Annals of Diagnostic Pathology 20 (2016) 29–35

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

The effect of neoadjuvant therapy on the size, number, and distribution of mesorectal lymph nodes

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ARTICLE INFO

Keywords:
Neoadjuvant therapy
Rectal adenocarcinoma
Lymph node

ABSTRACT

The current therapeutic approach to patients with locally advanced rectal cancer is neoadjuvant radiotherapy or chemoradiotherapy followed by total mesorectal excision. We aimed to investigate the number, size, and distribution of metastatic and nonmetastatic lymph nodes within the mesorectum; whether neoadjuvant therapy has any impact on the number and size of the lymph nodes; and the impact of metastatic lymph node localization on overall and disease-free survival. Specimens from 50 consecutive patients with stage II/III rectal cancer receiving either neoadjuvant radiotherapy or chemoradiotherapy were investigated. Lymph node dissection was carried out by careful visual inspection and palpation. The localization of the each lymph node within the mesorectum and the relation with the tumor site were noted. The size and the number of lymph nodes retrieved decreased significantly with neoadjuvant therapy. Majority of the metastatic and nonmetastatic lymph nodes were located at or proximally to the tumor level and posterior side of the mesorectum. No relation was observed between the overall and disease-free survival, and the localization of the metastatic lymph nodes. Presence of lymph node metastases proximal to the tumor level has no impact on survival compared with the presence of lymph node metastasis only in the peritumoral region of the mesorectum. Although neoadjuvant therapy decreases the size and the number of lymph nodes, reaching an ideal number of lymph nodes for accurate staging is still possible with careful naked eye examination and dissection of perirectal fat. As the majority of metastatic and nonmetastatic lymph nodes are located in peritumoral and proximal compartment, and posterior side of the mesorectum, these regions should be the major interest of dissection.

1. Introduction

The presence of lymph node metastases in colorectal adenocarcinomas considerably worsens the prognosis as compared with nonmetastatic tumors [1–3]. It has also been shown to be the most important independent prognostic factor after neoadjuvant therapy for rectal adenocarcinoma [4–8]. Many studies have been carried out to estimate the minimal number of nodes to be examined to provide the correct lymph node staging. These figures have ranged from 6 nodes to 28 in the literature [9–16]. Recent College of American Pathologists consensus meeting publications stated that the examination of at least 12 lymph nodes was sufficient for accurate identification of regional lymph node metastasis [17]. However, it is always desirable to assess as many lymph nodes as possible [14,18–20].

Lymph node collection from colorectal resection specimens may be influenced by several factors including the ones related to patient (sex, age, body mass index), tumor characteristics (site, type, grade), surgeon, the use of neoadjuvant therapy, and undoubtedly the skill and the energy of the pathologist [21–28]. As the current therapeutic approach to the patients with locally advanced rectal cancer is neoadjuvant short-course radiotherapy (RT) or chemoradiotherapy (CRT) followed by total mesorectal excision (TME) [28–30], it becomes one of the main factors influencing the lymph node retrieval.

Herein we aimed to investigate (1) the distribution of the metastatic and nonmetastatic lymph nodes within the mesorectum, (2) whether neoadjuvant therapy have any impact on the number and size of the dissected lymph nodes, and (3) the impact of metastatic lymph node localization on overall survival (OS) and disease-free survival (DFS) in rectal resection specimens.

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http://dx.doi.org/10.1016/j.anndiagpath.2015.10.008
1092-9134/

2. Materials and methods

Consecutive unselected 50 patients with histologically verified and radiologically staged as rT3 or rT4, and/or rN+ rectal adenocarcinoma were included in the study. The patients received either neoadjuvant short-course RT (25-Gy pelvic irradiation) or neoadjuvant long-course CRT (45-Gy pelvic irradiation and concominant 5 fluorouracil–based chemotherapy). Short-course RT was preferred in a selected group of patients without any risk of lateral margin positivity based on the findings of the pelvic phase array magnetic resonance imaging. Four and 8 weeks after the end of the short- and long-course neoadjuvant therapy, respectively, all patients were operated with curative intent by either one of the colorectal surgeons (OA, EB) in the Department of General Surgery. Low anterior resection (LAR), intersphincteric resection (ISR), or abdominoperineal resection (APR) with a standardized TME technique was performed for each patient according to the site of the tumor.

