

## LYMPH NODE FROZEN SECTION ANALYSIS DURING RADICAL PROSTATECTOMY\*

Božo Krušlin<sup>1</sup>, Stela Bulimbašić<sup>2</sup>, Hrvoje Čupić<sup>1</sup>, Ante Reljić<sup>3</sup>, Davor Tomas<sup>1</sup>, Igor Tomašković<sup>3</sup>,  
Ognjen Kraus<sup>3</sup> and Mladen Belicza<sup>1</sup>

<sup>1</sup>Ljudevit Jurak University Department of Pathology, Sestre milosrdnice University Hospital; <sup>2</sup>Department of Pathology, Sveti Duh General Hospital; <sup>3</sup>Department of Urology, Sestre milosrdnice University Hospital, Zagreb, Croatia

**SUMMARY** – Radical prostatectomy is a treatment of choice for localized prostatic adenocarcinoma. In most cases, radical prostatectomy is combined with pelvic lymph node dissection. During the last decade, the necessity to perform lymphadenectomy in all patients has been questioned. Lymph node dissection adds the risk of complications, and increases operation time and medical costs. Data of patients with prostatic adenocarcinoma who underwent radical prostatectomy at Department of Urology, Sestre milosrdnice University Hospital, Zagreb during the period from January 1, 1998 till December 31, 2002, were analyzed. There were 110 patients who had complete preoperative data including prostate-specific antigen (PSA) value, Gleason score, T stage and lymph node status on frozen section analysis. Using predictive nomograms the patients were divided into different risk groups. Positive lymph node(s) were found in one patient with T2 and in five patients with T3, whereby three, two and one of these patients had Gleason score 6, 7 and 8, respectively. There was a correlation between increasing PSA value and positive lymph nodes ( $p < 0.005$ ). A statistically significant correlation between T stage and PSA value ( $p < 0.005$ ) as well as between T stage and Gleason score ( $p = 0.0014$ ) was also observed. The majority of patients belonged to low and intermediate risk groups, known to benefit very little from lymph node dissection and frozen section analysis. Thus, it seems reasonable to reconsider the use of these predictive nomograms on advising and therapy strategy planning for newly diagnosed patients, especially those with clinically organ-confined disease.

**Key words:** *prostatic neoplasms – pathology; Prostatic neoplasms – surgery; Lymph node excision; Lymph node – pathology; Frozen sections*

### Introduction

Prostatic carcinoma is one of the most prevalent cancers in males in western world. Approximately 200,000 North American men were diagnosed with prostate cancer in 2000, with up to 40,000 deaths<sup>1</sup>. Due to the increased public awareness and better detection methods, especially serum prostate-specific antigen (PSA) testing, the num-

ber of patients with organ-confined disease is increasing. The majority of patients are detected in early asymptomatic stages of the disease.

Different therapy approaches can be offered to patients with newly diagnosed prostatic carcinoma: radical prostatectomy with or without pelvic lymph node dissection, external beam radiation therapy, brachytherapy, and hormonal therapy. Surgical approach with radical prostatectomy is still the best choice for managing localized carcinoma. Pelvic lymph node dissection is usually performed as an initial phase of radical prostatectomy. Lymph nodes can be analyzed on frozen sections or in paraffin embedded material as an integral component of TNM staging.

Oesterling *et al.* were the first to combine preoperative clinical data in 1987, in an attempt to predict final

Correspondence to: *Božo Krušlin, M.D., Ph.D.*, Ljudevit Jurak University Department of Pathology, Sestre milosrdnice University Hospital, Vinsogradska c. 29, HR-10000 Zagreb, Croatia  
e-mail: bkrušlin@kbsm.hr

