

Less than 12 lymph nodes in the surgical specimen after neoadjuvant chemo-radiotherapy: an indicator of tumor regression in locally advanced rectal cancer?

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Background: The number of lymph node retrieved in the surgical specimen is important for tumor staging and has paramount impact on prognosis in colorectal cancer and imitates the adequacy of lymph node surgical clearance. The paucity of lymph node yields in patients undergoing resection after preoperative chemo radiotherapy (CRT) in rectal cancer has seen. Lower total number of lymph nodes in the total mesorectal excision (TME) specimen after CRT, could a marker of better tumor response.

Methods: We retrospectively reviewed the prospectively managed data of patients underwent excision for rectal cancer, who treated by neoadjuvant radiotherapy with or without chemotherapy in locally advanced rectal cancer. From 2010 to 2014, 364 patients underwent rectal cancer surgery, of which ninety-one treated with neoadjuvant treatment. Standard surgical and pathological protocols were followed. Patients were categorized into two groups based on the number of total harvested lymph nodes with group 1, having 12 or more nodes harvested, and group 2 including patients who had <12 lymph nodes harvested. The total number of lymph nodes retrieved from the surgical specimen was correlated with grade of tumor regression with neoadjuvant treatment.

Results: Out of 91 patients, 38 patients (42%) had less than 12 lymph nodes examined in specimen. The difference in median number of lymph nodes was observed significantly as 9 (range, 2–11) versus 16 (range, 12–32), in group 2 and 1, respectively ($P < 0.01$). Patients with fewer lymph node group were comparable with respect to age, BMI, pre-operative staging, neoadjuvant treatment. Pathological complete response in tumor pCR was seen with significantly higher rate (40% vs. 26%, $P < 0.05$) in group 2. As per Mandard criteria, there was significant difference in tumor regression grade (TRG) between both the groups ($P < 0.05$). Among patients with metastatic lymph nodes, median LNR was lower in <12 lymph nodes group at 0.167 (range, 0.09–0.45) versus 0.187 (range, 0.05–0.54), difference was not statistically significant ($P = 0.81$).

Conclusions: Retrieval of fewer than 12 lymph nodes in surgical specimen of rectal cancer who had received neo-adjuvant radiotherapy with or without chemotherapy should be considered as a good indicator of tumor response with better local disease control, and a good prognostic factor, rather than as a pointer of poor diligence of the surgical and pathological assessment.

Keywords: Rectal carcinoma; pre-operative chemo-radiotherapy; mesorectal excision; lymph node yield; tumor regression

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Introduction

The importance of adequate staging of colorectal cancer for oncological outcomes is highlighted by the management guidelines. Survival impact of lymph node ratio (LNR) (number of metastatic lymph nodes to total number of nodes examined) has been proven to be an independent prognostic indicator in various recent studies, with low LNR shown to have a better survival (1-3). Survival advantage of higher total number of lymph nodes examined in the surgical specimen has been reported (4). The actual lymph node yield shows wide variation as reported in literature (5,6). Presence of at least 12 lymph nodes in surgical specimen is recommended by the American Joint Committee on Cancer (AJCC) and UIAC to ratify the competence of surgery for colorectal cancer, and it has been accepted universally as the standard in the colorectal cancer treatment based on two hypotheses (7-10). First, the accurate staging is an important subset in the treatment protocol in rectal cancer. Second, more precise surgery with higher number of lymph node clearance improves the local control of the disease. This cut-off value is looked as an indicator of quality of surgery and a proxy for adequate surgery, and considered as an important prognostic factor (11-13).

Consequently, fewer than standard recommended lymph nodes have hypothesised to be due to either an inadequate disease removal by the surgeon, or nodes missed from being picked up in the surgical specimen by the pathologist. This might also be due to a reduction in the size and numbers of lymph nodes with chemo radiotherapy (CRT) (14).

