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Is there a relationship between the number of lymph nodes and disease parameters in patients who underwent retropubic prostatectomy

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Abstract
Purpose We aimed to establish the relationship between lymph nodes (LNs) counts that were removed with standard pelvic lymph node dissection (sPLND) and different disease parameters in patients who underwent radical prostatectomy (RP).
Materials and methods A total of 70 patients who underwent sPLND during RP were scanned retrospectively. The scanned parameters were levels of serum PSA, the total weight of the removed prostate, the amount as a percentage of the tumor in the prostate tissue, the stage of the tumor, the total Gleason score (GS) and the number of standard pelvic lymph nodes that were removed from both right and left sides.
Results The average age of the patients was 59 years. A positive correlation was found between the total GS and the number of lymph nodes; while this correlation was significant ($p = 0.0038$), there was no significant difference between lymph nodes counts and other scanned parameters. The average pelvic lymph node numbers of patients with GS of 6–7 and 8 were 10.4–11.5 and 13.2, respectively. Lymph nodes metastases were found in 3 (4.2 %) patients whose average pelvic lymph node number was 17.3.
Conclusion The chance of cure or decreased recurrence is much more possible in patients who had received extended PLND or at least standard one, because of the removal of much more lymph node tissues that have a high probability of disseminating cancer cells. This position can especially be considered in patients with high GS.

Keywords Lymph nodes · Metastasis · Disease parameters · Prostate cancer

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Introduction

Prostate cancer (Pca) is the most common noncutaneous cancer and the second leading cause of death from cancer in the USA. Owing to effective treatment of some prostate cancers and biological indolence relative to life expectancy of others, only about 16 % of men diagnosed with Pca ultimately die of it [1]. Survival depends on the right treatment of the cancer. One of the most important issues in the treatment of prostate cancer is the correct staging of the disease. It is well known that one of the first organs that prostate cancer metastasizes to is the lymph nodes (LNs). Therefore, proper evaluation of the LN situation is of crucial importance in the management of newly diagnosed Pca as it holds not only prognostic but also tremendous therapeutic relevance, and additionally, recent data have shown a possible therapeutic benefit of lymphadenectomy in improving cancer-specific survival (CSS) [2].

In this study, we aimed to establish the relationship between the number of LNs that were removed with standard pelvic lymph node dissection (sPLND) and different disease parameters in patients with localized Pca who underwent radical retropubic prostatectomy (RRP).

Materials and methods

Between 2005 and 2009, the data of a total of 70 patients who underwent sPLND including the external iliac, hypogastric and obturator fossa nodal groups during RRP were scanned retrospectively. The scanned parameters were levels of serum PSA, the total weight of the removed prostate during RRP, the amount as a percentage of the tumor in the prostate tissue, the stage of the tumor, the total Gleason score (GS) and the number of standard pelvic lymph nodes that were removed from both right and left sides. All the operations and lymph node dissections were performed by a single surgeon (LT).

Statistical analysis

The relationship between the number of LNs and the above scanned parameters was analyzed using Pearson correlation tests, and the LN numbers according to the side of the tumor were compared using paired T tests. A p value less than 0.05 was considered statistically significant.

Results

The average age of the patients was 59 years, and the median age was 60. The total number of removed LN was 756 (range 3–25). The average LN number was established as 5.6 (range 1–14) and 5.5 (range 1–13) for the right and left side, respectively. There was no statistically significant difference between the two sides ($p = 0.862$). Tumor was detected in only one side in 24 out of 70 patients. In cases where the tumor was localized to only one side, no significant difference in average LN number was found between the sides with and without tumor. The average LN number was found to be 5.23 and 5.4 in sides with and without tumor, respectively ($p = 0.756$).