Received February 6, 2004, accepted February 28, 2005

\*Presented in part at the International Symposium on Prostatic Adenocarcinoma, Zagreb, November 2002

pathohistologic stage for patients with clinically organ-confined disease<sup>2</sup>. After them, several groups have attempted to derive models for predicting nodal disease based on a combination of multiple factors<sup>3-6</sup>. Partin *et al.* combined 3 preoperative factors to predict pathologic stage and risk of extraprostatic spread, including lymph node metastases. They divided patients into categories with low, intermediate and high risk of lymph node metastases according to clinical stage, serum PSA value and tumor Gleason score on small biopsy specimen<sup>6,7</sup>. Nomograms generated from these analyses have been added to the 1996 prostate cancer practice guidelines of the National Comprehensive Cancer Network<sup>8</sup>. In 1997 the model was validated in a multicenter study of 4133 men and accurately predicted nodal metastases in 82.9% of patients<sup>7-9</sup>. The nomograms predict that men from the low risk group have less than 4% and men from the intermediate group less than 18% possibility of lymph node involvement. Men from the high risk group have a higher but more variable incidence of lymph node metastases.

Using a similar concept Bluestein *et al.* found that 29% of patients with clinically organ-confined disease (T1a to T1c) could be spared lymph node dissection with only 3% rate of missed nodal metastases<sup>8</sup>. Bishoff *et al.* report on similar results and suggest that up to 60% of patients with prostatic carcinoma could be spared pelvic lymphadenectomy when accepting a 2% to 10% risk of missed nodal disease<sup>9</sup>.

In the literature we also found other well documented articles and reviews which estimated diagnostic accuracy of frozen section lymph node analysis, complications linked to the lymphadenectomy procedures as well as costs of pelvic lymphadenectomy<sup>9-13</sup>. Beissner *et al.* compared the sensitivity and negative predictive values of frozen section analysis of pelvic lymph nodes during radical prostatectomy with predictive nomograms for nodal metastasis<sup>10</sup>. According to their research the sensitivity for detecting lymph node metastasis on frozen section analysis for all risk group is 33%, which is less sensitive than using risk stratification by the published nomograms.

In our Hospital, radical prostatectomy as a gold standard for the treatment of prostatic carcinoma is usually performed in combination with pelvic lymph node dissection and frozen section lymph node analysis. In our study we tried to estimate whether using nomograms some of our patients could be spared pelvic lymphadenectomy and/or frozen section analysis.

## Materials and Methods

Records of all patients who underwent radical prostatectomy with or without lymph node dissection due to prostate adenocarcinoma at Sestre milosrdnice University Hospital in the period from January 1, 1998 till December 31, 2002, were identified and reviewed. Patient data were obtained from computer based Urologic Pathology Registry at Ljudevit Jurak University Department of Pathology. Clinical data were used including age, serum PSA value measured in ng/ml, digitorectal exam and transrectal ultrasound results when available. Pathohistologic analysis was performed on frozen section and on paraffin embedded material. Needle core biopsy results, number of dissected and examined lymph nodes, Gleason score on surgery specimen and T stage were analyzed. Clinical data for some of the patients were insufficient, and they were not included in the study.

According to published nomograms, patients were divided preoperatively into low, intermediate and high risk groups for extracapsular spread of prostatic carcinoma<sup>7</sup>. The low risk group had T1 or T2 stage, with Gleason score 6 or less and serum PSA value less than 10 ng/ml. The intermediate risk group had T1 or T2 stage, Gleason score 7 and serum PSA value of 10.1 to 20 ng/ml. The high-risk group had T3 or T4 stage, Gleason score greater than 7 and serum PSA value greater than 20 ng/ml.

For statistical analysis ANOVA test was used to compare Gleason score, PSA value, T stage, and lymph node metastases. Statistical significance was established at  $p < 0.05$ .

## Results

During the 1998-2002 period, 128 radical prostatectomies were performed. Patient age ranged from 47 to 75 years, median 64.8 years. In 125 cases radical prostatectomy was combined with pelvic lymph node dissection. In the remaining 3 cases lymph node dissection was not performed. Two of these three patients had advanced stage of the disease (T3 and T4), and one had organ-confined disease with low Gleason score and low PSA value (T2, Gleason score 6, serum PSA 6.5 ng/ml) (Table 1).

In 10 (8.0%) cases lymph nodes were analyzed on paraffin embedded material only. From this group two patients had T1 stage, five T2 stage and three T3 stage. Eight patients had Gleason score 6 or less and two Gleason score 8.

