

## The incidence of lymph node metastases in prostate carcinoma depends not only on tumor characteristics but also on surgical performance and extent of pelvic lymphadenectomy

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**Key words:** lymph node metastasis; pelvic lymphadenectomy; prostate cancer; radical retropubic prostatectomy; surgical performance.

**Summary.** *Objectives.* The purpose of the present study was to determine whether predictions of the incidence of pelvic lymph node metastases in patients with similar prostate cancer characteristics are influenced by the extent of pelvic lymphadenectomy or surgical performance.

*Material and methods.* Data from a prostate cancer database were analyzed to investigate associations between incidence of lymph node metastasis and preoperative prostate-specific antigen level, clinical stage, biopsy Gleason score, extent of pelvic lymphadenectomy, and surgical performance. Subgroups of patients with the same characteristics were formed, and a multivariate analysis was performed.

*Results.* Data of 668 patients with cT1-T2c prostate cancer who underwent radical retropubic prostatectomy with pelvic lymphadenectomy were analyzed. Lymph node metastases were found in 8.7% of these patients. In the subgroup of patients undergoing limited pelvic lymphadenectomy, 6.3% were affected compared with 14.7% of patients undergoing extended pelvic lymphadenectomy ( $P < 0.0005$ ). In the subgroups of patients with the same tumor characteristics (with only two exceptions), the impact of the extent of lymphadenectomy on the incidence of lymph node metastases was evident. The results of the multivariate analysis corroborated the influence of the extent of pelvic lymphadenectomy ( $P < 0.03$ ) and surgical performance ( $P < 0.04$ ) on the incidence of lymph node metastases.

*Conclusions.* The incidence of lymph node metastases was dependent not only on preoperative prostate-specific antigen level, clinical stage, and biopsy Gleason score but also to a large degree on surgical performance and the extent of pelvic lymphadenectomy. Our data suggest that a limited and/or not thoroughly performed pelvic lymphadenectomy results in failure to detect a relevant proportion of lymph node metastases.

### Introduction

Pelvic lymphadenectomy (PLA) is currently the most sensitive method for identification of lymph node metastases in patients with prostate cancer (PCa).

In limited PLA (LPLA), the lymph nodes in the obturator fossa and the nodes along the external iliac vein are removed. Whereas in extended PLA (EPLA), the lymph nodes along the internal iliac artery and the presacral lymph nodes are also removed. As a result, the incidence of detected metastases is two to three times greater, and the diagnostic value of the PLA is substantially increased (1, 2).

A widespread practice is to select patients with a low risk of lymphogenic metastasis in whom PLA is

deemed unnecessary. Patients are selected based on various predictive models; the Partin tables are best known (3, 4). In the last few years, there have been various studies indicating that even in patients with so-called low-risk PCa (preoperative prostate-specific antigen (PSA) level  $< 10.0$  ng/mL, Gleason score  $< 7$ , and clinical stage  $< T2a$ ), the actual number of lymph node metastases is in fact considerably higher than that predicted based on various nomograms (1, 5). Bader et al. reported a 12% incidence of positive nodes in patients with preoperative PSA level of  $< 10$  ng/mg; even in the low-risk group, the incidence was still 7% (6). The working group of Heidenreich et al. reported lymph node metastases in 27% and 58% of patients,

respectively, with PSA level <10 ng/mL and biopsy Gleason score  $\leq 7$  (7).

In view of the above-described discrepancy, we decided to compare the incidence of lymphogenic metastases in patients with clinically localized PCa as determined by EPLA versus LPLA. We also evaluated the prognostic value of clinical parameters such as preoperative PSA level, biopsy Gleason score, and clinical stage for prediction of lymph node metastases, analyzing the subgroups of patients with low-risk and high-risk PCa separately. In addition, two procedures were also examined in regard to differences in the numbers of lymph nodes removed. To rule out the influence of unequal distribution of the above-mentioned variables, as well as of preoperative hormonal treatment and performance of different surgeons, on the incidence of lymph node metastases in the subgroups of patients examined, an additional stepwise multivariate analysis was performed. These results have already been presented at an oral session during the 47th congress of the Association of North German Urologists in 2005.