A positive correlation was found between the total GS and the number of LNs; while this correlation was statistically significant ($p = 0.0038$), there was no significant difference between the number of pelvic LNs and other scanned parameters. The average pelvic LN numbers of patients with GS of 6–7 and 8 were 10.4–11.5 and 13.2, respectively. LN metastases were found in 3 (4.2 %) patients whose average pelvic LN number was 17.3. The total number of positive LN was 22 (2.9 %). The rate of positive LN number for the first, second and third case was 7/21 (33 %), 8/19 (42 %) and 7/12 (58 %), respectively. The results are summarized in the tables below (Tables 1, 2).

Table 1 The correlation between scanned parameters and lymph node counts

Scanned parameter	Pearson correlation	p value
Stage	0.19	0.121
Gleason score	0.252	0.038*
Preoperative PSA	0.15	0.195
Prostate weight	−0.053	0.669
Tumor percentage	0.156	0.203

* $p < 0.05$ was considered statistically significant

Table 2 The average lymph node counts

Side	The average lymph node counts	p value
Right	5.6	0.862
Left	5.5	
Tumor side	5.23	0.756
Without tumor side	5.4	

$p < 0.05$ was considered statistically significant

Discussion

Pelvic lymph node dissection (PLND) has been performed as a part of RRP because of its diagnostic and probable therapeutic benefits ever since the popularization of the modern operation in the last few decades. However, the role of lymphadenectomy in Pca has shifted from necessary to optional. This change is partly a result of the downward stage migration seen in Pca with the advent of PSA and the extensive use of personal screening, whereby more patients diagnosed today show less aggressive tumors of much smaller volume [3, 4]. The probability of a more aggressive approach to Pca has nearly ceased due to diagnosis at the early stages of the disease.

It is well known that one of the modes of dissemination of cancer is through the lymphatic vessels. Therefore, logically, blockage of these vessels can stop or slow down the spreading of cancer. The chance of cure or decreased recurrence is much more possible in patients who had received ePLND or at least sPLND, because of the removal of much more lymph node tissues that have a high probability of disseminating cancer cells. Therefore, a longer interval for periodic follow-up may be considered in these patients than in patients who had undergone lPLND. More prospective randomized clinical studies are required about this issue for making a proper conclusion. The development of metastases determines the prognosis of this malignant disease. The dynamic processes by which lymphatic and systemic metastases occur remain partly theoretical. Therapeutic paradigms are essentially governed by the understanding of the mechanism of cancer dissemination. In many cancers, the

surgical therapeutic strategy has followed the breast cancer model of Halsted [5]. On the basis of the concept that cancer cells do migrate through the lymphatics first, before disseminating systemically, the advocated treatment consists of complete excision of the primary tumor and locoregional lymph nodes [5]. For that reason, within the historical procedure, understanding the prostatic lymphatic pathways had been the most important step in the treatment of Pca. The lymphatic drainage of the prostate has been well described and confirmed by scintigraphic studies [6, 7]. Cellini et al. demonstrated ascending, lateral and posterior ducts that drain into the external iliac nodes, hypogastric and obturator nodes, and subaortic sacral nodes, respectively. Despite this detailed understanding, quite a bit of research has gone into determining which of these nodal groups, if any, represent the primary landing site for metastatic Pca [8]. In a study of metastatic cancer deposits from a cohort of 88 relatively high-risk men with node-positive disease after RRP and extended pelvic lymphadenectomy, the most common site for metastasis (60 %) was the obturator fossa. Overall, however, 58 % had deposits in the internal iliac (hypogastric) and 36 % in the external iliac nodal areas, while 19 % had positive nodes in the hypogastric distribution alone [9].

PLND is considered the most reliable procedure for the detection of LN metastases in Pca; however, in order to decrease the need for PLND, new imaging techniques such as 11C-choline positron emission tomography/CT [10] or MRI with lymphotropic superparamagnetic nanoparticles [11] as well as other conventional imaging procedures such as computed tomography and standard magnetic resonance imaging were considered because of the debated therapeutic benefit of PLND that caused some serious complications such as lymphocele formation, obturator nerve and vascular injury and possibly venous thromboembolism (VTE). Conventional computed tomography (CT) and magnetic resonance imaging (MRI) are generally unreliable in predicting pathologic lymph node status, either for the detection of small metastatic deposits (<1–1.5 cm) or for detecting pathologic enlargement, as enlarged pelvic LNs do not reliably indicate the presence of metastasis [12]. It is well known that discovering the status of the lymph nodes in terms of metastasis is very important for treatment of Pca. Due to the current limitations regarding imaging and lymph node status determination, PLND has remained as the gold standard for establishing lymph node invasion (LNI) in Pca.