The rectal cancer is rather different from colon cancer regarding lymph node metastasis due to its anatomical configuration and circumferential by mesorectum with the fascial inclination. Nevertheless, circumferential radial margin has as much importance as the distal mucosal margin. Higher local recurrence rates in locally advanced rectal cancers have leads to an increased use of pre-operative radiotherapy with or without chemotherapy. Preoperative treatment empirically downstages the primary tumor and the lymph nodes covered in the radiation field as well. Therefore, preoperative CRT followed by routine total mesorectal excision (TME) has become the standard protocol of treatment in locally advanced rectal cancer (15). At our centre, we noticed a paucity of lymph node yield in patients undergoing resection after preoperative CRT in rectal cancer. There are several factors affecting the number of harvested lymph nodes, including radiation technique, radiation dose, tumor responsiveness to radiotherapy and

use of additional chemotherapy, etc. High lymph node yield after pre-operative CRT denotes a compromised radiation field and poor response of the tumor.

The standard surgical technique of TME for proximal rectum and partial TME for the lower rectal cancer would have resulted in high variability of the number of lymph nodes in post CRT patients (14,16). This contemplates the presence of the few lymph nodes in the mesorectum due to neoadjuvant treatment. We propose this study as an orientation, which might help to revise the future guidelines regarding the lymph node yield for proper staging of rectal cancer patients who received neoadjuvant CRT. We also investigated that lower total number of lymph nodes in the TME specimen after CRT is a marker of better tumor response.

Methods

Patients

A prospectively sustained, institutional, confidential record of patients with rectal cancer was probed to identify patients undergoing total mesorectal excision after neoadjuvant CRT for the primary rectal adenocarcinoma between January, 2010 and December, 2014. For each patient, demographics, preoperative diagnosis, clinical staging, preoperative chemoradiotherapy schedule, dose and duration, post neoadjuvant treatment response, operative course, intraoperative events and follow-up assessment were documented. Exclusions included patients who, on presentation had metastatic disease, recurrent cancer, and previous pelvic surgery and radiation. Patients who underwent local excision and who had followed up less than 12 months also excluded. A total of 92 patients were included with full database and retrospectively analysed.

Pre-treatment assessment

At the initial evaluation, clinical and digital rectal examination (DRE), colonoscopy with biopsy, chest radiography and computed tomography (CT) of the abdomen and pelvis to confirm the diagnosis were done. Pathological confirmation was performed on tissue biopsy of the primary lesion. Magnetic resonance imaging (MRI) of the pelvis was performed to stage the local transmural extension and nodal status for all patients. In addition to that, blood cell count, serum biochemistry including liver and renal function tests and serum CEA levels were

obtained. Patients with suspected distant metastasis underwent image guided biopsy and positron emission tomography if possible. Clinical stages were recorded according to the AJCC Staging System, seventh edition (7).

Neo-adjuvant treatment

All patients who had clinical or radiological stage T3, T4 with N0 or N+ received whole pelvis radiotherapy with doses 45 to 54 Gy at 1.8 Gy per fraction in prone position. Local tumor boost radiation was given to patients with cT4 category, as a sequential boost on the primary tumor and corresponding mesorectum with a concomitant dose of 10 Gy (twice in a week, total ten fractions immediately after the daily dose), over five weeks. Radiotherapy was delivered for five sessions per week.

During preoperative radiotherapy, patients who had T4 and N+ stage also received chemotherapy concurrently as per institutional protocol. The chemotherapy regimens used were 5-FU and leucovorin (FL) (n=11) and capecitabine (n=14).

Treatment response

All patients underwent CECT abdomen with pelvis after 4 weeks of completion of neoadjuvant treatment. Serum CEA levels were also performed for all patients. The grade of tumor regression was recorded based on abnormal surface area, size or longitudinal extent of lesion and intramural involvement. Radiological TRG is classified as (17):

- (I) Complete: no residual tumor, no surface abnormality, no induration;
- (II) Good: barely perceptible, 75% or greater reduction in surface abnormality and induration;
- (III) Moderate: 25% to 75% reduction in surface abnormality and induration;
- (IV) Minimal: less than 25% reduction in surface abnormality and induration;
- (V) No change: no change in surface abnormality and induration.