### Material and methods

Between June 1997 and October 2004, we performed radical retropubic prostatectomy (RRP) with bilateral EPLA or LPLA in 691 patients with clinical stage T1-T2c prostate cancer. Twenty-three of these patients had to be excluded because of incomplete data, leaving 668 patients suitable for analysis. The demographic and disease-related data were collected prospectively.

The clinical stage was established preoperatively by digital rectal examination. In the majority of cases, the PSA level was determined by the referring urologist who also performed the prostate biopsy in the majority of cases. Patients with PSA level of >10 ng/mL were evaluated further for metastatic disease by computed tomography of the abdomen and pelvis, and whole-body bone scan.

### Surgical technique

The operations were performed by five staff surgeons (Surgeon keys 1 to 5) and residents under their supervision (Surgeon key 6) (Table 1). The indication for an extended or limited PLA depended on the particular surgeon. The dissection boundaries of the LPLA encompassed the nodes from the obturator fossa and along the external iliac vein. In EPLA, the lymph drainage basins of the internal iliac artery and vein and of the external iliac artery were also included. Systematic exploration of presacral lymph nodes was

not performed. In both procedures, the lymphatic ducts were secured with titanium clips or absorbable ligatures. Finally, two 16-French suction drains per side were placed in the small pelvis. The drains were removed when the drainage volume was less than 50 mL in 24 hours. All patients were given standard perioperative thromboprophylaxis with unfractionated heparin. The heparin was always injected into the upper arm in order to avoid increased lymph secretion in the small pelvis (8).

### Pathological assessment

The lymphadenectomy specimens from each side separately were fixed en bloc in formalin and submitted for histological assessment. The assessment was performed according to a standard protocol by different pathologists at the Institute of Pathology of the University of Witten-Herdecke in all cases.

Larger lymph nodes are isolated by palpation and peeled out of the tissue. Smaller lymph nodes are then obtained by squeezing the tissue between the fingers and an underlying glass plate. The tissue is scrupulously examined in this manner, and the lymph nodes thus identified are then counted. Nodes larger than 5 mm are cut in half, and the cut surface is examined macroscopically for metastases. Then the lymph nodes are measured, and the smallest and the largest diameters are documented. All very small structures ( $\leq 2$  mm) suspected of being lymph nodes are also embedded and examined histologically. The number of lymph nodes detected microscopically may therefore change, both positive and negative changes being possible. The lymph nodes are then cut into at least four slices and stained with hematoxylin and eosin (standard stain). Any metastatic disease detected microscopically is documented separately for each side. At the end, the findings for both sides are added together to give the appropriate pN stage in the TNM classification. In the written report, the number of positive nodes and the total number of nodes examined are documented in addition to the location of the nodes.

### Risk group assessment and statistical analysis

Two main groups of patients undergoing extended and limited lymphadenectomy – subdivided into the clinical stages T1-T2a and T2b-T2c – were then divided into the following subgroups: 1) PSA level <10 ng/mL, Gleason score <7; 2) PSA level <10 ng/mL, Gleason score  $\geq 7$ ; 3) PSA level  $\geq 10$  ng/mL, Gleason score <7; and 4) PSA level  $\geq 10$  ng/mL, Gleason score  $\geq 7$  (Fig.).