Frozen section lymph nodes analysis was performed in 115 cases. There were 22 patients (19.1%) with T1, 67

*Table 1. All patients who underwent prostatectomy with lymph node dissection (N=125)*

	T1	T2	T3
Gleason 6 or less	22	47	14
Gleason 7	2	24	11
Gleason more than 7	0	1	4
Total	24	72	29

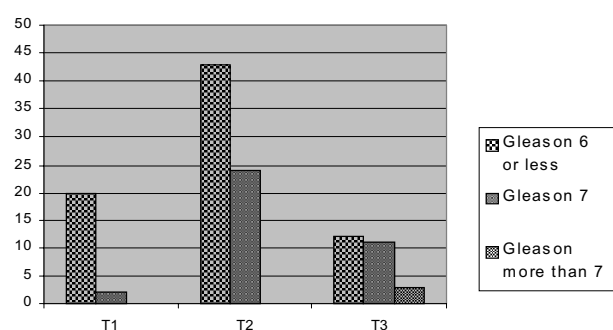
(58.3%) with T2, and 26 (22.6%) with T3 stage. Gleason score 6 or less was recorded in 75 (65.2%), Gleason score 7 in 37 (32.2%), and Gleason score 8 in three (2.6%) patients (Fig. 1, Table 2).

The number of submitted and analyzed lymph nodes varied from 4 to 42, with a mean of 15 lymph nodes *per* biopsy. In cases where more than 20 lymph nodes were submitted, the largest and most suspicious ones were analyzed on frozen sections, and others on paraffin embedded material.

Serum PSA value was known in 110 patients. It ranged from the lowest value of 1.03 ng/ml to the highest value of 45.2 ng/ml, mean 11.98 ng/ml. Twenty-one (19.1%) patients had T1, 66 (60%) had T2, and 23 (20.9%) had T3 stage. Their age ranged from 50 to 74 years, median 65.0 years. There were no significant age differences between stages (Fig. 2, Table 3).

Gleason score 6 or less was determined in 72 (65.5%), Gleason score 7 in 36 (32.7%) and Gleason score higher than 7 in two (1.8%) patients. Nineteen of 21 (90.5%) patients in T1 stage had Gleason score 6 or less, and two had Gleason score 7. Serum PSA ranged from 1.03 to 19.7 ng/ml, median 9.54 ng/ml.

T2 stage was recorded in 42 (63.6%) patients with Gleason score 6 or less and 24 (36.4%) patients with Gleason score 7. Serum PSA ranged from 3.6 to 24 ng/ml, median 11.54 ng/ml.

*Fig. 1. Distribution of 115 patients who underwent lymph node frozen section analysis according to T stage and Gleason score**Table 2. Patients with frozen section lymph node analysis according to T stage and Gleason score (n=115)*

	T1	T2	T3
Gleason 6 or less	20	43	12
Gleason 7	2	24	11
Gleason more than 7	0	0	3
Total	22	67	26

Eleven (47.8%) patients in T3 stage had Gleason score 6 or less, ten (43.5%) had Gleason score 7, and two patients had Gleason score 8. Serum PSA ranged from 6.6 to 45.2 ng/ml, median 15.49 ng/ml.

In five cases frozen section lymph node analysis was positive. There also was one case (patient aged 75; T3; Gleason 6; PSA 9.1) with a false negative result on frozen section analysis, where a micrometastasis was detected in one of 13 lymph nodes from paraffin embedded material. These six patients had PSA value ranging from 9.1 to 45.2 ng/ml (mean 18.91 ng/ml), whereas node-negative patients had PSA between 1.03 and 34.3 ng/ml (mean 11.67 ng/ml). There was a statistically significant difference in PSA value between node-positive and node-negative patients ( $p < 0.005$ ). Positive lymph node(s) was found in one patient with T2 and five patients with T3, whereby three, two and one of these patients had Gleason score 6, 7 and 8, respectively. A statistically significant correlation between PSA value and T stage was also found with higher PSA in higher T stages ( $p < 0.005$ ) as well as between Gleason score and T stage ( $p = 0.0014$ ). However, there was no significant difference between other parameters and lymph node positivity (data not shown).