All specimens adressed to the Department of Pathology were opened anteriorly from proximal resection margin to peritoneal reflection and fixed in formalin for 48-72 hours. Before fixation, macroscopic examination of mesorectal surfaces was done according to the quality assesment system proposed by Nagtegaal et al [31], and colorant inking of the mesorectal surface for the assesment of the circumferential resection margin was done. All were managed by 2 pathologists with special interest in gastrointestinal pathology (GY and MB). After fixation, the specimens were divided transversly into upper, middle, and lower thirds as shown in Fig. 1A. The upper third is accepted as the 4 cm of the rectum above the peritoneal reflection, middle third is accepted as the 4 cm of the rectum below the peritoneal reflection, and lower third is accepted as the distal part of the rectum >4 cm below the peritoneal reflection. The lower and middle parts of the rectum were cut in consecutive transversal 5-mm sectional slices, and then each slice, consisting of full thickness of the rectal wall with mesorectum, was further divided radially into 4 areas as the right lateral, left lateral, anterior, and posterior as shown in Fig. 1B. As the mesorectum lies within posterior and lateral sides of the upper rectum, it is further divided into 3 areas as the right lateral, left lateral, and posterior. After the evaluation of the deepest invasion area of the tumor and the relation of the tumor with the circumferential resection margin, and tumor sampling were done, a rigorous search of the mesorectum by careful visual inspection, palpation, and dissection was carried out to identify as many lymph nodes as possible. The stalk of the mesenteric artery and the pericolic mesenteric adipose tissue were dissected separately. Each lymph node dissected was analyzed in its entirety in separate blocks, and the localization of each lymph node in the mesorectum and relation with the tumor site were noted.

The histopathologic examination was performed on standard hematoxylin-eosin–stained microscopic sections. The pathologic stage of tumor was determined according to the seventh version of TNM