Surgical treatment

At our institute, the assessment for surgery usually starts at four weeks' completion of neoadjuvant treatment to decide the timing of surgery. All patients were planned for surgical exploration after 4 weeks of completion of neoadjuvant treatment with anaesthetic fitness under

ASA class I–III. Mean interval between completion of neoadjuvant treatment and surgery was 7 weeks (range, 4–11 weeks) in this study. Forty-six patients (50.5%) underwent low anterior resection, 41 patients (45.5%) underwent abdominoperineal resection and 4 patients (4%) had pelvic exenteration. Laparoscopic surgery was done in 8 patients (9%). The technique of resection was standardized and all patients underwent TME or partial TME with preservation of the hypogastric nerves.

Surgical pathological assessment

Pathological examination of the specimen was done by the qualified pathologist with manual dissection of the mesenteric and mesorectal fat of the specimen in whole length. During latter half of this study, in our institution the fat clearing technique and lymph node harvesting immediately after surgery followed by submission of the specimen in formalin to the pathologist was followed. Pathologist performed a second attempt to harvest the lymph nodes from the specimen. Each pathological slide was assessed by the consultant pathologist qualified in onco-histopathology. Pathological staging done according to AJCC 7th edition (7). Pathological parameters included tumor transmural extension, tumor differentiation, depth of tumor penetration, lymph node metastasis, circumferential resection margin (CRM), lymphovascular invasion, and tumor regression grade (TRG) as suggested by Mandard *et al.* (18). Positive CRM is defined as the presence of tumor microscopically at the outermost margin of the lesion or <1 mm depth of the circumferential surface of the specimen. Patients were categorized into two groups based on the number of total harvested lymph nodes with group 1, having 12 or more nodes harvested, and group 2 including patients who had <12 lymph nodes harvested.

Follow up

Clinical examination was performed at every 3 months for the first year, every 6 months for the next 2 years, and then annually. Serum CEA level, liver function test, chest X-ray and liver ultrasound performed at every 3 months for the first year and then 6 monthly. At every 6 months, pelvic CT was obtained for all patients and colonoscopy was performed at 1 and 3 years. The occurrence of recurrent lesion in the pelvis, perineum and at the anastomosis was considered as local recurrence, while any other areas considered as distant metastasis. Recurrence was confirmed cytologically

Table 1 Demographic characteristics

Variables	≥12 lymph nodes (N=53) (n, %)	<12 lymph nodes (N=38) (n, %)	P value
Gender			$\chi^2=0.0215$; P=0.8
Male	34 (64.0)	24 (63.0)	
Female	19 (36.0)	14 (37.0)	
Age (years)	51 [29–70]	57 [32–74]	SE =2.128; 95% CI, 1.77–10.22; P=0.005
BMI (kg/m ²)	23.5±3.24	23±3.19	SE =0.68; P=0.46
ASA			$\chi^2=1.078$; P=0.58
I	6 (11.3)	5 (13.2)	
II	36 (67.9)	23 (60.5)	
III	11 (20.8)	10 (26.3)	

or histologically for all cases. Disease free survival was calculated from the time of surgery to appearance of the recurrence. Overall survival was calculated from the day of diagnosis to death.

Statistical analysis

The analysis was done with SPSS statistical software version 20.0 for Windows. Continuous variable (e.g., age, BMI, distal margin from anal verge, time interval, number of lymph nodes, etc.) groups were compared independent t test and chi-square test performed for the proportions (e.g., gender, TNM stage, neo-adjuvant treatment, TRG, ypTNM stage, LNR, etc.). Quantitative and ordinal variables were compared (e.g., number of lymph nodes) with Mann-Whitney test. The value of $P \leq 0.05$ was considered statistically significant.