In addition to all previously mentioned and analyzed cases, our computer based Urologic Pathology Registry contained data on five more patients in whom pelvic lymphadenectomy as an initial phase of radical prostatectomy had been performed, but the surgical procedure was subsequently aborted when frozen section analysis proved positive. Except for intraoperative biopsy, no data were available for these patients who had undergone needle core biopsy at another hospital.

## Discussion

During the five-year period, 133 patients with prostatic carcinoma confirmed by needle core biopsy underwent surgical procedure at Department of Urology, Sestre milosrdnice University Hospital. In a study from Mayo Clinic, reported by Blute *et al.*, 15 of 2475 (0.6%) patients had

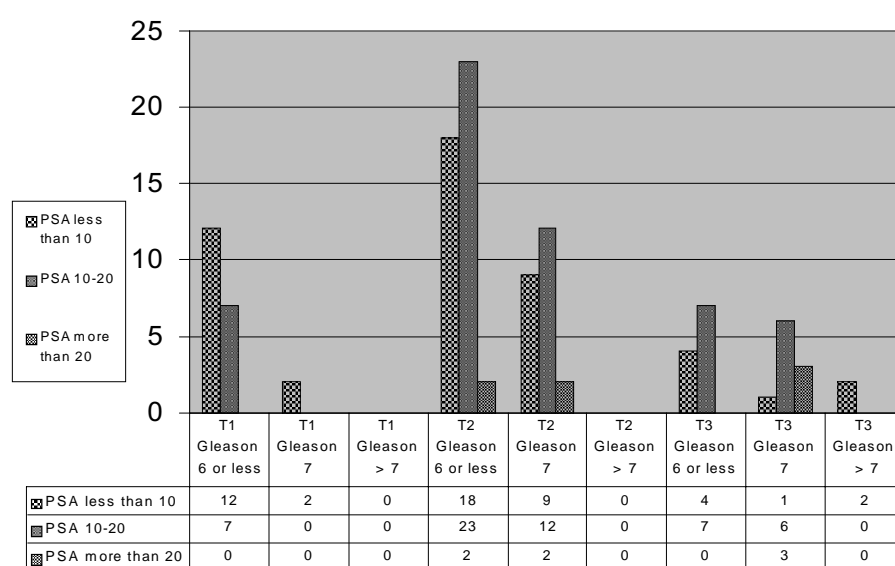


Fig. 2. Distribution of 110 patients with complete preoperative data according to T stage, Gleason score and serum PSA level

positive lymph nodes and planned prostatectomy was abandoned<sup>14</sup>.

In our study, radical prostatectomy was performed and specimens were examined in 128 cases. Organ-confined disease was detected in 81.3% of our patients. Blute *et al.* report on 67% of their 2475 patients to have organ-confined disease confirmed on prostatectomy<sup>14</sup>. At Mayo Clinic, radical prostatectomy and bilateral pelvic lymphadenectomy were performed in 5780 patients during the 1990-1996 period. All inclusion criteria (no preoperative treatment, known biopsy Gleason score, available preoperative PSA, clinical stage T1, T2 and T3) were met in 2475 patients<sup>14</sup>.

In our study, by use of Partin's nomograms 27.3% of patients belonged to the low risk group according all 3 criteria (T stage, Gleason score and preoperative serum PSA), and 37.3% of patients satisfied 2 of 3 criteria. None of them had positive lymph nodes. Frozen section analysis was performed in 121 of 131 (92.4%) cases. There were 10 positive results and one false-negative result diagnosed on paraffin embedded samples. Recent radical retropubic prostatectomy series indicate the incidence of lymph node metastasis to be less than 10%<sup>12</sup>. With the 9% incidence of metastatic lymph node disease in our patients, our results are consistent with literature reports<sup>8,12,13,15</sup>. However, if there are many lymph nodes it might be very difficult to analyze all of them in frozen sections. Therefore, one should select nodes for frozen section or the surgical procedure would be prolonged. After frozen section analysis, the material is usually fixed in formalin and embedded in paraffin. Deeper sections of the same blocks that

were analyzed in frozen sections occasionally reveal micrometastatic foci, as was the case in our series.