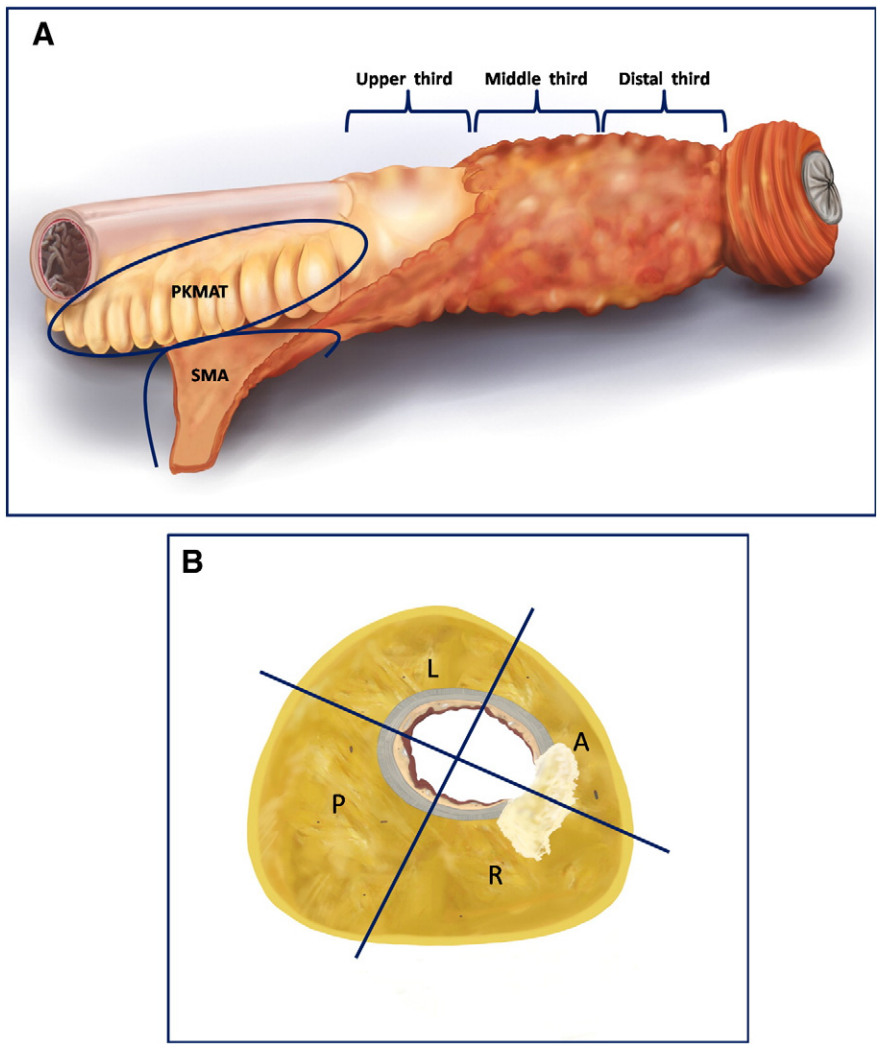

Fig. 1. (A) Illustration of right anterolateral aspect view of abdominoperineal resection specimen showing the division of rectal thirds (PCMAT = pericolic mesenteric adipose tissue; SMA = stalk of the mesenteric artery). (B) Illustration of transversal sectional slice, from tumor level, of an abdominoperineal resection specimen showing the division of the slice into anterior (A), posterior (P), right (R), and left (L) lateral areas.

classification [32]. Tumor response to preoperative therapy was evaluated on the basis of semiquantitative 5-point grading system proposed by Dworak et al [33].

The size of each lymph node was measured on hematoxylin-eosin–stained glass slide. Only entirely encapsulated lymphoid tissue with marginal sinus was—regardless of size—counted as lymph node.

The distribution of metastatic lymph nodes was grouped as distal, proximal, and peritumoral according to the occurrence of the metastases below the inferior edge, above the proximal edge (including the stalk of the mesenteric artery and pericolic adipose tissue), and between the proximal and distal edges of the tumor.

Additional 5 patients who did not received neoadjuvant therapy and underwent LAR with TME were evaluated in the same manner as the control group of the study.

3. Statistical analysis

The demographic, clinical, and histopathologic parameters were analyzed using χ^2, Mann-Whitney *U*, and Student *t* tests. The survival outcomes (OS, DFS) were analyzed using the Kaplan-Meier method, and comparisons were made using the log-rank test. Disease-free survival and OS were calculated as time between the surgery and disease-specific event (recurrence, death). For all statistical analyses, we used SPSS 21 (Statistical Package for Social Sciences; SPSS Inc, Chicago, IL) for personal computer, and $P \leq .05$ was regarded as statistically significant.

4. Results

The demographic, operative, and histopathologic characteristics of the patients in the study and the control groups are summarized in Table 1. In the study group, 26 (52%) were male and 24 (48%) were female. The average age was 56 years, ranging between 30 and 84 years. Thirty (60%) of the patients received neoadjuvant long-course CRT, and the rest received neoadjuvant short-course RT. Type of surgery was LAR in 34 (68%) patients, ISR in 8 (16%) patients, and APR in 8 (16%) patients. In the control group, 3 (60%) patients were male, 2 (40%) patients were female, and the average age was 54 years, ranging between 28 and 76 years. Low anterior resection was performed in all cases.

Table 1
Clinicopathologic characteristics of the study and control groups.