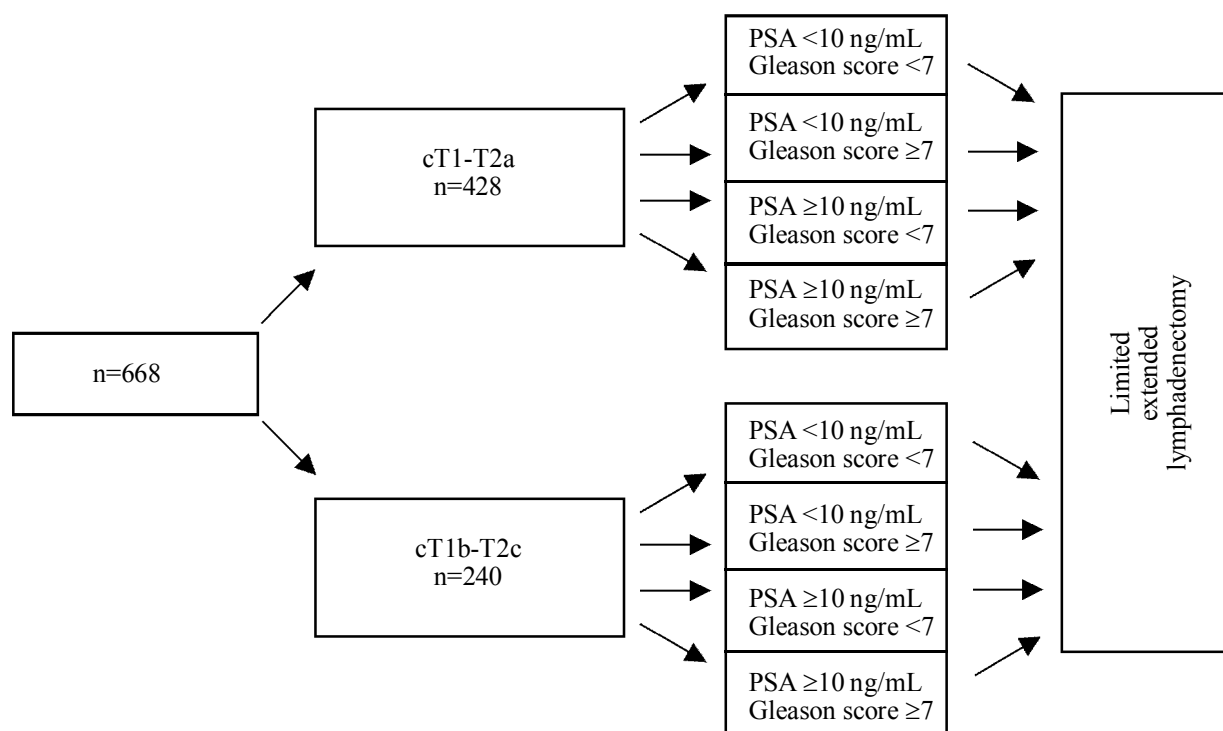
**Table 1. Demographic data, PSA values, tumor characteristics, preoperative hormonal treatment, lymph node metastases, number of lymph nodes examined, surgical performance, and extent of lymphadenectomy in the patients studied**

Parameter	All patients n=668	Limited PLA n=477	Extended PLA n=191	P value
Age, years Range Mean±SD	40–81 64.9±6.0	40–78 64.8±6.0	42–81 65.1±5.9	0.5
PSA level, ng/mL Range Mean±SD	0.11–254.0 12.0±14.9	0.5–135 10.7±11.5	0.11–254.0 15.1±20.9	<0.01
<10 from 10 to 20 >20	411 182 75	325 113 39	86 69 36	<0.01
Clinical stage T1-T2a T2b-T2c	428 240	315 162	113 78	0.1
Pathological stage pT2a pT2b-T2c pT3-T4	47 260 361	34 193 250	13 67 111	0.4
Biopsy Gleason score Gleason score <7 Gleason score ≥7	543 125	415 63	128 62	<0.01
Lymph node metastases pN+	58/668 (8.7%)	30/477 (6.3%)	28/191 (14.7%)	<0.01
Number of lymph nodes examined [mean (min – max)] Examined nodes	9 (1–34)	8 (1–27)	11 (1–34)	<0.01
– Surgical performance – Number of lymph nodes removed by particular surgeons [mean (min – max)] Surgeon Key 1 Surgeon Key 2 Surgeon Key 3 Surgeon Key 4 Surgeon Key 5 Surgeon Key 6	n.a.	10 (3–19) 6 (1–17) 7 (2–15) 10 (2–27) 7 (1–18) 5 (2–10)	12 (6–34) 8 (3–17) 9 (2–19) 13 (1–27) 9 (6–15) 7 (7–7)	<0.04
Preoperative hormonal treatment With preoperative hormonal treatment Without preoperative hormonal treatment	60 608	45 432	15 176	0.65

PLA – pelvic lymphadenectomy; PSA – prostate-specific antigen.