All patients with positive lymph nodes had intermediate or combined criteria of the intermediate and high risk group. None of them had T1 stage, Gleason score 6 or less, and PSA lower than 10 ng/ml. Based on the success to distinguish patients who satisfied all low risk group criteria and had negative lymph nodes in both frozen section and paraffin embedded material, we may conclude that using Partin's predictive nomograms in the decision making process it could be possible to select the group of patients with organ-confined disease who can be spared lymphadenectomy. However, Rees *et al.* describe a predictive model to identify patients with less than 3% likelihood of harboring

Table 3. Distribution of 110 patients with complete preoperative data according to T stage, Gleason score and PSA level

	PSA less than 10	PSA 10.1-20	PSA more than 20
T1 Gleason 6 or less	12	7	0
T1 Gleason 7	2	0	0
T1 Gleason more than 7	0	0	0
T2 Gleason 6 or less	18	23	2
T2 Gleason 7	9	12	2
T2 Gleason more than 7	0	0	0
T3 Gleason 6 or less	4	7	0
T3 Gleason 7	1	6	3
T3 Gleason more than 7	2	0	0
Total	48	55	7

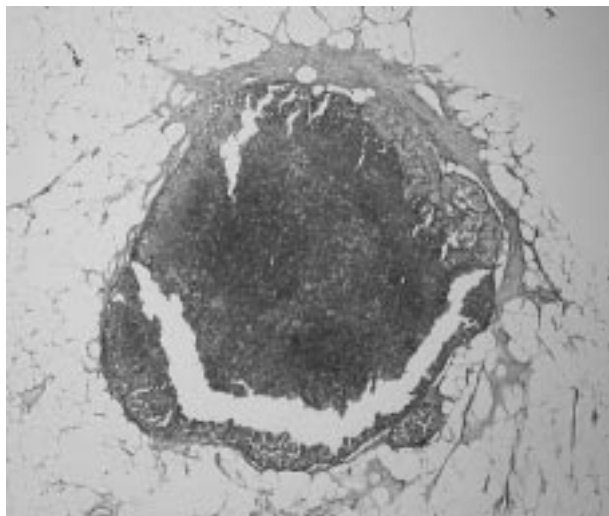


Fig. 3. Frozen section of a lymph node showing metastatic adenocarcinoma of the prostate (H&Ex100)

lymph node disease (PSA not greater than 5 ng/ml, Gleason score not higher than 5)<sup>16</sup>. Osterling *et al.* proposed a similar model earlier, in 1987, by combining the predictive value of clinical stage, serum prostatic acid phosphatase and preoperative Gleason grade<sup>2</sup>. Positive and negative predictive values reported by Blute *et al.* were 0.83 and 0.69<sup>14</sup>.

Staging lymphadenectomy can be performed without frozen section analysis, along with prostatectomy, to determine follow up and therapy. In patients from the high risk group, frozen section lymph node analysis can be performed. The false-negative rate for frozen section analysis in comparison with permanent sections has been reported to range from 7% to 27.5%<sup>17-19</sup>.

If the results prove positive, surgery can be stopped and patients with detected extraprostatic disease can be spared the risk of additional complications associated with radical prostatectomy. Staging information from pelvic lymphadenectomy can be used to justify cancellation of subsequent prostatectomy.

However, radical prostatectomy has a significant degree of associated longterm morbidity, most notably incontinence and erectile dysfunction. Therefore, evaluation of nodal packets would be performed by simple gross inspection or with frozen section analysis in accordance with the surgeon's preference. Furthermore, one should always think about charge for pelvic lymph node dissection in addition to that for radical retropubic prostatectomy, estimated to 1750 USD<sup>11</sup>. The average cost of frozen section analysis of pelvic lymph nodes obtained during radical

prostatectomy in Croatia ranges from 150 to 300 USD, depending on the number of submitted lymph nodes.