	Study group	Control group
Sex	n (%)	n (%)
Male	26 (52)	3 (60)
Female	24 (48)	2 (40)
Age (y)	Mean (range)	Mean (range)
	56 (30-84)	54 (28-76)
Type of neoadjuvant therapy	n (%)	–
Short-course RT	20 (40)	–
Long-course CRT	30 (60)	–
Type of surgery	n (%)	n (%)
LAR	34 (68)	5 (100)
ISR	8 (16)	0
	8 (16)	0
APR		
Specimen length (cm)	24.1 (14-1)	21 (17-27)
Mean (range)		
TME	n (%)	n (%)
Complete	12 (24)	4 (80)
Near complete	34 (68)	1 (20)
Incomplete*	4 (8)	0
Circumferential resection margin	n (%)	n (%)
Involved	3 (6)	0
Not involved	47 (94)	5 (100%)
Tumor site	n (%)	n (%)
Lower	9 (18)	0
Middle	28 (56)	2 (40)
Upper	11 (22)	3 (60)
Unknown†	2 (4)	0
Regression score	n (%)	–
0	1 (2)	–
1	12 (24)	–
2	26 (52)	–
3	4 (8)	–
4	7 (14)	–
pT stage	n (%)	n (%)
pT0	7 (14)	‡1 (20)
pT1	3 (6)	0 (0)
pT2	9 (18)	2 (40)
pT3	31 (62)	2 (40)
pN stage	n (%)	n (%)
pN0	29 (58)	3 (60)
pN1	14 (28)	1 (20)
pN2	4 (8)	1 (20)
pNx	3 (6)	0 (0)

* Incomplete mesorectal excision due to tumor or iatrogenic perforation.
† Total tumor regression, without macroscopic evidence of tumor.
‡ Operated because of a tubulovillous adenoma with high-grade displasia.

4.1. Number of lymph nodes dissected

We identified a total number of 1410 lymph nodes in the group who received neoadjuvant therapy. The median number was 28.5, ranging between 5 and 52. A minimum number of 12 lymph nodes were harvested, and therefore proper pathologic N staging according to current guidelines [17] was possible in 47 patients (94%). No correlation was identified between the number of dissected lymph nodes and the age, sex, type of surgery, specimen length, tumor site, regression score of the tumor, ypT stage, and ypN status.

Thirty (60%) patients received long-course CRT (LC group); 20 (40%) patients received short-course RT (SC group). The number of lymph nodes retrieved was significantly lower in the LC group than in the SC group (median number, 24.5 vs 34; $P = .006$). Moreover, 3 patients who had less than 12 lymph nodes received long-course neoadjuvant CRT.

A total of 145 lymph nodes were dissected from the patients in the control group. The median number was 30 lymph nodes, ranging between 14 and 48. A higher number of lymph nodes were dissected in the control group than the study group. However, this result was found to be statistically insignificant ($P = .97$).

Metastatic lymph nodes were detected in 18 specimens (38%). The median number of lymph nodes harvested from these patients was 30, ranging between 15 and 49. Among nonmetastatic cases (n = 32), 3 cases (9.4%) had less than 12 lymph nodes and were categorized as ypNx. The nonmetastatic cases had a median number of 28 lymph nodes, ranging from 5 to 52. The number of lymph nodes dissected did not differ between the metastatic and the nonmetastatic groups ($P = .17$).

Within the control group (n = 5), 2 patients had lymph node metastases, and the median number of lymph nodes dissected from those patients was 39.5 (31 and 48 lymph nodes). Three nonmetastatic patients had a median number of 22 lymph nodes, ranging from 14 to 30. Even though more lymph nodes were dissected from the metastatic group, statistical analysis between the metastatic and nonmetastatic controls could not be performed, as the control group was too small.

4.2. Size of the dissected lymph nodes

The median diameter of the dissected lymph nodes was 0.3 cm (range, 0.1-1.3 cm). Among the 1410 lymph nodes, 1008 (71.48%) were ≤0.3 cm and 402 (28.52%) were >0.3 cm in size.

The median size of all 145 dissected lymph nodes in the control group was 0.3 cm (range, 0.1-1.3 cm), as it was in the study group. Eighty-five (58.62%) of the lymph nodes dissected were ≤0.3 cm and 60 (41.38%) were >0.3 cm in size.

Although the median sizes of the lymph nodes in the control and the study groups were the same, the size of the lymph nodes in the study

group tended to be smaller than that in the control group, and the difference was statistically significant ($P = .001$) (Fig. 2).

