Extended Pelvic Lymph Node Dissection: Before or after Radical Cystectomy? A Multicenter Study of the Turkish Society of Urooncology

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Purpose: We aimed to ascertain the effects of performing extended pelvic lymph node dissection (PLND) on the duration of surgery, morbidity, and the number of lymph nodes removed when the dissection was performed before or after radical cystectomy (RC).

Materials and Methods: We used the database of our previous prospective multicenter study. A total of 118 patients underwent RC and extended PLND. Of the 118 patients, 48 (40.7%) underwent extended PLND before RC (group 1) and 70 (59.3%) underwent extended PLND after RC (group 2). The two groups were compared for extended PLND time, RC time, and total operation times, per operative morbidity, and the total numbers of lymph nodes removed.

Results: Clinical and pathologic characteristics were comparable in the two groups (p > 0.05). The mean RC time and mean total operation times were significantly shorter in group 1 than in group 2 (p < 0.001). The mean number of lymph nodes removed was 27.31 ± 10.36 in group 1 and 30.87 ± 8.3 in group 2 (p = 0.041). Only at the presacral region was the mean number of lymph nodes removed significantly fewer in group 1 than in group 2 (p = 0.001). Intraoperative and postoperative complications and drain withdrawal time were similar in both groups (p = 0.058, p = 0.391, p = 0.613, respectively).

Conclusions: When extended PLND was performed before RC, the duration of RC and consequently the total duration of the operation were significantly shorter than when extended PLND was performed after RC. Practitioners may consider performing extended PLND before RC and rechecking the presacral area for additional lymph nodes after RC, particularly in elderly patients with high co-morbidity for whom the duration of surgery matters.

Key Words: Extended lymph node dissection; Lymph node excision; Morbidity; Radical cystectomy; Urinary bladder neoplasms

INTRODUCTION

Radical cystectomy (RC) with pelvic lymph node dissection (PLND) is the standard of care for muscle-invasive bladder cancer [1]. Previous studies have demonstrated that extended PLND ensures more accurate staging and prognostic information and has therapeutic benefits in a select subset of patients with positive and even in patients with negative lymph nodes [2-6]. Especially during the past decade, numerous articles have been published focusing on issues such as the extended PLND technique (open, laparoscopic, or robotic-assisted), indications and restrictions, ef-
effects on survival and morbidity, the minimum number of lymph nodes to be removed to elicit prognostic and therapeutic benefit, the reliability of examination of frozen sections from the obturator fossa, and the impact on lymphadenectomy margins, lymph node density, and submission of pelvic lymph nodes from different sites separately or en bloc [3,4,6-19]. However, to the best of our knowledge, no study had been conducted to evaluate the effects of the timing of lymphadenectomy during RC, that is, before or after. Therefore, to evaluate this issue, we used the database of our previous prospective multicenter study in which RC and extended PLND was performed [14]. The aim of this study was to ascertain the effects of performing extended PLND before or after RC on the duration of operation, morbidity, and the number of lymph nodes removed.

MATERIALS AND METHODS

In our previous prospective study, 15 surgeons in 13 centers performed open RC and extended PLND on 118 patients diagnosed with bladder cancer [14]. The World Health Organization 1998 classification was used for histopathological typing and grading [20]. Pathologic staging was assigned according to the 2002 tumor-node-metastasis classification [21]. All patients underwent extended PLND, for which margins were determined previously by a protocol [14]. The tissues removed from 12 distinct lymph node regions (Fig. 1) were sent to pathological examination separately.

Of the 118 patients, 48 (40.7%) underwent extended PLND before RC (group 1), whereas 70 (59.3%) underwent extended PLND after RC (group 2). The two groups were compared for extended PLND time, RC time, and total operation (RC+extended PLND without urinary diversion) times, per operative morbidity; the number of lymph nodes removed; and the number of lymph nodes removed from three lymphadenectomy levels (Fig. 1) as described by Leissner et al. [19] and which were also used in our previous study [14].

Statistical analyses were performed by using SPSS ver. 11.5 (SPSS Inc., Chicago, IL, USA). Student’s t-test or the Mann Whitney U test was used to compare the two groups for continuous variables and the chi-square test was used for categorical variables. Only p-values < 0.05 were considered statistically significant.

RESULTS

Mean patient age was 61.09±9.755 years (range, 27 to 82 years). Of the 118 patients, 107 were men and 11 were women. The clinical and pathological characteristics of the patients are shown in Table 1. Histological cell type, grade, and clinical and pathological tumor and node stage were similar in the two groups (all p-values > 0.05).