Results

Patient characteristics

One-hundred-two patients underwent surgery for rectal cancer after preoperative chemo-radiotherapy between the period of January, 2010 and December, 2014 at our institute. Four patients had evidence of systemic metastasis at the time of initial evaluation and seven patients did not come for the follow, and were excluded from the study. Out of them, ninety-one patients with complete information, were enrolled into the study. Based on the total number of lymph nodes retrieved, allocation was done into two groups as described earlier. Among these groups, fifty-three patients (58.2%) had 12 or more lymph nodes retrieved and 38 patients (41.8%) had less than 12 lymph nodes. Gender

distribution between both the groups was similar (P=0.8). Patients with fewer lymph nodes (group 2) were older than group 1. Median age was 57 years (range, 32–74) compared with 51 years (range, 29–70), respectively (P=0.005). No significant differences were seen in BMI and ASA grade of the patients between these groups (Table 1).

Tumor characteristics

At the time of initial evaluation, the tumor location was more likely to be in the lower rectum in group 1, but the difference was statistically insignificant (P>0.05). Although, preoperative T, N, and TNM stage in relation to lymph node yield was not significantly different (P=0.29, P=0.20 and P=0.80), but patients in group with higher lymph node retrieved had more advance lesions in terms of cT3, node positive and overall TNM stage. Clinical T3 stage was the most commonly seen T stage in both the groups. Approximately, one third of the patients had clinically positive nodes as evident by radiological imaging. The level of serum CEA was found to be more than 5 IU/mL in 58.2% patients in the whole study population with insignificant difference between both the groups (P=0.56) (Table 2).

Neoadjuvant treatment

As per institutional protocol, patients with clinical or radiological stage T3, T4 and N positive received neoadjuvant radiotherapy. In addition to that, patients with T4 and node positive also received concurrent chemotherapy either infusion or oral. All ninety-one patients received radiotherapy with dose of 50–54 Gy, only a few patients received boost radiotherapy, the difference between the

Table 2 Clinical staging

Variables	≥12 lymph nodes (N=53) (n, %)	<12 lymph nodes (N=38) (n, %)	P value
Location of tumor (DAV in cm)	6 [3–8]	5 [2–8]	0.056
T stage			$\chi^2=2.426$; P=0.29
cT2	4 (7.5)	1 (2.6)	
cT3	42 (79.2)	32 (84.2)	
cT4	7 (13.3)	5 (13.2)	
N stage			$\chi^2=3.187$; P=0.20
cN0	29 (54.7)	24 (63.2)	
cN1	20 (37.7)	13 (34.2)	
cN2	4 (7.6)	1 (2.6)	
TNM stage			$\chi^2=1.316$; P=0.8
II	29 (54.7)	24 (63.2)	
III	24 (45.7)	14 (36.8)	
Serum CEA (ng/mL)			
Pre-neoadjuvant therapy			$\chi^2=0.327$; P=0.56
≤5	30 (56.6)	23 (60.5)	
>5	23 (43.4)	15 (39.5)	
Post-neoadjuvant therapy			$\chi^2=1.333$; P=0.24
≤5	43 (81.1)	33 (86.8)	
>5	10 (18.9)	5 (13.2)	

two groups was not markedly different (P=0.48). Additional concurrent chemotherapy was given to patients with indications to forty-two patients (46.1%) without obvious difference between the two groups (P=0.20) (Table 3).

Time to surgery

Median time from the completion of the neoadjuvant treatment to surgery was shorter in group 1 than in that with group 2. The median interval was 7 weeks (range, 4–11 weeks) and 8 weeks (range, 4–11), respectively, with no statistically difference (P=0.055) (Table 3).

Type of surgery

Majority of the patients in both groups underwent open surgery, only 10% patients underwent laparoscopic exploration. In both the groups, patients underwent LAR and APR almost equally (P=0.63) (Table 3).

Lymph node retrieval

The number of harvested lymph nodes was significantly

different between two groups. Patients in group 2, had a median number of the total lymph nodes 9 (range, 2–11), fewer than the other group, for which the median number of lymph nodes was 16 (range, 12–32) (P<0.001) (Table 4).