In the subgroup analysis, the size of the lymph nodes in the LC (n = 30) and SC (n = 20) groups was compared. A total of 745 (52.8%) and 665 (47.2%) lymph nodes were retrieved in the LC and SC groups, respectively. The lymph nodes in the LC group were smaller than the ones in the SC group ($P = .002$). Seventy-five percent of the lymph nodes in the LC group were ≤0.3 cm (median = 0.2 cm), whereas 67.5% of the lymph nodes in the SC group were ≤0.3 cm (median = 0.3 cm) (Fig. 3).

Among the 1410 dissected lymph nodes in the study group, only 36 (2.5%) were metastatic; 1374 (97.5%) were nonmetastatic. Metastatic lymph nodes tend to be larger than the nonmetastatic ones (median size was 0.5 cm vs 0.3 cm). Within the metastatic group, only 6 lymph nodes (16.7%) were ≤0.3 cm in size (range, 0.2-1.1 cm). Conversely, 1002 (72.9%) of the nonmetastatic lymph nodes were ≤0.3 cm in size (range, 0.1-1.3 cm). The difference was statistically significant ($P < .001$) (Fig. 4). Although metastatic lymph nodes tend to be larger, the majority (61.1%) were still ≤0.5 cm in size.

The results were similar in the control group. Eight (5.5%) out of 145 dissected lymph nodes were metastatic. Among them, only 1 (12.5%) was ≤0.3 cm, whereas 7 (87.5%) were >0.3 cm. Among the nonmetastatic lymph nodes (n = 137), 84 (61.5%) were ≤0.3 cm. Size of the nonmetastatic lymph nodes was lower than that of the metastatic lymph nodes, and the difference was statistically significant as it was in the study group ($P = .006$).

In the subgroup analysis, 10 cases (33.3%) from the LC group and 8 cases (40%) from the SC group had metastasis. Median size of the dissected lymph nodes was 0.5 cm in both groups. There was no statistically significant difference between the LC and SC groups in the size of the lymph nodes ($P = .75$).

4.3. Distribution of the lymph nodes

The distribution of lymph nodes was investigated in the ISR and APR specimens, as they contain all 3 parts (lower, middle, and upper thirds) of the rectum. A total of 480 lymph nodes were dissected from the 16 (8 ISR and 8 APR) specimens. Mesorectum, pericolic mesenteric adipose tissue, and the stalk of the mesenteric artery contained 63.55% (n = 305), 27% (n = 128), and 9.8% (n = 47) of the lymph nodes retrieved, respectively. The majority (82%, n = 250) of the lymph nodes dissected were located in the upper and middle third of the mesorectum and mostly (50.2%, n = 153) within the posterior side. The anterior side of the mesorectum contained only 4.3% (n = 13) of the lymph nodes dissected, whereas the right and left sides together contained 45.6% (n = 139) of the dissected lymph nodes.

The distribution of the lymph nodes regarding to the tumor site was as follows: 19.2% (n = 92) were located at the same level with the tumor, 2.3% (n = 11) were located distally, and 78.5% (n = 480) were located proximally to the tumor.

The majority (59.3%, n = 86) of the lymph nodes in the control group were localized in the mesorectum and within the mesoretum in the upper third (40.7%, n = 59), and the posterior side (40.7%, n = 35) of the mesorectum. Pericolic mesenteric adipose tissue and the stalk of the mesenteric artery contained 32.4% (n = 47) and 8.3% (n = 12) of the lymph nodes dissected, respectively.

Among the 1410 lymph nodes dissected in the study group, 36 (2.55%) were metastatic. The distribution of these nodes was as follows: 32 (88.8%) in the mesorectum, 3 (8.3%) in the stalk of the mesenteric artery, and 1 (2.7%) in the pericolic adipose tissue. Twenty (62.5%), 1 (3.1%), and 11 (34.4%) of the 32 metastatic lymph nodes within the mesorectum (n = 32) were localized in the posterior, anterior, and lateral sides of the mesorectum, respectively.

When the association of the distribution of the metastatic lymph nodes with tumor level was investigated, 20 (55.5%) of them were peritumoral, whereas 14 (38.9%) and 2 (5.6%) of them were proximal and distal metastases, respectively.

