers affected the nodal yield but not the detection of nodal metastases. In these studies, the submission technique also did not affect oncologic outcomes, which requires further research in prostate cancer 11-13. In a study by Abdollah et al., it was found that more extensive LND with more LNs removed resulted in better oncologic outcomes in patients with PC with nodal involvement [14]. This would suggest that the separate submission technique is superior in terms of oncologic outcome, but this was outside the scope of this study.

RP with pelvic lymph node dissection is currently the most reliable diagnostic technique for staging patients with PC and selecting those who will benefit most from adjuvant therapy. Currently, there is no consensus on the optimal handling of LND specimens collected during radical prostatectomy.

Conventional imaging techniques are poor at detecting lymph node metastases from PC, and 25-40% of patients undergoing RP with an extended PLND have these identified by histology[15].

Therefore, our results lead us to question the strength of nodal count as an accurate prognosticator for optimal surgical dissection. Ultimately, careful removal of all fibroadipose tissue with complete skeletonization of the pelvic structures within the confines of an extended template is more important than the LN submission technique or the total number of LNs identified. This approach is likely to achieve both the most accurate postoperative staging based on a representative total number of LNs and the most effective removal of metastatic LNs.

## Conclusion

In conclusion, submission of separate nodal packets after LND instead of the *en bloc* technique significantly increased the total number of LNs identified; however, the modified LND specimen submission did not increase the number of positive LNs. It is possible that tissue processing, rather than submission methodology, limited the results[16]. Consequently, adherence to a meticulous LND technique within a well-defined extended template is more important than the total number of LNs identified.

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Sažetak

## RADIKALNA PROSTATEKTOMIJA S PROŠIRENOM ZDJELIČNOM LIMFADENEKTOMIJOM: UTJECAJ ODVOJENOG VS. ZAJEDNIČKOG SLANJA LIMFNIH ČVOROVA NA PATOHISTOLOŠKU ANALIZU

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**UVOD:** U raku prostate od ranije je ustanovljeno što su širi anatomski rubovi disekcije limfnih čvorova više limfnih čvorova je nađeno, a što je veći ukupan broj limfnih čvorova bolje se otkrivaju metastaze u istima.[1,2]

**CILJEVI:** Ciljevi ove studije bili su istražiti da li promjena u metodi uzorkovanja (u odvojenim spremnicima vs *en bloc*) ima utjecaja na ukupan broj limfnih čvorova otkrivenih po pacijentu i na broj otkrivenih pozitivnih limfnih čvorova te koji je utjecaj pojedinog patologa na ukupan broj limnih čvorova i broj pozitivnih limfnih čvorova.

**MATERIJALI I METODE:** U ovoj retrospektivnoj analizi koristili smo podatke iz bolničke arhive za sve pacijente kojima je učinjena radikalna prostatektomija sa zdjeličnom limfadenektomijom u periodu od studenog 2012 do prosinca 2018 u Kliničkom bolničkom centru Rijeka. Koristili smo podatke pacijenata koji su imali istog vodećeg kirurga da bi izbjegli individualni utjecaj pojedinog kirurga na anatomski opseg limfadenektomije. Dva urogenitalna patologa naše bolnice su provela sve patohistološke preglede. Pacijenti su bili podijeljeni na bolest visokog i srednjeg rizika prema smjernicama Europske udruge urologa (EAU), zatim prema metodi uzorkovanja limfadenektomijskog tkiva i prema patologu koji je proveo patohistološku analizu. Ukupan broj limfnih čvorova i broj pozitivnih limfnih čvorova je zatim uspoređen koristeći Mann Whitney test.

**REZULTATI:** Kada se tkivo limfadenektomije uzorkuje u odvojenim spremnicima otkrije se značajno više limfnih čvorova, ali nema razlike u broju nađenih metastaza u limfnim čvorovima. Kada smo uspoređivali naše patologe, nije bilo značajne razlike u broju nađenih limfnih čvorova niti u broju otkrivenih metastaza u limfne čvorove kada se uspoređuju prema metodi uzorkovanja limfadenektomijskog tkiva.

**ZAKLJUČAK:** Uzorkovanje limfadenektomijskog tkiva u odvojenim spremnicima rezultira većim ukupnim brojem nađenih limfnih čvorova, ali ne dovodi do većeg broja nađenih metastaza u limfne čvorove.

Ključne riječi: *Rak prostate, limfadenektomija, broj čvorova, odvojeno, en bloc*