Pathological staging

The pathological characteristics and staging are shown in Table 4. Thirty-eight patients (41.7%) had less than 12 lymph nodes examined in the surgical specimen. There was no significant difference of mean size of the lesion, distance from the anal verge with respect to the total lymph nodes in the surgical specimen. But, patients in the <12 LNs group had smaller tumor size compared to patients in ≥12 LNs (mean size: 3.07±1.59 vs. 3.43±1.97 cm, P=0.35). On pathological evaluation, the proportion of the patients with ypT0 stage was higher in group with fewer lymph nodes 42.1% versus 37.7%, but difference was statistically not significant (P=0.71). Consequently, ypT stage was deviated higher in the group with high lymph node yield as ypT1 was 1.8% vs. 5.2%, ypT2 22.7% vs. 18.4%, ypT3 34% vs. 31.7% and ypT4 was 3.8% vs. 2.6%. The ypN stage was more favourable in the <12 lymph node group (ypN0, 76%

Table 3 Neoadjuvant therapy and perioperative parameters

Variables	≥12 lymph nodes (N=53) (n, %)	<12 lymph nodes (N=38) (n, %)	P value
Chemotherapy*			$\chi^2=1.613$; P=0.20
5-FU infusion + leucovorin	11 (44.0)	9 (53.0)	
Oral capecitabine	14 (56.0)	8 (47.0)	
Radiotherapy dose (cGy)			$\chi^2=1.467$; P=0.48
<5,000	7 (13.2)	3 (7.9)	
5,000–5,400	37 (69.8)	29 (76.3)	
>5,400	9 (17.0)	6 (15.8)	
Interval to surgery (weeks with range)	7 [4–11]	8 [4–11]	0.055
Surgical approach			$\chi^2=0.243$; P=0.62
Open	48 (90.5)	35 (92.0)	
Laparoscopic	5 (9.5)	3 (8.0)	
Surgical procedure			$\chi^2=0.938$; P=0.63
LAR	28 (52.8)	18 (47.4)	
APR	23 (43.4)	18 (47.4)	
Exenteration	2 (3.8)	2 (5.2)	

*, means number of patients who had received chemotherapy along with radiotherapy.

vs. 71%; P=0.29). The pCR rate was statistical different between both the groups (39.4% *vs.* 26.4%, P=0.05). The grade of differentiation of the tumor was more favourable in the patients with fewer lymph nodes, but was statistically insignificant, as well-differentiation was seen in 71.1% patients in group 2 compared to 56.6% in group 1 (P=0.1). The grade of tumor regression was recorded according to Mandard's criteria, which denoted statistically significant better regression was seen with <12 lymph nodes (TRG 1, 2, 3 was 71.1% *vs.* 62.3%; P=0.05).

Lymph node status

The median number of total harvested lymph nodes was statistically different between both the groups, as <12 lymph nodes group had 9 lymph nodes (range, 2–11) compared to 16 lymph nodes (range, 12–32) in ≥12 lymph nodes group (P<0.001). The lymph node stage (ypN) was more favourable with <12 lymph node group, 76.4% patients as ypN0 stage versus 71.1% in ≥12 lymph nodes group (P=0.52). Among patients with metastatic lymph nodes, median LNR was lower in <12 lymph nodes group at 0.167 (range, 0.09–0.45) versus 0.187 (range, 0.05–0.54),

difference was not statistically significant (P=0.81) (Table 4).

Although differences regarding lymphocytic infiltration, lympho-vascular invasion and peri-neural invasion were not statistically significant, findings were more favourable with fewer lymph node group (Table 4).

Surgical margin status

Positive circumferential radial margins were more common in patients with >12 lymph nodes (9.4% *vs.* 5.2%, P=0.26). The distal edge of the tumor was located lower in <12 lymph node group (median distance from anal verge 2.2 cm (range, 0–5.3) compared to 2.4 cm (range, 0–6.9) in ≥12 lymph nodes group (P=0.56) (Table 4).