In the control group, 8 (5.5%) of the dissected lymph nodes were involved, and all were at the same level with the tumor.

4.4. The impact of lymph node metastases and the localization of the metastatic lymph nodes on OS and DFS

The follow-up data were available in 42 patients. Clinicopathologic characteristics of the patients' were summarized in Table 2. The mean follow up time was 48.9 (3-61) months. At the end of the follow-up, 27 (64.3%) patients were alive without disease, 8 (19%) patients were alive with disease, and 7 (16.7%) patients were dead because of the disease. Mean estimated survival time was 54.7 ± 2.4 months (95% confidence interval, 50.027-59.315). Mean estimated recurrence time was 47 ± 3.3 months (95% confidence interval, 40.592-53.531).

5. Discussion

Lymph node collection from colorectal resection specimens may be influenced by several factors related to the patient, surgeon, pathologist, and neoadjuvant therapy [4,21–26]. In our study, the factors related to the surgeons and pathologists were eliminated because both were experienced in gastrointestinal surgery and pathology, respectively. Under these circumstances, we found no association between the number of lymph nodes retrieved and variables such as the age, sex, type of surgery, and specimen length. In our study, the only variable affecting the lymph node yield was the neoadjuvant therapy.

Several studies have shown the negative impact of neoadjuvant therapy on the number of nodes dissected from the resection specimens. Significantly fewer [16,26,34–38] and smaller nodes are harvested in patients who underwent preoperative therapy than those who did not [21,27,36,39,40]. Conversely, Sprenger et al [41] reported a mean number of 31.6 nodes per specimen by embedding and microscopically examining the whole mesorectal soft tissue compartment of

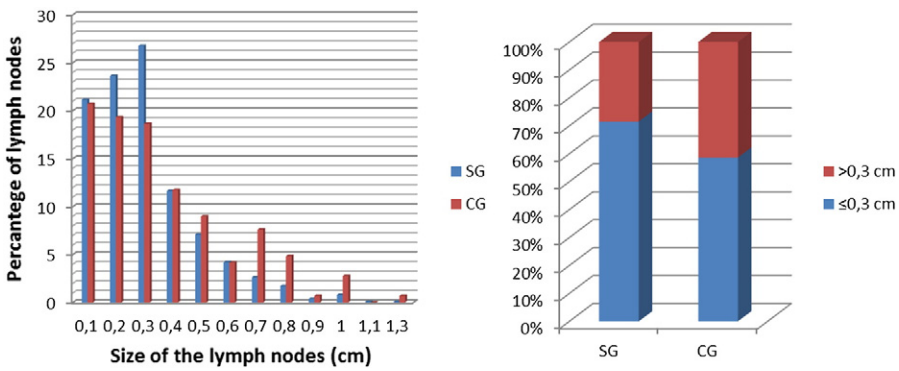

Fig. 2. The distribution of the size of the dissected lymph nodes in the study (SG) and the control groups (CG).

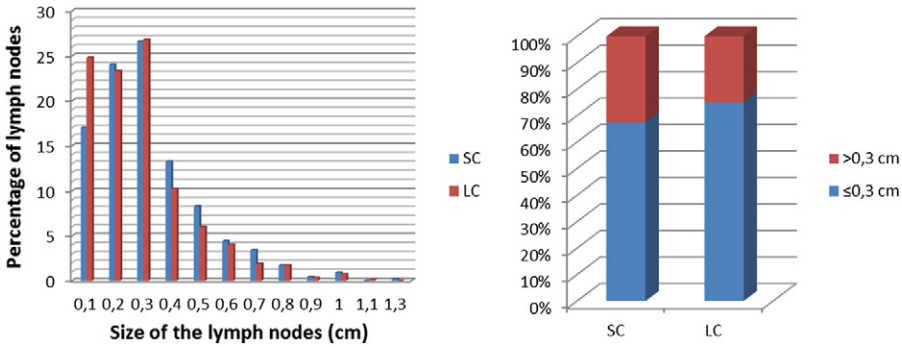

Fig. 3. The distribution of the size of the dissected lymph nodes in the LC and SC neoadjuvant therapy groups.