Finally, it seems important to attempt to identify subsets of patients with prostate cancer in whom pelvic lymphadenectomy can be omitted with an acceptable risk of failing to identify metastatic disease.

**Acknowledgement.** Supported by grants 0108001/02 (B.K.) and 0134002/02 (M.B.) from the Ministry of Science and Technology, Republic of Croatia.

## References

1. FERLAY J, BRAY F, PISANI P, PARKIN DM. Globocan 2000: cancer incidence, mortality and prevalence worldwide CD-ROM. Lyon: IARC Press, 2001.
2. OESTERLING JE, BRENDLER CB, EPSTEIN JI, KIMBALL AW Jr, WALSH PC. Correlation of clinical stage, serum prostatic acid phosphatase and preoperative Gleason grade with final pathological stage in 275 patients with clinically localized adenocarcinoma of the prostate. *J Urol* 1987;138:92-8.
3. OESTERLING JE, CHAN DW, EPSTEIN JI, KIMBALL AW Jr, BRUZEK DJ, ROCK RC, BRENDLER CB, WALSH PC. Prostate specific antigen in the preoperative and postoperative evaluation of localized prostatic cancer treated with radical prostatectomy. *J Urol* 1988;139:766-72.
4. ACKERMAN DA, BARRY JM, WICKLUND RA, OLSON N, LOWE BA. Analysis of risk factors associated with prostate cancer extension to the surgical margin and pelvic node metastasis at radical prostatectomy. *J Urol* 1993;150:1845-50.
5. BANGMA CH, HOP WC, SCHRODER FH. Eliminating the need for perioperative frozen section analysis of pelvic lymph nodes during radical prostatectomy. *Br J Urol* 1995;76:595-9.
6. PARTIN AW, YOO J, CARTER HB, PEARSON JD, CHAN DW, EPSTEIN JI, WALSH PC. The use of prostate specific antigen, clinical stage and Gleason score to predict pathological stage in men with localized prostate cancer. *J Urol* 1993;150:110-4.
7. BLUESTEIN DL, BOSTWICK DG, BERGSTRAHL EJ, OESTERLING JE. Eliminating the need for bilateral pelvic lymphadenectomy in selected patients with prostate cancer. *J Urol* 1994;151:1315-20.
8. PARTIN AW, KATTAN MW, SUBONG EN, WALSH PC, WOJNO KJ, OESTERLING JE, SCARDINO PT, PEARSON JD. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer: a multi-institutional update. *JAMA* 1997;277:1445-51.
9. BISCHOFF JT, REYES A, THOMPSON IM, HARRIS MJ, ST CLAIR SR, GOMELLA L, BUTZIN CA. Pelvic lymphadenectomy can be omitted in selected patients with carcinoma of the prostate: development of a system of patient selection. *Urology* 1995;45:270-4.
10. BEISSNER RS, STRICKER JB, SPEIGHTS VO, COFFIELD KS, SPIEKERMAN AM, RIGGS M. Frozen section diagnosis of meta-