Differences between the incidences of lymph node metastases in the different groups were tested for statistical significance using the chi-square test. The Mann-Whitney *U* test was used to identify differences in distribution of continuous variables. To isolate independent variables as predictors for the development

of lymph node metastases, we used stepwise multivariate analysis. All *P* values are presented descriptively without correction for multiple testing. The statistical analysis was performed at the Institute for Medical Informatics, Biometry and Epidemiology of the University Duisburg-Essen using SAS®.



**Fig. Risk group assessment**

## Results

Our patient cohort consisted of 668 patients with clinically localized PCa. Of these, 477 had undergone LPLA and 191 EPLA.

Table 1 compares two groups in regard to age, PSA level, preoperative hormonal treatment, clinical and pathological stage as well as Gleason score, surgical performance, and number of lymph nodes examined. The distribution of clinical and pathological stages and patients who underwent preoperative hormonal treatment in the LPLA and EPLA groups was approximately the same. On the other hand, the group of patients undergoing extended lymphadenectomy had a higher median PSA level and a higher biopsy Gleason score ( $P<0.001$ ).

Lymph node metastases were found in 58 (8.7%) of the 668 patients: in 30 (6.3%) of the 477 patients undergoing LPLA compared with 28 (14.7%) of the 191 patients undergoing EPLA ( $P<0.001$ ). The average number of lymph nodes identified and examined as described above was 11 (1–34) in the EPLA patients and 8 (1–27) in the LPLA patients ( $P<0.001$ ). The number of lymph nodes removed by different surgeons during LPLA and EPLA was significantly different ( $P<0.04$ ) (Table 1).

In the two subgroups of patients with clinical stage T1c-T2a and T2b-T2c disease, the impact of the extent of lymphadenectomy on the incidence of lymph node

involvement was clear in all PSA level and Gleason score groups considered, with only two exceptions. Only patients with clinical stage T1c-T2a disease and PSA level of  $\geq 10$  ng/mL and Gleason score of  $<7$  and patients with clinical stage T2b-T2c disease and PSA level of  $\leq 10$  ng/mL and Gleason score of  $\geq 7$  had higher numbers of lymph node metastases when limited lymphadenectomy was performed. In both groups, the incidence of lymph node metastases was also dependent on the preoperative PSA level and the Gleason score at biopsy. There was a very high incidence of lymph node metastases in the subgroup of patients with clinical stage T2b-T2c disease (Table 2). Table 3 shows the results of the stepwise multivariate analysis. It is shown that clinical stage and biopsy Gleason score have a substantial impact on the rate of lymph node metastases. Furthermore, surgical performance (i.e. the number of lymph nodes removed by particular surgeons) and the extent of lymphadenectomy significantly influenced the number of lymph node metastases detected. Patient's age, PSA level, and preoperative hormonal treatment were proved not to be statistically significant predictors.

## Discussion

In view of the inadequate sensitivity and specificity of imaging procedures, PLA is currently the most reliable method for diagnosis of lymph node metastases

**Table 2. Incidence of pelvic lymph node metastases in clinically localized prostate cancer as a function of the extent of PLA, PSA level, clinical stage, and Gleason score**