Although the diagnosis of Pca has shifted to early clinical stages in the PSA era, nodal metastases are indeed still diagnosed in a wide range of patients [13, 14]. However, the positivity percentage of lymph nodes has shown changes according to the method of PLND—whether it is a limited, standard or extended approach. A limited PLND (lPLND) can be considered for the removal of the fibrofatty and lymphatic tissue inferior to the bifurcation of the common iliac artery, bound inferiorly by the femoral canal, laterally by the pelvic sidewall, and medially and inferiorly by the obturator nerve, collectively known as the external iliac nodes [14, 15]. A standard PLND (sPLND) consists of an lPLND and, in addition, all fibrofatty and lymphatic tissued in the obturator fossa, deep and proximal to the obturator nerve [16]. Finally, an extended PLND (ePLND) should include both of the above along with all fibrofatty tissue surrounding the hypogastric vessels posteriorly [14, 17], though some surgeons include the additional removal of subaortic and presacral nodes in their definitions of ePLND [15, 18].

The reason that different PLND methods affect CSS depends not only on complication rates but also on lymph node positivity rates.

Some surgeons may prefer lPLND to decrease complication rates, whereas others may prefer ePLND to increase lymph node positivity rates.

Complications after both ePLND and lPLND are well described and have been reported to range from 5 % to 50 % [9, 15, 18, 19]. The most commonly described complication specific to a PLND is the subsequent formation of a lymphocele. Other less common complications associated with a node dissection include obturator nerve and vascular injury, increased operating room time, and possibly VTE [20, 21]. Briganti et al. compared the complication rates of an extended ($n = 767$) vs. limited ($n = 196$) dissection and found that the lymphocele formation rates were 10.3 and 4.6 %, respectively [19]. In contrast, Heidenreich et al. [18] noted no increase in complications comparing sPLND to ePLND, reporting a relatively high (15 %) rate of lymphocele and/or VTE in each group.

Several studies have shown that the rate of LNI in Pca patients increases almost linearly with the extent of PLND [22]. Indeed, ePLND might be necessary to detect occult lymph node metastases that would not otherwise be detected by lPLNDs, as Pca nodal metastases do not follow a predefined pathway of spread [23]. Heidenreich et al. [18] as well as Bader et al. [24] pioneered a systematic assessment of the concept of PLND extent, and LNI. Heidenreich et al. found twice as many positive nodes using the extended versus limited technique in a historical control group (26 vs. 12 %; $p < 0.03$). Similarly, ePLND with a mean count of 13.1 LNs was associated with a 2.8-fold higher LNI rate versus lPLND (mean: 10.1 removed LNs; 11.4 vs. 4.1 %; $p = 0.009$) in another recent retrospective laparoscopic series [16]. These results are similar to ours. The relationship between PLND extent and the rate of LNI was also examined by Briganti et al. [13, 22]. These authors showed that the ability to correctly predict the likelihood of LNI increases when the number of removed

nodes is increased [22]. Interestingly, the probability of correctly predicting the rate of LNI was close to zero when <10 nodes were removed. According to our results, the average removed lymph node count was 17.3 in patients with LNI. Conversely, a virtually perfect ability was reported when ≥30 lymph nodes were removed [24]. The only prospective randomized study that assessed the rate of LNI in 123 patients randomly assigned to either lPLND or ePLND did not find a significant difference in the rate of LNI between the two surgical approaches (3.2 vs. 4 %, respectively; $p = 0.1$) [15].