The mean RC, extended PLND, and total operation times of the two groups are presented in Table 2. The mean extended PLND time was similar in both groups (p=0.160). However, the mean RC time and mean total operation times were significantly shorter in group 1 than in group 2 (p<0.001) (Table 2).

The mean number of lymph nodes removed was 27.31±10.36 in group 1 and 30.87±8.3 in group 2 (p=0.041). Table 3 shows the mean and median number of lymph nodes removed from the three distinct lymphadenectomy levels (Fig. 1) described by Leissner et al. [19] for both groups in a comparative manner. The number of lymph nodes removed from level 2 was significantly fewer in group 1 than in group 2 (p=0.005), whereas the numbers of lymph nodes removed from level 1 and level 3 were similar in both groups (p=0.083 and 0.261, respectively) (Table 3). At level 2, where the number of lymph nodes removed was significantly fewer in group 1 than in group 2, there were 3 lymph node regions: region 4 (right common iliac), region 6 (left common iliac), and region 8 (presacral) (Fig. 1). Of 118 patients, in 32 patients at least one region on level 2 was reported to have no pathological lymph nodes. The distribution of the regions in the patients was as follows: region 8 in 14 patients, region 6 in 5 patients, region 4 in 3 patients, regions 4 and 8 in 5 patients, regions 6 and 8 in 3 patients, regions 4 and 6 in 1 patient, and regions 4, 6,
and 8 in 1 patient. For both groups, the mean and median numbers of lymph nodes removed from these three lymphadenectomy regions at level 2 are shown in Table 4. Two patients in group 1 and two patients in group 2 had positive lymph nodes at region 8 (p=0.699). The mean lymph node density values for region 8 were 0.368±0.175 and 0.328±0.179 in groups 1 and 2, respectively (p=0.562).

Intraoperative arterial or venous injury emerged and was repaired in 12 of 118 patients, 8 in group 1 and 4 in group 2. Of these 12 patients, 7 required blood transfusion, 4 in group 1 and 3 in group 2. The frequency of intraoperative complications was comparable between the two groups (p=0.058). Postoperative complications occurred in 27 patients, including prolonged lymphatic drainage in 20 (10 patients in each group), deep vein thrombosis in 3 (all in group 2), prolonged ileus in 3 (2 patients in group 1 and one patient in group 2), and late hemorrhage in 1 patient (in group 1). The frequency of postoperative complications was comparable between the two groups (p=0.391).

The mean surgical drain withdrawal time was 11.62 days for all patients included in the study. It was 12.02 days in group 1 and 11.34 days in group 2. Mean surgical drain withdrawal time was similar in both groups (p=0.613).

**DISCUSSION**

Lymph node metastases are found in approximately one third to one fourth of patients with bladder cancer who undergo RC and PLND and are the most important prognostic factor in these patients [4,14,22-24]. The importance of the extent of PLND for bladder cancer has become clearer with increasing evidence supporting improved outcomes with more extensive dissections [2,5,6]. However, no recommendation before now has been made with regard to performing extended PLND before or after RC. Some surgeons prefer to perform extended PLND before RC, whereas others prefer to perform it after RC. Both options have advantages and disadvantages. The potential advantages of performing extended PLND before RC are clear visualization of the pedicles and clarified tissue planes. Thus, RC can be performed more rapidly and without significant blood loss. The disadvantages of performing extended PLND before RC result from the narrow space in the pelvis, especially in patients with large solid bladder tumors, which makes the dissection difficult during PLND. On the other hand, performing extended PLND after RC has the advantage of a wide working area in the narrow pelvic cavity and, because the blood vessels are clearly identified, PLND can be performed easily.

However, many studies have suggested that the morbidity associated with extended PLND is comparable with that of a more limited approach [4,9,10]. To our knowledge, however, none of the studies reported evaluated the effect of the timing of extended PLND on the operative morbidity. In our study, we showed that performing extended PLND before or after RC did not result in differences with regard to morbidity. Thereby, considering morbidity, the timing