PSA level (ng/mL) and Gleason score	cT1c-T2a, pN+			cT2b-T2c, pN+		
	Altogether	Limited PLA	Extended PLA	Altogether	Limited PLA	Extended PLA
All PSA and Gleason scores	17/428 (4.0%)	10/315 (3.2%)	7/113 (6.2%)	41/240 (17.1%)	20/162 (12.3%)	20/162 (26.9%)
PSA <10 Gleason score <7	7/249 (2.8%)	5/207 (2.4%)	2/42 (4.8%)	5/96 (5.2%)	3/78 (3.8%)	2/18 (11.1%)
PSA <10 Gleason score ≥7	4/38 (10.5%)	1/22 (4.5%)	3/16 (18.7%)	7/28 (25.0%)	5/18 (27.8%)	2/10 (20.0%)
PSA ≥10 Gleason score <7	4/118 (3.4%)	4/77 (5.2%)	0/41 (0%)	13/80 (16.3%)	7/53 (13.2%)	6/27 (22.2%)
PSA ≥10 Gleason score ≥7	2/23 (8.7%)	0/9 (0%)	2/14 (14.3%)	16/36 (44.4%)	5/13 (38.5%)	11/23 (47.8%)

PLA – pelvic lymphadenectomy; PSA – prostate-specific antigen.

**Table 3. Results of univariate and multivariate analysis (stepwise selection) showing the probability of lymph node metastases**

Variable	Univariate analysis	Multivariate analysis		
		odds ratio estimate	95% CI	P value
Preoperative Gleason score 1–4 vs. 8–10 5–6 vs. 8–10 7 vs. 8–10	<0.0001	0.070 0.199 0.520	0.021–0.239 0.078–0.506 0.192–1.408	<0.0001
Clinical stage 1 vs. 2c 2a vs. 2c 2b vs. 2c	<0.0001	0.193 0.129 0.466	0.082–0.454 0.046–0.360 0.216–1.005	<0.0001
Surgeon key 1 vs. 6 2 vs. 6 3 vs. 6 4 vs. 6 5 vs. 6	0.0031	0.161 0.132 0.173 0.230 0.325	0.037–0.696 0.043–0.407 0.038–0.784 0.081–0.652 0.077–1.365	<0.04
Extent of PLA limited vs. extended	<0.001	0.470	0.242–0.913	<0.03
Preoperative PSA level 0–3.9 ng/mL 4–10 ng/mL 10.1–20 ng/mL >20 ng/mL	<0.001	not significant in stepwise selection		0.1227
Age years	0.74	not significant in stepwise selection		0.48
Hormonal treatment no vs. yes	0.07	not significant in stepwise selection		0.19

PLA – pelvic lymphadenectomy; PSA – prostate-specific antigen.

(7, 9). Nevertheless, the role of PLA in RRP is controversial. The reported indications for performing PLA in patients with PCa vary. PLA is often not performed in patients with low-risk PCa (Gleason score  $<7$ , PSA level  $<10$  ng/mL, and clinical stage  $\leq T2a$ ) (4, 10). At some centers, PLA is not performed in patients with Gleason score  $\leq 6$ , PSA level  $\leq 10$  ng/mL, and clinical stage T1c (4). Some hospitals use a primary Gleason score of 4 as the most important criterion for performing PLA (3, 10). On the other hand, many centers perform PLA in all patients with PCa because as a result of the introduction of EPLA and/or use of the sentinel lymph node method, a considerably higher incidence of lymph node metastases has been found in patients in whom the aforementioned criteria would have predicted a low rate of lymph node metastases (1, 2, 11).

The incidence of lymph node metastases found in prostate cancer patients by PLA has varied in the course of time depending on the risk profile of the patients and presumably also on the extent of lymphadenectomy.

In 1990, McDowell et al. reported lymph node metastases in 58.6% of patients undergoing EPLA (12). However, this is partly due to a disproportionately high rate of pT3 cancers (68%). With increasing use of the PSA in the early detection of Pca, the number of organ-confined cancers increased considerably, and the incidence of lymph node metastases decreased from 20–40% to 4–9% according to various authors (7, 12, 13). In a series published by Campbell in 1995, 6.5% of all patients undergoing radical prostatectomy had lymph node metastases, patients with a PSA level of  $<10$  ng/mL having a considerably lower risk of 1.3% (13).

In the 1990s, therefore, there was a trend towards not performing PLA in patients with low-risk PCa. On the other hand, several recent studies have pointed out that particularly when EPLA was performed, the numbers of lymphogenic metastases in patients with low-risk PCa were in fact considerably higher than had been calculated on the basis of the various nomograms, which are often based on LPLA. In these studies, the incidence of lymph node metastases was 12–27% (1, 2, 14).