Various preoperative staging nomograms have been designed to predict LNI and thus identify patients who may derive most benefit from PLND. The predictive ability of any nomogram is limited by the data used to create it, which, for predicting lymph node status, includes the data obtained from either a limited, sPLND or ePLND series. Using such nomograms and other available data, expert panels from the American Urological Association, National Comprehensive Cancer Network and European Association of Urology have created guidelines suggesting in whom a PLND should be performed. The ultimate goals of these guidelines and nomograms are to accurately predict who is at risk of lymph node positive prostate cancer and to predict who might derive a therapeutic benefit from lymphadenectomy [25].

Most nomograms, including the well-known Partin tables and Memorial Sloan-Kettering nomograms, predict pathologic stage using preoperative clinical stage, biopsy GS and preoperative PSA, and were derived using pathologic data from radical prostatectomy (RP) and either lPLND or sPLND [25]. We studied the relationship between the clinical stage of the disease, preoperative PSA levels, GS, the total weight of the removed prostate during RRP, the amount as the percentage of the tumor in the removed prostatic tissue and the number of removed pelvic lymph nodes with the sPLND method. We found a positive correlation between GS and the pelvic LN count [Pearson correlation value: 0.252, $p = 0.038$ (Table 1)].

There is likely to be a diagnostic and prognostic benefit to PLND in terms of disease stating. It has become clear that as more nodes are harvested, more positive nodes are found [14, 16, 18, 22]. Estimates of lymph node counts necessary for optimal stating accuracy have ranged from 20 to as high as 28 according to the Briganti et al. and Weingartner et al. studies [12, 22].

According to a study by Schiavina et al. using multivariate analysis, pathological GS and LN groups were significantly associated with CSS, while for overall survival (OS), only the LN group was an independent predictor [26]. The Schiavina et al. [26] study results show that patients with positive LNs who receive RP and PLND for Pca are not all at the same risk of cancer-specific and overall mortality. The number of metastatic LNs was found to be a statistically significant prognostic variable: patients with 1–3 positive LNs had higher CSS and OS than those with >3 positive lymph nodes. Furthermore, considering the GS as well as the number of positive nodes, they found three risk group categories (group 1:1–3 positive LNs and GS ≤ 7; group 2: >3 positive LNs or GS 8–10 and group 3: >3 positive LNs and GS 8–10) with considerable differences in terms of survival. Patients in group 1 had significantly better CSS compared with group 2, and group 2 patients had significantly better CSS and OS compared with group 3. Thus, according to their results, patients with LN-positive disease should be stratified into different groups to obtain a better prediction of oncological outcomes. Similar results had been obtained from the Briganti et al. [27] study. They demonstrated that the number of positive nodes represents a key variable for CSS predictions. Patients with up to 2 positive nodes experienced an excellent CSS rate, which was significantly higher than that for patients with more than 2 positive nodes. These results reinforce the need for stratification of node-positive patients according to the number of positive nodes and may warrant consideration in the next revision of the pathological TNM classification. Depending on this study's results, it can be concluded that ePLND or at least sPLND is much more effective than the limited method in terms of CSS, because of the advantage of removing more lymphoid tissues. The pathological GS is the most important prognostic variable after RP [28]. In addition to these studies, Arenas et al. [29] suggested that pelvic lymphadenectomy, especially extraction of the LNs of the internal iliac, is important in patients with preoperative GS 7 or greater and/or serum PSA greater than 10 ng/ml, according to their results. The counts of removed pelvic LN in patients with high GS should be higher than those of patients with low GS.

There are several limitations of our study. The investigation had a retrospective nature and included single institution's data with small sample size.

Conclusion

LN dissection is of crucial importance in patients who undergo retropubic prostatectomy. There is a statistical correlation between the GS and the LN numbers. Our study revealed that the higher the GS, the more the LNs there are. We believe that higher number of LNs should be excised in patients having high GS when compared to patients with low GS.

Conflict of interest The authors have declared that they have no conflict of interests.

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