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### TABLE 1. Clinical and pathological characteristics of the patients

| Characteristic                                    | Total (n=118) | Group 1 (n=48) | Group 2 (n=70) | p-value |
|--------------------------------------------------|---------------|----------------|----------------|---------|
| Histology                                        |               |                |                | 0.303   |
| Transitional                                    | 114 (96.6)    | 45 (93.75)     | 69 (98.5)      |         |
| Non-transitional                                 | 4 (3.4)       | 3 (6.25)       | 1 (1.5)        |         |
| Clinical stage (T)                               |               |                |                | 0.086   |
| ≤cT1                                            | 16 (13.6)     | 5 (10.4)       | 11 (15.7)      |         |
| cT2                                             | 70 (59.3)     | 29 (60.4)      | 41 (58.6)      |         |
| cT3                                             | 26 (22)       | 14 (29.2)      | 12 (17.1)      |         |
| cT4                                             | 6 (5.1)       | 0 (0)          | 6 (8.6)        |         |
| Clinical lymph node status (N)                   |               |                |                | 0.282   |
| cN0                                             | 103 (87.3)    | 44 (91.7)      | 59 (84.3)      |         |
| cN+                                             | 15 (12.7)     | 4 (8.3)        | 11 (15.7)      |         |
| Pathologic stage (T)                            |               |                |                | 0.181   |
| ≤pT1                                            | 25 (21.2)     | 10 (20.8)      | 15 (21.4)      |         |
| pT2                                             | 32 (27.1)     | 12 (25.0)      | 20 (28.6)      |         |
| pT3                                             | 42 (35.6)     | 21 (43.8)      | 21 (30.0)      |         |
| pT4                                             | 19 (16.1)     | 5 (10.4)       | 14 (20.0)      |         |
| Pathologic lymph node metastasis (N)             |               |                |                | 0.385   |
| pN0                                             | 75 (63.6)     | 29 (60.4)      | 46 (65.7)      |         |
| pN+                                             | 43 (36.4)     | 19 (39.6)      | 24 (34.3)      |         |
| Grade<sup>a</sup>                                |               |                |                | 0.051   |
| 1                                               | 4 (3.4)       | 0 (0)          | 4 (5.7)        |         |
| 2                                               | 13 (11.0)     | 2 (4.2)        | 11 (15.7)      |         |
| 3                                               | 98 (83.1)     | 44 (91.7)      | 54 (77.1)      |         |

Values are presented as number (%).

<sup>a</sup>:Information about grade was not available for three patients.

Group 1 underwent extended pelvic lymph node dissection (PLND) before radical cystectomy (RC); group 2 underwent extended PLND after RC.

### TABLE 2. Extended PLND times, RC times, and total operation times of the two groups

| Time                                | Total (n=118) | Group 1 (n=48) | Group 2 (n=70) | p-value |
|-------------------------------------|---------------|----------------|----------------|---------|
| Extended PLND time (min)            | 82.71±27.077  | 87.08±29.496   | 79.71±25.063   | 0.160   |
| RC time (min)                       | 94.11±44.867  | 70.42±39.489   | 110.36±41.146  | <0.001  |
| Total operation time (min)          | 176.82±47.671 | 157.50±37.573  | 190.07±49.5538 | <0.001  |

Values are presented as means±SD.

PLND, pelvic lymph node dissection; RC, radical cystectomy.

Group 1 underwent extended PLND before RC; group 2 underwent extended PLND after RC.
of extended PLND, before or after RC, has no importance.

Many studies have reported that extended PLND takes up to 60 minutes longer than a lymphadenectomy that cranially ends at the level of the iliac arteries [4,9,10,19]. Hence, in daily practice, some surgeons avoid extended PLND in patients with high comorbidity for whom operative time is important. In our study, the mean extended PLND time was 87.08 minutes in group 1 (pre-RC group) and 79.71 minutes in group 2 (post-RC group). Performing extended PLND before or after RC makes an 8-minute difference in the duration of extended PLND, which is statistically insignificant. Therefore, the timing of extended PLND does not result in any significant differences in the duration of extended PLND. In contrast, when we consider the mean RC time, it was shortened by 40 minutes when RC was performed after extended PLND instead of before extended PLND, which was statistically significant. The total mean operation time was also shortened by 33 minutes in group 1 (pre-RC group) compared with group 2 (post-RC group) and this was also statistically significant. These data indicate that performing extended PLND before RC shortens the total operation time by shortening particularly the RC time. Because extended PLND before RC fully skeletonizes the pelvic vascular structures, isolation and control of pedicles during RC is easier, which might be an explanation for the shortening of RC time. Thereby, because there is no difference in morbidity, it can be recommended that extended PLND be performed before RC because the total operation time is shorter than when extended PLND is performed after RC.