Discussion

Total number of lymph node harvested in the surgical specimen has paramount impact on prognosis in colorectal cancer and imitates the adequacy of lymph node surgical clearance: number of metastatic lymph nodes higher with increase the total number of lymph nodes examined. The standard guidelines for the minimum number of lymph

Table 4 Pathological characteristics

Variables	≥12 lymph nodes (N=53) (n, %)	<12 lymph nodes (N=38) (n, %)	P value
Tumor size, cm, mean ± SD	3.43±1.97	3.07±1.59	0.35
Distance from anal verge, cm, n (%)			$\chi^2=0.992$; P=0.31
≤5	28 (52.8)	23 (60.5)	
>5	25 (47.2)	15 (39.5)	
ypT stage			$\chi^2=2.089$; P=0.71
0	20 (37.7)	16 (42.1)	
1	1 (1.8)	2 (5.2)	
2	12 (22.7)	7 (18.4)	
3	18 (34)	12 (31.7)	
4	2 (3.8)	1 (2.6)	
ypN stage			$\chi^2=2.443$; P=0.29
0	38 (71.7)	29 (76.3)	
1	11 (20.7)	8 (21.1)	
2	4 (7.6)	1 (2.6)	
yp stage			$\chi^2=3.692$; P=0.29
pCR	14 (26.4)	15 (39.4)	$\chi^2=3.833$; P=0.05
I	10 (18.8)	6 (15.8)	
II	14 (26.4)	8 (21.1)	
III	15 (28.4)	9 (23.7)	
Tumor differentiation			$\chi^2=4.522$; P=0.1
Well	30 (56.6)	27 (71.1)	
Moderate	13 (24.5)	7 (18.4)	
Poor	10 (18.9)	4 (10.5)	
Tumor regression grade			$\chi^2=3.837$; P=0.05
1, 2, 3	33 (62.3)	27 (71.1)	
4, 5	20 (37.7)	11 (29.9)	
Total No. of harvested lymph nodes, median [range]	16 [12–32]	9 [2–11]	<0.001
No. of metastatic nodes			0.52
0	38 (71.1)	29 (76.4)	
1	4 (7.5)	4 (10.5)	
2, 3	7 (13.3)	4 (10.5)	
≥4	4 (7.5)	1 (2.6)	
Median LNR (range)	0.167 (0.09–0.45)	0.187 (0.05–0.54)	0.81
CRM			$\chi^2=1.223$; P=0.26
Positive	5 (9.4)	2 (5.2)	
Negative (>1 mm)	48 (90.6)	36 (94.8)	
Lymphocytic infiltration			$\chi^2=0.832$; P=0.36
Positive	15 (28.3)	13 (34.2)	
Negative	38 (71.7)	25 (65.8)	
LVI			$\chi^2=3.702$; P=0.54
Positive	11 (20.7)	4 (10.5)	
Negative	42 (79.3)	34 (89.5)	
Perineural invasion			$\chi^2=0.737$; P=0.39
Positive	4 (7.5)	2 (5.2)	
Negative	49 (92.5)	36 (94.8)	
Distal resection margins, cm, median (range)	2.4 (0–6.9)	2.2 (0–5.3)	0.56

nodes to be examined in colorectal specimen is mainly to avoid the probability of under-staging, which is an important prognostic factor (7,19-21). These guidelines have some drawbacks with rectal cancer specifically, and are more suitable for the colonic cancers. This could be explained as following. First, the length of the specimen is variable in rectal cancer compared to colon cancer, which leads to fewer number of total lymph nodes retrieved in rectal cancer (20). Second, lymph nodes in mesocolon are larger in size than those in mesorectum, which may be difficult to identify (22). And third, neoadjuvant treatment has an established role in locally advanced rectal cancer, but not in colon cancers, and thus, has become the standard treatment in rectal cancer (23,24).