- static prostate adenocarcinoma in pelvic lymphadenectomy compared with nomogram prediction of metastasis. *Urology* 2002;59:721-5.
11. LINK RE, MORTON RA. Indications for pelvic lymphadenectomy in prostate cancer. *Urol Clin North Am* 2001;28:491-8.
  12. BURKHARDT JH, LITWIN MS, ROSE CM, CORREARJ, SUNSHINE JH, HOGAN C, HAYMAN JA. Comparing the costs of radiation therapy and radical prostatectomy for the initial treatment of early-stage prostate cancer. *J Clin Oncol* 2002;20:2869-75.
  13. MAKHLOUFAA, BOYD JC, CHAPMAN TN, THEODORESCU D. Perioperative costs and charges of prostate brachytherapy and prostatectomy. *Urology* 2002;60:656-60.
  14. BLUTE ML, BERGSTRALH EJ, PARTIN AW, WALSH PC, KATTAN MV, SCARDINO PT, MONTIE JE, PEARSON JD, SLEZAK JM, ZINCKE H. Validation of Partin tables for predicting pathological stage of clinically localized prostate cancer. *J Urol* 2000;164:1591-5.
  15. MENG MV, CARROLL PR. When is pelvic lymph node dissection necessary before radical prostatectomy? A decision analysis. *J Urol* 2000;164:1235-40.
  16. REES MA, RESNICK MI, OESTERLING JE. Use of prostate-specific antigen, Gleason score and digital rectal examination in staging patients with newly diagnosed prostate cancer. *Urol Clin North Am* 1997;24:379-88.
  17. KAKEHI Y, KAMOTO T, OKUNO H, TERAJ A, TERACHI T, OGAWAO. Perioperative frozen section examination of pelvic nodes is unnecessary for the majority of clinically localized prostate cancers in the prostate-specific antigen era. *Int J Urol* 2000;7:281-6.
  18. YOUNG MP, KIRBY RS, O'DONOGHUE EP, PARKINSON MC. Accuracy and cost of intraoperative lymph node frozen sections at radical prostatectomy. *J Clin Pathol* 1999;52:925-7.
  19. EPSTEIN JI, OESTERLING JE, EGGLESTON JC, WALSH PC. Frozen section detection of lymph node metastases in prostatic carcinoma: accuracy in grossly uninvolved pelvic lymphadenectomy specimens. *J Urol* 1986;136:1234-7.

## Sažetak

INTRAOPERACIJSKA ANALIZA LIMFNIH ČVOROVA KOD RADIKALNE PROSTATEKTOMIJE:  
JE LI ONA DOISTA NEOPHODNA?

*B. Krušlin, S. Bulimbašić, H. Čupić, A. Reljić, D. Tomas, I. Tomašković, O. Kraus i M. Belicza*

Radikalna prostatektomija je metoda izbora u liječenju lokaliziranog karcinoma prostate, a najčešće se izvodi u kombinaciji s disekcijom zdjelčnih limfnih čvorova. Disekcija zdjelčnih limfnih čvorova povećava rizik komplikacija, produžava trajanje operacije, povisuje troškove liječenja i medicinske skrbi, pa se je potreba za njenim provođenjem u svih bolesnika s dijagnosticiranim karcinomom prostate tijekom prošloga desetljeća višekratno preispitala. Radi boljeg probira bolesnika sa značajnijom koristi od disekcije zdjelčnih limfnih čvorova različiti autori su obrađivali čimbenike kojima je moguće predvidjeti rizik metastaziranja u regionalne limfne čvorove. Studijom su obuhvaćeni svi bolesnici kojima je zbog dijagnoze karcinoma prostate u razdoblju od 1. siječnja 1998. do 31. prosinca 2002. u Kliničkoj bolnici Sestara milosrdnica učinjena radikalna prostatektomija. Uz primjenu prediktivnih nomograma bolesnici su bili podijeljeni u različite rizične skupine. Većina bolesnika pripadala je skupini niskog i srednjeg rizika metastaziranja, s vrlo ograničenom koristi od disekcije zdjelčnih limfnih čvorova i njihove intraoperacijske analize. Od 110 bolesnika za koje su dobiveni svi podaci uključujući vrijednost antigena specifičnog za prostatu (PSA), Gleasonog zbroj, T stadij i stanje limfnih čvorova analiziranih na intraoperacijskim rezovima, pozitivni limfni čvorovi su utvrđeni u 6 slučajeva. Utvrđena je statistički značajna povezanost između vrijednosti PSA i pozitivnih limfnih čvorova ( $p < 0,005$ ). Također je opažena korelacija između T stadija i vrijednosti PSA ( $p < 0,005$ ) odnosno T stadija i Gleasonova zbroja ( $p = 0,0014$ ). Zaključeno je kako bi bilo uputno razmotriti uporabu prediktivnih nomograma kod planiranja terapijskog pristupa bolesnicima s novootkrivenim, a poglavito onima s klinički lokaliziranim karcinomom prostate.

Ključne riječi: