

Extent of lymphadenectomy in patients with bladder cancer undergoing radical cystectomy – a multi-institutional analysis

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Lymph node dissection (LND) performed at radical cystectomy (RC) has therapeutic and staging significance. However, the extent of LND remains controversial. The aim of this study was to analyze surgical patterns and results of LND in a contemporary series of patients with bladder cancer.

This is a retrospective analysis of 113 consecutive patients subjected to RC in seven urological centres in the year 2013. The mean age of the cohort was 66.6 years. There were 49 cases of organ confined and 64 cases of locally advanced disease. Study endpoints were: status and extent of LND, number of LNs removed, and number of positive LNs.

LND was performed in 102 patients (90.3%). Detailed data on the anatomical extent of LND was available in 82 patients (80.4%). Limited (lLND) and extended LND (eLND) was performed in 68.3% (n = 56) and 31.7% (n = 26) of patients, respectively. Obturator fossa LNs were removed in 84.1%, external iliac in 72.0%, internal iliac in 40.2%, common iliac in 31.7%, and presacral in 15.9% of cases. The median number of LNs removed in the whole study cohort, in patients who underwent lLND, and eLND, was 8.5, 5, and 16.5, respectively. In 28 patients (27.5%), LN metastases were diagnosed, including 6 cases (12.5%) in the organ-confined cohort and 22 cases (34.4%) in the locally advanced disease cohort.

LND is an integral part of radical cystectomy in patients with bladder cancer. However, in the majority of patients, the extent of the procedure was suboptimal, potentially negatively affecting the survival and adequacy of pathological staging.

Key Words: bladder cancer ↔ cystectomy ↔ lymphadenectomy ↔ staging ↔ survival

INTRODUCTION

Bladder cancer is the most common malignancy within the urinary tract. In cases of muscle-invasive disease, curative treatment consists of radical surgery, which includes the removal of regional lymph nodes (LNs) [1]. While the diagnostic and therapeutic importance of lymph node dissection (LND) is well established, the optimal extent has been a mat-

ter of debate for many years. Most authors identify it as the removal of all pelvic LNs located caudally to the aortic bifurcation, a technique termed 'extended lymphadenectomy' (eLND), which is strongly supported by independent meta-analyses and systematic reviews [2–5]. However, the real-life clinical data on the extent and results of LND is limited. In Poland, patients with muscle-invasive bladder cancer (MIBC) account for about 22% of newly

diagnosed bladder cancer cases [6]. While the majority of Polish patients with MIBC are qualified for radical cystectomy [7], the overall postoperative survival is relatively low and does not exceed 32% at five years [8]. Among many potential reasons, the quality of the surgery seems to be one of the most important factors.

Therefore, we wanted to analyze the extent and results of LND in a contemporary series of patients with bladder cancer undergoing radical cystectomy (RC) in selected Polish institutions.

MATERIAL AND METHODS

This retrospective analysis evaluated 113 consecutive patients who underwent RC due to bladder urothelial carcinoma in seven Polish urological institutions during the year 2013. The mean age of the cohort was 66.6 years. RC was associated with the following urinary diversion techniques: ileal conduit in 76 patients (67.3%), transuretero-ureterocutaneostomy in 22 patients (19.5%), and orthotopic neobladder in 15 patients (13.3%).

Study endpoints were: status and extent of LND, number of LNs removed, and number of positive LNs. After initial analysis of the material, two study subgroups were formed and compared: patients who underwent limited LND (lLND) and extended LND (eLND). Limited LND (lLND) was defined as the bilateral removal of at least the external iliac and obturator fossa LNs. eLND was defined as lLND with the additional bilateral removal of internal and common iliac LNs, optionally complemented by the removal of presacral LNs and/or LNs at the region of the aortic bifurcation. The term of standard LND was not adopted within this study, as few patients fulfilled the anatomical criteria of this approach according to clinical guidelines of European Association of Urology [1]. Comparison between lLND and eLND was performed with unpaired t-student, U Mann-Whitney, and Chi square tests for quantitative variables with normal distribution, quantitative variables without normal distribution, and qualitative variables, respectively.

RESULTS

Within the cohort of 113 cystectomized patients, stage T1 and T2 (organ confined disease) was diagnosed in 49 patients (43.4%), while stage T3 and T4 (locally advanced disease) was diagnosed in 64 patients (56.6%), according to the TNM staging system. LND was performed in 102 patients (90.3%). Among 11 patients in whom LND was not performed, there were 10 cases of locally advanced bladder cancer. None of the surgeries had palliative character.

Table 1. Results of LND depending on the extent of LND

	Overall	lLND*	eLND*	P value
Number of patients	102	56	26	–
Mean age	66.6	65.0	65.8	0.05
Number of removed LNs	Median 8.5 Mean 10.9 Range 1-31	5 7.0 1-31	16.5 17.4 4-31	0.00
Rate of positive LNs	28.4%	26.8%	30.8%	0.71

*Detailed information on anatomical regions of LND was available in 82 patients (80.4%).

Detailed information on anatomical regions of LND was available in 82 patients (80.4%). lLND and eLND was performed in 68.3% and 31.7% of patients, respectively. Obturator fossa LNs were removed in 84.1% of cases, external iliac in 72.0% of cases, internal iliac in 40.2% of cases, common iliac in 31.7% of cases, and presacral in 15.9% of cases.