The influence of minimum number of lymph nodes in rectal cancer is a matter of discussion for the surgeon and the pathologist both. The survival impact of the number of lymph nodes retrieved in rectal cancer is also a matter of debate, in contrast to colon cancer and non-irradiated rectal cancer.

In modern circumstances, preoperative radiotherapy is broadly established for locally advanced rectal cancers with stage T3-T4 or N-positive, to improve the local control of disease and facilitate margin negative resection and increase the probability of successful sphincter preserving surgery (15,25).

Total number of lymph nodes harvested, varies in each individual patient and depends up-on several factors including gender, age, location of tumor and use of preoperative radiotherapy or chemo-radiotherapy (26-28). In our study, the median age was significantly higher in group 2 patients with median age in 57 [32-74] years in comparison to group 1 was 51 [29-70] years ($P=0.005$). However, Shen *et al.* reported that the mean number of lymph nodes was lower in younger patients ($P=0.002$) (27,29). The location of the tumor in relation to the number of lymph nodes retrieved is also controversial as some authors have a notion that distal rectum has tendency to have higher lymph node retrieval and <12 lymph nodes reflects suboptimal radicality of the surgery (29). In contrast, other authors have observed that in the group of fewer lymph nodes tumor located at the lower level with similar results in our study (30,31).

There is obvious clinical importance of the number of lymph nodes in surgical specimen after chemo-radiation, and the association of fewer lymph nodes with poor oncological procedure and outcome should be declined. The disease control in the group of patients with low or nil lymph nodes retrieved is proved better as compared to

ypN+, and is not inferior to ypN0 (32).

The reason behind this, lower lymph nodes retrieval might be radiation induced lymphocytes depletion and development of stromal fibrous tissue leading to decrease in the size of these lymph nodes, and thus less likely to have malignant cells (33). Down-staging in locally advanced rectal cancer after chemo-radiation has been universally accepted with respect to T as well as N stage (23). The normal mesorectal fibro-fatty tissue also atrophies due to radiation induced fibrosis. These factors confound to make it difficult to recognize lymph nodes in irradiated specimen by gross examination (17,32,34,35). In addition, the lymphoid tissue is highly sensitive to radiation and shows more rapid apoptosis, leading to more favourable response than rectal wall thickness (36-39).

Preoperative TNM staging is not a significant factor to affect the number of lymph node retrieval. The degree of decline in serum CEA level after chemo-radiation in patients with raised CEA, correlated with the grade of regression which was proved by the high conversion rate in group 2 (67% vs. 56%, $P=0.24$).

Only a few patients received concurrent chemotherapy in both the groups, almost in equal numbers. However, it is a limitation in our study that the additional chemotherapy was not given to all patients. The dose of the radiation was not uniformly used in study group, varied from 45 to 54 Gy. The drawback is overlooked with the non-significant difference between both groups.

Although, the standardized treatment including preoperative chemo-radiation followed by TME and complete pathological evaluation is unanimously followed worldwide, but the number of lymph nodes harvested varies greatly with ranging 29% to 72% (17,29-31,39,40).

To consider, a rectal cancer non-metastatic to regional lymph nodes, the World Congress of Gastroenterology, Sydney, formulated the guidelines that require a minimum of 12 lymph node to be examined because of the prognostic value (41). Preoperative irradiation has been recognized as a factor to decrease the number of lymph nodes in the specimen and questioned the diligence of surgeon while operating and pathologist during specimen assessment. Subsequently, several studies recommended to revise the guidelines about minimum number of lymph nodes to be reduced in irradiated patients for adequate staging (42,43).

Longer time interval between completion of neoadjuvant treatment and surgery is associated with a lower lymph node yield because of development of more stromal fibrosis. In our study, this factor was negligible because the difference

of time interval from CRT to surgery was statistical insignificant (7 weeks, range: 4–11 *vs.* 8 weeks, range: 4–11; $P > 0.05$).

Type of surgery, i.e., anterior resection or abdominal perineal resection was performed according to the status of lower edge of the tumor with respect to anal verge. Successively, proximal tumors underwent, in majority of cases, anterior resection or low anterior resection, and were associated with higher lymph node retrieval. In our study, both the groups were comparable regarding type of surgery performed ($P = 0.63$) (Table 3).