Several studies have indicated that the number of lymph nodes removed has prognostic significance in both lymph-node-positive and lymph-node-negative patients [2-4,11,25,26]. In most of the studies and in the European Association of Urology 2010 guidelines on bladder cancer, removal of more than 15 lymph nodes was postulated to be sufficient for the evaluation of lymph node status as well as beneficial for overall survival [4,12,27,28]. In another collaborative review article, it was reported that removal of ≥20 lymph nodes per patient reflects the mean number of nodes that are removed during a meticulous PLND [26]. In our study, we also evaluated the effect of performing extended PLND before or after RC on the number of lymph nodes removed. The mean number of lymph nodes removed during extended PLND before (group 1) and after (group 2) RC was 27.3 and 30.9, respectively, which was a statistically significant difference (p=0.041). Although the number of lymph nodes removed was slightly reduced when extended PLND was performed before RC, it was much higher than 15 or 20, which are the values accepted as cutoffs for improving staging, prognosis, and survival [4,26-28]. In our study, in order to determine whether the mean number of lymph nodes removed at one level made a difference between the two groups with regard to the mean total number of lymph nodes removed, the mean numbers of lymph nodes removed from 3 lymphadenectomy levels (Fig. 1) were compared. Regarding the mean number of lymph nodes removed, we found a significant difference between the two groups only at level 2. We then tried to determine whether the mean number of lymph nodes removed was significantly different in any 1 of the 3 regions (right common iliac, left common iliac, and presacral) at level 2. Regarding the mean number of lymph nodes removed, we found a significant difference between the two groups only at region 8 (presacral region). At this region, a significantly lower mean number of lymph nodes was removed in group 1 than in group 2.

The statistically significant decrease in the mean

### Table 3. Mean and median number of lymph nodes (LNs) removed from three distinct lymphadenectomy levels and comparison of the two groups

| No. of LNs removed | Group 1 (n=48) | Group 2 (n=70) | p-value |
|--------------------|---------------|---------------|---------|
| Level 1            |               |               |         |
| Mean±SD           | 17.7±6.6      | 16.9±7.6      | 0.083   |
| Median (range)     | 17 (7-39)     | 14 (7-39)     |         |
| Level 2            |               |               |         |
| Mean±SD           | 6.8±3.2       | 5.8±3.2       | 0.005   |
| Median (range)     | 6 (0-16)      | 6 (1-16)      |         |
| Level 3            |               |               |         |
| Mean±SD           | 5±3.1         | 4.7±2.9       | 0.261   |
| Median (range)     | 4 (1-20)      | 4 (1-12)      |         |

Group 1 underwent extended pelvic lymph node dissection (PLND) before radical cystectomy (RC); group 2 underwent extended PLND after RC.

### Table 4. Mean and median number of lymph nodes (LNs) removed from three lymphadenectomy regions at level 2 and comparison of the two groups

| No. of LNs removed | Group 1 (n=48) | Group 2 (n=70) | p-value |
|--------------------|---------------|---------------|---------|
| Region 4           |               |               | 0.516   |
| Mean±SD           | 2.3±1.9       | 2.4±1.7       |         |
| Median (range)     | 2 (0-9)       | 2 (0-10)      |         |
| Region 6           |               |               | 0.248   |
| Mean±SD           | 2.04±1.5      | 2.31±1.5      |         |
| Median (range)     | 2 (0-8)       | 2 (0-6)       |         |
| Region 8           |               |               | 0.001   |
| Mean±SD           | 1.44±1.3      | 2.73±2.1      |         |
| Median (range)     | 1 (0-4)       | 3 (0-8)       |         |

Group 1 underwent extended pelvic lymph node dissection (PLND) before radical cystectomy (RC); group 2 underwent extended PLND after RC.
CONCLUSIONS

Performing extended PLND before RC shortens the total operation time in comparison with performing extended PLND after RC by shortening the RC time in particular and does not lead to any additional morbidity. On the other hand, when extended PLND is performed before RC, particularly owing to the difficult dissection of the presacral region, the total number of lymph nodes removed is reduced compared with when extended PLND is performed after RC. It can be recommended that extended PLND be performed before RC and that the presacral area be rechecked for additional lymph nodes after cystectomy, particularly in patients with high comorbidity for whom the operation area during RC.

There are several limitations to this study. First, this was not a randomized clinical study and therefore it bears all the biases inherent with such a study. It could be argued that all of the differences were due to differences in the experience of the surgeons. However, such a magnitude of difference in the technical skills of the surgeons from major centers participating in this study is unlikely. Second, there were no criteria set up front to evaluate the surgical quality of this complicated surgery. On the other hand, the prospective data collection, which was based on a standard protocol, might have decreased the possible biases.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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