The results of LND are presented in Table 1. The mean age of patients undergoing lLND and eLND did not differ significantly ($p > 0.05$). eLND was associated with a significantly higher number of LNs assessed by a pathologist (5 vs. 16.5, $p < 0.05$). LN metastases were diagnosed in 29 patients (28.4%), including 6 cases (12.5%) of T1–T2 disease and 23 cases (42.6%) of T3–T4 disease. The most common sites of metastases were the external iliac (16.9%) and common iliac (15.4%) LNs, followed by obturator fossa (14.5%) and internal iliac (12.1%) LNs. No metastases in presacral LNs were detected. Nodal metastases were diagnosed more frequently in patients submitted to eLND as compared to lLND; however, the difference did not reach statistical significance (30.8% vs. 26.8%, RR 1.15, $p < 0.05$).

DISCUSSION

LND in patients with bladder cancer undergoing radical cystectomy has clear staging, as well as therapeutic, benefit. In 12% of cases, nodal dissemination is the sole metastatic manifestation of bladder cancer [9]. However, the optimal extent of LND in patients undergoing radical surgery for bladder cancer remains controversial. An expert panel of the European Association of Urology recognizes that the extent of LND has not been established to date [1]. We performed a multi-institutional retrospective cohort study aimed at the characterization of patterns and results of LND in Polish patients undergoing radical cystectomy for bladder cancer. Our main

finding is that LND is performed in the vast majority of patients; however, the median number of LNs removed during the surgery is relatively low and the extension of LND above the bifurcation of the common iliac arteries is not common.

In the past, it was postulated that patient survival improves with the number of removed LNs. This statement was based mainly on a retrospective observational study presented by Koppie et al. [10]. However, this study is limited by the inclusion of the historical cohort of patients, who underwent only ILND in substantial part. Based on the SEER database, Wright et al. suggested that the removal of at least 10 LNs increases overall survival [11]. However, analysis by Froehner et al. revealed a difference only in the overall and not in the cancer specific survival between patients who had less and more than ten LNs removed at RC [12]. Apart from methodological limitations and discrepancies between the studies, a minimal number of LNs that need to be removed at radical cystectomy to improve survival has never been established in any randomized controlled trial. Nowadays, it is known that the number of LNs removed during the surgery is not the issue of only surgical quality, but also depends on the surgical approach, pathologist performance, and patient characteristics. Davies et al. found in a cadaveric study that the number of LNs varies significantly between individuals. In their study, ILND and super-extended LND yielded a mean of 18 and 28 LNs with a wide range of 8–28 and 10–53 LNs, respectively [13]. For these reasons, it is currently accepted that the extent of LND is more important than the number of removed LNs itself. In our analysis, we found that the extent of LND in selected Polish urological centres was suboptimal. Only one third of patients underwent LND above the bifurcation of the common iliac arteries, the region that is the metastatic site in as many as 41% of patients with nodal metastases from bladder cancer [14]. Moreover, presacral LNs were removed in only one of six patients, which precluded clinical interpretation of LND in this anatomical region. For this study, we adopted terms of limited and extended LND, as defined before. Due to the very low percentage of patients who underwent standard LND, defined as the removal of internal iliac, presacral, obturator fossa, and external iliac LNs [1], this subgroup was not formed in our study.

The extent of LND at RC was addressed by many studies in the past. Finally, it became a matter of four independent systematic reviews and/or meta-analyses. They all suggested the survival benefit of eLND as compared to ILND [2–5]. In the meta-analysis published by Mander et al., eLND was associated with the overall odds ratio of 1.63 for the 5-year

recurrence-free survival and no difference in morbidity related to treatment [4]. In the second meta-analysis published by Bi et al., the chance of recurrence in patients undergoing ILND was 1.5-fold higher than in those undergoing eLND, with significant benefit among patients with locally advanced disease, both node positive and node negative [5]. Suboptimal extent of LND noted in the present study indicates that the quality of RC and LND may have significant influence on the survival of Polish patients with bladder cancer.

In the present study, we found that the median number of LNs removed during LND does not exceed 10, while the median number in patients who underwent eLND is over three-fold higher than in patients who underwent ILND. Based on the anatomical study by Davies [13], one can suspect there were still LNs left in the critical regions after surgery in substantial portion of patients. This raises the question related not only to oncological outcomes, but also related to the adequacy of pathological staging. In our cohort, nodal metastases were diagnosed in 28% of patients. However, this number can be underestimated, as the odds of diagnosing positive LNs increase with the extent of LND. Capitanio et al. suggested that removing 25 LNs might represent the lowest threshold at radical cystectomy, resulting in a 75% probability of finding one or several positive LNs [15]. These facts probably explain the lack of difference in the rate of positive LNs between ILND and eLND groups in the present study. Therefore, interpretation of this finding requires special caution. Finally, the minimal number of LNs that need to be assessed histologically for proper staging remains unknown.

Our present study brings information not only on the number of positive LNs, but also on the location of metastatic sites. However, this data should be interpreted with caution. The most commonly affected region was found to be the common iliac; however, the removal of common iliac LNs was performed in only 32% of patients from our analysis. Our analysis did not cover the information on specific indications for ILND and eLND, hence it is possible that the percentage of positive common iliac LNs is affected by selection of higher risk patients for more extensive LND.

The main limitations of our study are the low number of included patients and the lack of information on the use of neoadjuvant chemotherapy. Moreover, we were not able to analyze reasons for omitting LND in 10% of patients. Simultaneously, our analysis covered seven institutions, including both academic and non-academic centres; hence, it presents high-quality data, not biased by institutional surgical habits.

CONCLUSIONS

While LND was an integral part of radical surgical treatment in the vast majority of patients with bladder cancer in analyzed institutions, the median number of removed LNs seems inad-

equated for proper staging. Moreover, the extent of LND was frequently suboptimal for therapeutic purposes.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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