Heidenreich et al. reported a 26.2% incidence of lymph node metastases for EPLA and only 12% for LPLA (2). In addition, it was shown that about two-thirds of the lymph node metastases detected were outside the dissection boundaries of LPLA. Bader et al. also reported a higher incidence of lymph node metastases after EPLA. In 365 patients, tumor-positive

lymph nodes were found in 24% of the cases. More than half of these metastases (58%) were in the region along the internal iliac artery; in 19% of the patients, only lymph node metastases in this region were described (1). A further study by Wawroschek et al. found lymph node metastases in 34.6% of the cases in the patient subgroup with PSA level of  $<10$  ng/mL (14). Had only the obturator lymph nodes been removed in this study, only 44.2% of the metastases actually identified would have been detected. With additional removal of the lymph nodes along the external iliac artery, 65.4% of the metastases would have been correctly diagnosed (14). However, the highest incidence, i.e. 98%, would only have been reached by EPLA, which also includes dissection of the lymph nodes along the internal iliac artery. A particularly interesting aspect of this study is the fact that if only the obturator lymph nodes had been removed, all lymph node metastases in the low-risk PCa group would have been overlooked (14).

The findings of our study agree well with the results of other studies described above. In our study too, the PSA level, Gleason score, and clinical stage were together the most important factors influencing the incidence of lymph node metastases. The data presented here show a 4.0% incidence of lymph node metastases in patients with clinical stage T1–T2a disease and a 17.1% incidence in patients with clinical stage T2b–T2c disease. In both groups, the incidence of lymph node metastases was also dependent on the preoperative PSA level and the Gleason score at biopsy. The altogether high incidence of lymph node metastasis in the subgroup of patients with clinical stage T2b–T2c disease was particularly striking. In addition, there was a marked trend towards a higher incidence of lymph node metastases in patients with a Gleason score of  $\geq 7$  (Table 2). Here too, with two exceptions, a considerably higher percentage of lymph node metastases were found by EPLA in all subgroups. This confirms the results of Heidenreich and Bader, who showed that the incidence of lymph node metastases in PCa is also dependent on the extent of the PLA (Table 2).

We believe that the number of lymph nodes examined and the number of positive nodes would have been higher if different methods of harvesting and examining the lymph nodes had been used. Although we submitted the lymph nodes to the pathologist separately for each side of the pelvis, we did not differentiate between the different anatomical locations of the respective side, which according to Bochner et al., leads to examination of a higher number of nodes

(15). The relatively low number of nodes examined in our series may also be due to the fact that the pathologists used the standard clinical protocol rather than a procedure designed specifically for study purposes. Another reason is most probably that the surgeons did not perform PLA with equal accuracy; this is shown by the substantial differences in the number of lymph nodes removed by individual surgeons.

To our knowledge, this is the first study to address this problem in prostate cancer patients. We feel that the striking differences in the numbers of lymph nodes removed by the individual surgeons allow the presumption that the incidence of lymph node metastases might have been even higher if all surgeons had removed equally high numbers of lymph nodes. Similar discrepancies in the numbers of lymph nodes removed by particular surgeons during pelvic lymphadenectomy in bladder carcinoma patients have been described by Leissner et al. (16). Obviously, there is standardization and continuous quality control on the extent and thoroughness of the node dissection necessary.

Finally, the number of lymph nodes assessed by the pathologist depends not only on the extent of dissection of the PLA but also and particularly on the method of histological work-up used. This becomes clear when different studies are compared (1, 14). The working group from Bern reports that after fixation in formalin, the specimen is placed in acetone solution in order to dissolve the fatty tissue around the lymph nodes, a procedure that also permits the identification of extremely small nodes (1). This contrasts with the

widely used technique – also used in our study – of identifying individual lymph nodes in the specimen by digital exploration. We can assume that this procedure does not allow to detect very small lymph nodes, and the average number of nodes is therefore lower than that found by the acetone method. Various authors also describe an improvement in sensitivity when immunohistochemical methods and serial sections are used for lymph node staging (14). In the study by Wawroschek et al., serial sectioning of the individual lymph nodes led to detection of 44.2% of the lymph node metastases with a diameter of <2 mm. With routine histological workup, these may not have been detected at all (14).