the patients treated with neoadjuvant CRT. Similar with Sprenger et al, we found a high mean number of lymph nodes, and at least 12 lymph nodes were available in 94% of the patients. The number of lymph nodes retrieved from the study and control groups does not differ significantly. However, as our control group contained small number of cases, it is hard to claim that neoadjuvant therapy does not influence the number of lymph nodes. On the other hand, it is significantly lower in the LC group than the SC group, reflecting the effect of RT dose. Similar results were reported by Rullier et al [38]. They demonstrated that the dose of RT has an impact on the number of lymph nodes retrieved. Addition of 1 Gy decreased the number of lymph nodes retrieved by 0.21% [38]. Because of the high radiosensitivity of lymphoid tissue, higher dose results to a lower number.

Similarly, the size of the lymph nodes in the LC group was significantly smaller than that of the ones in the SC group, which is a similar finding with the study of Scott et al [40]. In addition, nodes from the study group were significantly smaller than those of the control group. It seems that both SC therapy and LC therapy significantly reduce the size of mesorectal lymph nodes, and higher dose results to smaller size as well as number, presumably as a result of apoptosis and involution. The median diameter of the dissected lymph nodes was 0.3 cm, and the majority were ≤0.3 cm in size as previously reported [21,27,36,39–41]. This will definitely make nodes harder to find, but it seems that careful visual inspection and dissection by a dedicated pathologist can still discover substantial numbers.

Several authors advocated that detection of positive lymph nodes is associated with the number of lymph nodes retrieved [10,42,43]. We did not support this finding, as the number of lymph nodes retrieved does not differ between the metastatic and nonmetastatic groups, which is a similar finding with that of Sprenger et al [41].

In the study and the control groups, majority of the metastatic lymph nodes were ≤0.5 cm in size. As in our study, Herrera-Ornelas et al [44] showed that most nodal metastases in colorectal adenocarcinomas are found within lymph nodes less than 5 mm in diameter. Although the majority of the metastatic lymph nodes in both the study and the control groups were ≤0.5 cm, they tended to be larger than the nonmetastatic ones. The smaller size of the negative lymph nodes in the study group is probably caused by rapid apoptosis of lymphocytes in contrast to tumor cells [36]. Interestingly, metastatic lymph node size does not differ significantly between the short- and long-course neoadjuvant therapy groups (median size, 0.5 cm in both groups).

The frequency of lymph nodes within the mesorectum decreased from upper to lower third, and the posterior side of the mesorectum contained the majority of the lymph nodes retrieved in both study and the control groups, which is a finding similar to earlier anatomic studies [45–47].

Most of the metastatic lymph nodes were located in the posterior side of the mesorectum. Majority (55.5%) and the whole (100%) of the metastatic lymph nodes in the study and the control groups, respectively, were found to be at the same level with the tumor. These findings make the posterior side of the mesorectum and the tumor level strategic during the lymph node dissection.

The negative impact of lymph node involvement on OS and DFS, which is a well known fact, was confirmed in our study as well [4–8,17,32,48]. Rödel et al [6] have reported that the presence of positive lymph nodes after preoperative CRT indicates both an aggressive potential of the malignant cells to spread to the regional lymph nodes and resistance of these cells toward CRT, and so has an unfavorable prognosis irrespective of tumor regression grade of the primary tumor. Therefore, an accurate assessment of the pathologic status of the lymph nodes in the rectal cancer patients treated with neoadjuvant therapy, besides the status of the tumor, is essential for reducing the risk of understaging.