Smaller tumor size had high association with < 12 lymph nodes but statistically not proved to be a significant factor affecting lymph node harvest (mean size of lesion 3.07 ± 1.59 *vs.* 3.43 ± 1.97 ; $P = 0.35$). However, smaller residual lesion size is an indirect indicator of the tumor response to neoadjuvant CRT, that supports our hypothesis that fewer lymph nodes correlate with treatment response (30,31).

Pathological TNM staging (ypTNM) showed that the patients in < 12 lymph nodes group had significantly higher rate of complete response of the primary lesion (39.4% *vs.* 26.4%; $P < 0.05$). This is an important prognostic factor in locally advanced rectal cancer after neoadjuvant CRT. We noticed a significant difference of the pCR in our study compared to previous studies. This could be due to some of the poor response patients not undergoing surgical intervention after neo-adjuvant treatment. Thus, complete pathological response in this group strongly suggests that low lymph node yield after neoadjuvant treatment in rectal cancer indicates the treatment response rather than an insufficient oncological resection or inappropriate pathological assessment (30,39,41).

Well differentiated tumors were more prevalent in patients with < 12 lymph nodes. Poorly differentiated tumor usually showed low response and resulted in more residual tumor and lymph node retrieval.

Tumor regression was graded according to Mandard's grading score, which found statistically significant higher grade 1–3 response in group of < 12 lymph nodes (71.1% *vs.* 62.3%; $P = 0.05$). Median number of the lymph nodes were significantly different between both the groups with 9 lymph nodes (range, 2–11) compared to 16 lymph nodes (range, 12–32) in group 2 and group 1, respectively. This wide variability of lymph nodes retrieval despite a high level constant standard practice of preoperative CRT, surgical and pathological techniques followed, which is proves the difference in biological response of the tumor

to neoadjuvant treatment between the two groups. In this study, the level of difference in TRG between both groups strongly concludes our hypothesis.

However, the absolute minimum number of 12 lymph nodes to be examined, as proposed by AJCC and IUAC reports in colo-rectal cancers, is copiously reinforced worldwide. In contrast, this report strongly declines such approach in rectal cancer patients who have received neoadjuvant treatment. In addition to the total number of lymph nodes examined, the absolute number of metastatic lymph nodes and LNR of metastatic to total number of lymph nodes examined have been recognized as new prognostic factors for the survival in rectal cancer similar to other malignancies including breast, pancreas and gastric carcinoma (4,11,12,44–46). Moreover, LNR has been identified superior than pN stage in rectal cancer in view of reflecting the response of preoperative therapy as well as regulating the administration of post-operative adjuvant treatment (47–49).

This study also has a few limitations commonly seen in retrospective studies, such as lack of data of all patients, lack of absolute standardization of pre-operative treatment planning and pathological analysis, the pathologist might not be keen in a comprehensive search of lymph nodes in a specimen with evidence of complete response in the primary lesion. Relative small sample size was also a limitation. Introduction of chemotherapy in our study was not uniformly done. This report calls into question the current recommendation regarding minimum target of lymph node retrieval for the locally advanced rectal cancer treated with neo-adjuvant treatment and stresses to institute in future a large prospective study to endorse a similar correlation of TRG as well as cancer outcome with the number of lymph nodes examined.

Furthermore, we are concentrating on regular follow up of these patients to evaluate the correlation between lymph node yield and local recurrence, distant recurrence and survival and planning to document in the literature shortly.

Conclusions

Even with a few drawbacks in our study, the retrieval of fewer than 12 lymph nodes in surgical specimen of rectal cancer who had received neo-adjuvant radiotherapy with or without chemotherapy should be considered as a good indicator of tumor response with better local disease control, and a good prognostic factor, rather than as a

pointer of poor diligence of the surgical oncologist and onco-pathologists.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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