### Conclusions

Our study shows that the incidence of lymph node metastases in patients with clinically localized prostate cancer depends not only on the clinical stage, preoperative PSA level, and biopsy Gleason score but also largely on surgical performance and the extent of pelvic lymphadenectomy. The standardization and continuous quality control of the thoroughness of node dissection have to be incorporated in the clinical routine. A limited and/or not thoroughly performed pelvic lymphadenectomy results in failure to detect a relevant proportion of the lymph node metastases actually present.

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## Metastazių limfmazgiuose dažnumas, sergant prostatos vėžiu, priklauso nuo naviko savybių, operacinės technikos bei atliekamos limfadenektomijos apimties

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**Raktažodžiai:** limfmazgių metastazės, dubens srities limfadenektomija, prostatos vėžys, radikali retropubinė prostatektomija, chirurginė technika.

**Santrauka.** *Tyrimo tikslas.* Įvertinti, kokią įtaką turi dubens srities limfadenektomijos apimtis ir operacinė technika nustatant metastazių dažnumą regioniniuose limfmazgiuose ligoniams, sergantiems prostatos vėžiu.

*Tyrimo medžiaga ir metodai.* Prospektyviai buvo analizuojami duomenys, sukaupti mūsų klinikoje įdiegtoje prostatos vėžio kompiuterinėje duomenų bazėje, siekiant įvertinti, kokią įtaką metastazavimui į regioninius dubens limfmazgius turi prieš operaciją nustatyta prostatos specifinio antigeno koncentracija kraujo serume, klinikinė stadija, biopsijos metu nustatytas Gleason balas, limfadenektomijos apimtis bei operacinė technika.

Visi ligoniai, atsižvelgiant į atitinkamus klinikinius požymius, suskirstyti į grupes. Statistinė analizė atliekama naudojantis SAS® programa. Statistinės hipotezės reikšmingumo lygmuo pasirinktas 0,05.

**Rezultatai.** 668 ligoniams dėl diagnozuoto cT1-T2c prostatos vėžio atlikta radikali retropubinė prostatektomija ir sritinė dubens limfadenektomija. Metastazės limfmazgiuose diagnozuotos 8,7 proc. ligonių. Taigi, ligoniams, kuriems buvo atlikta limituota limfadenektomija, metastazės nustatytos 6,3 proc., o atliekant išplėstinę limfadenektomiją – 14,7 proc. atvejų ( $p < 0,0005$ ). Lyginant ligonių grupes, išskyrus dvi išimtis, visose kitose grupėse nustatyta akivaizdi išplėstinės limfadenektomijos įtaka diagnozuojant metastazes regioniniuose limfmazgiuose. Atlikta statistinė analizė patvirtino statistiškai patikimą išplėstinės limfadenektomijos ( $p < 0,03$ ) ir chirurginės technikos ( $p < 0,04$ ) įtaką metastazių regioniniuose dubens limfmazgiuose nustatymo dažnumą sergantiesiems prostatos vėžiui.

**Išvados.** Metastazių regioniniuose dubens limfmazgiuose dažnumui, sergant prostatos vėžiu, įtakos turi ne tik prieš operaciją nustatyta prostatos specifinio antigeno koncentracija kraujo serume, klinikinė stadija ir biopsijos metu nustatytas Gleason balas, bet ir operacinė technika bei limfadenektomijos apimtis. Remiantis atlikto tyrimo duomenimis, galima daryti prielaidą, kad ribota ir (ar) nekvalifikuotai atlikta limfadenektomija gali sąlygoti, kad lieka nenustatyta žymi dalis metastazių regioniniuose dubens limfmazgiuose, ligoniams, sergantiems prostatos vėžiu.

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