Shida et al [49] reported that the location, rather than the number, of nodal metastases has a higher impact on prognosis in colorectal cancer patients. Similarly, Thilo et al [50] reported that patients with proximal metastases after neoadjuvant CRT have decreased survival rates compared with patients with lymph node metastases confined to the peritumoral compartment only. In our study, we could not support this finding. Overall survival and DFS did not differ significantly

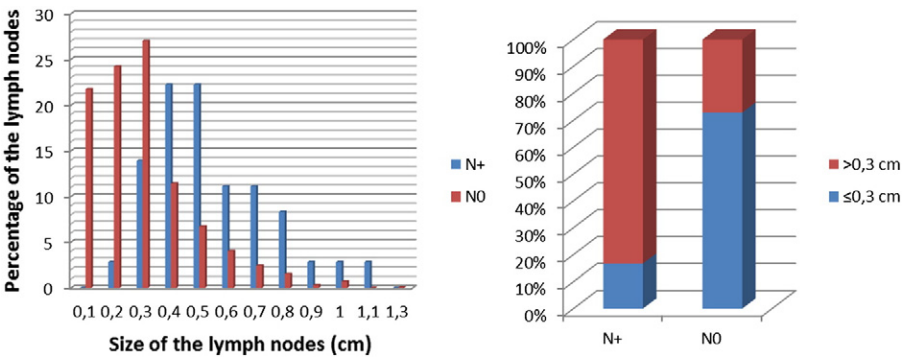

Fig. 4. The distribution of the size of the dissected lymph nodes in the ypN+ and ypN0 groups.

Table 2
Clinicopathological characteristics of the patients who have survival data.

Follow up (mo) Median (range)	53 (3-61)
Survival	n (%)
Alive	35 (83.3)
Dead	7 (16.7)
Recurrence	n (%)
Yes	14 (33.3)
Local	4 (9.5)
Distant	8 (19)
Local and distant	2 (4.8)
No	27 (64.3)
Unknown	1 (2.4)
Sex	n (%)
Male	21 (50)
Female	21 (50)
Age (y)	
Mean (range)	57 (32-84)
Type of neoadjuvant thearpy	n (%)
Short-course RT	19 (45.2)
Long-course CRT	23 (54.8)
Type of surgery	n (%)
LAR	30 (71.4)
ISR	6 (14.3)
APR	6 (14.3)
TME	n (%)
Complete	9 (21.4)
Nearly complete	29 (69)
Incomplete*	4 (9.6)
Circumferential resection margin	n (%)
Involved	3 (7.2)
Not involved	39 (92.8)
Tumor site	n (%)
Lower	7 (16.7)
Middle	27 (64.3)
Upper	8 (19)
Regression score	n (%)
0	0 (0)
1	11 (26.2)
2	22 (52.4)
3	3 (7.1)
4	4 (9.5)
pT stage	n (%)
pT0	4 (9.5)
pT1	3 (7.2)
pT2	8 (19)
pT3	27 (64.3)
pN stage	n (%)
pN0	24 (57.1)
pN+	18 (42.9)

* Incomplete mesorectal excision due to tumor perforation or iatrogenic perforation.

according to the location of the metastatic lymph node regarding the tumor level. It seems that although the lower third of the rectum contains fewer lymph nodes, the distal mesorectum should be excised as much as possible because lymph node metastases to these nodes can occur especially from the tumors of the mid and lower third of the rectum.

6. Conclusion

Majority of lymph nodes are posteriorly located in the upper and mid rectum as expected. Neoadjuvant therapy for locally advanced carcinoma of mid and distal rectum decreases the size and the number of regional lymph nodes, and this effect seems to be dose dependent. However, it is possible to dissect the maximum or ideal number of nodes within TME specimens with careful naked eye examination and palpation of finely sliced perirectal fat. Majority of metastatic lymph nodes were located at the same level and proximally to the tumor and the posterior side of the mesorectum, making these regions strategic for accurate staging. Presence of lymph node metastases has an impact on both OS and DFS; however, there is no survival difference between the patients with only peritumoral lymph node metastases and those with peritumoral and proximal regional lymph node metastases. In the light of these results, we concluded that the accurate nodal staging is much more important than the localization of the metastatic regional lymph nodes.

Acknowledgments

This work is the product of unfunded research.

We thank Yasemin ÖZLÜK, from Istanbul University, Istanbul Faculty of Medicine, Department of Pathology, for statistical analysis and Özge Papakçı Aydın, from Istanbul University Istanbul Faculty of Medicine, Department of Publication Support, for medical illustration.

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