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Lymph node harvest in rectal cancer surgery following neoadjuvant chemoradiotherapy

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Abstract: Purpose: The purpose of the study is to investigate the effect of neoadjuvant chemoradiation, as well as clinicopathological features, on the yield of lymph nodes and survival in rectal carcinoma. Methods: We conducted a retrospective cohort study using an institutional database. 93 patients with rectal cancer treated with curative surgery from 2009 through 2012 at a single District General Hospital in the United Kingdom were included in the study. Follow up perioed was 4 years. Patients had neoadjuvant long course chemoradiotherapy if they were stage II or III. Results: A total of 93 patients were included. 51 received neoadjuvant therapy (NEO) before resection and 42 proceeded to surgery (SURG). There was less lymph node yield in patients who received neoadjuvant therapy (21 vs. 16, $p < 0.05$). Examination of pathology reports revealed that all patients in the NEO group had more nodes with metastatic disease compared to the SURG group (23 vs 18, $p<0.05$). The sphincter preservation rate was 83% for patients operated with neoadjuvant treatment versus 95 % for those in surgery group, Patients within the neoadjuvant group had a statistically significant higher number of APR (NEO 17% vs. SURG 5% vs. $p<0.01$). There was no survival advantage in the neoadjuvant group. Conclusion: Preoperative CRT is associated with a reduction in the yield of lymph nodes in rectal cancer surgery. This is mainly related to radiotherapy, which exerts its effects on the lymph nodes. Also factors such as sex and the level of the tumour may affect lymph node yield.

Keywords: Lymph Nodes, Neoadjuvant Therapy, Rectal Cancer, Survival

1. Introduction

Preoperative chemoradiotherapy followed by surgery is the standard therapy for locally advanced rectal carcinoma [1–5]. Preoperative radiotherapy is thought to decrease the lymph node yield after surgical excision. This is probably caused by the immune response and fibrosis in lymph nodes exposed to radiotherapy, which results in diminution in their size, making their identification in the pathology specimen difficult. According to the recommendations of the International Union Against Cancer (UICC) [6] and current guidelines set by the Royal College of Pathologists in the United Kingdom, a minimum number of 12 lymph nodes per specimen must be found by the pathologists for proper staging [7].

Studies specifically in patients with rectal cancer have demonstrated that the number of retrieved lymph nodes is associated significantly with relapse and survival rates in patients with stage II rectal cancer.[8-10] The inability to examine a sufficient number of lymph nodes may lead to failure in identifying metastatic lymph nodes and, thus, may portend a worse prognosis. However, many studies have reported a significant decrease in the number of lymph nodes retrieved from patients with locally advanced rectal cancer who receive preoperative chemoradiation.[11-15].

This study aims to look at the effect of preoperative chemoradiotherapy (CRT) on the number of lymph nodes retrieved in the mesorectal specimen.

2. Study Population and Design

We conducted a retrospective cohort study using an institutional database. 93 patients with rectal cancer treated with curative surgery from 2009 through 2012 at a single District General Hospital in the United Kingdom were included in the study. Their surgery was performed at the center by four colorectal surgeons. Patients were categorized into two groups: those treated with surgery alone (SURG) and those treated with neoadjuvant therapy (NEO). The follow up period for the patients was 4yrs.

2.1. Treatment

Preoperative staging was performed using a combination of clinical examination, and cross-sectional imaging (computed tomography or magnetic resonance imaging). Indications for neoadjuvant treatment included stage II or III tumors based on clinical and radiologic examinations. Long-course chemoradiotherapy was employed and involved a total dose of 50.4 Gy delivered in 26 fractions with fluorouracil (FU) -based single-agent chemosensitization. Rectal resection was performed using the principles of total mesorectal excision, with appropriately high ligation of the inferior mesenteric artery.

About 6-8 weeks after finishing the CRT, patients underwent surgery. The type of surgery depended on the level of the tumour. If it was not possible to preserve the sphincter, abdominoperineal resection (APR) was performed. Otherwise, low anterior resection (LAR) was done. In all cases total mesorectal excision (TME) was performed.

2.2. Pathologic Examination

Pathology reports included histologic type, margins, vascular and lymphovascular invasion, pathology stage (TNM), total number of regional lymph nodes present in the resected specimen, and number of tumor-positive lymph nodes.

2.3. Statistical Analysis

The primary outcome was number of nodes assessed. The main independent variable for this analysis was treatment group (SURG *v* NEO). Covariates including patient factors (age, sex), tumor factors (location, pathologic stage), and type of surgery (low anterior *v* abdominoperineal resection) were assessed as potential confounding variables. Linear regression was used to compare number of nodes in the two groups. Kaplan-Meier survival analysis was used to analyze disease specific survival (DSS), with the log-rank test used to compare groups. DSS was defined as time from diagnosis to death as a result of disease. Patients who were alive or died as a result of other causes were censored at date of death or last follow-up.

3. Results

A total of 42 patients underwent surgery without receiving preoperative chemoradiotherapy (SURG), and 51 patients were treated with neoadjuvant chemoradiotherapy before the surgery (NEO). Our SURG group included 29 of males and 13 of females with a mean age of 72 years (range, 42–89 years); in the NEO group, there were 31 of males and 20 of females with a mean age of 76 years (range, 43–86 years). The sphincter preservation rate was 83% for patients operated with neoadjuvant treatment versus 95 % for those in surgery group, Patients within the neoadjuvant group had a statistically significant higher number of APR (NEO 17% vs. SURG 5% vs. $p<0.01$). Distribution of the patients by demography and tumour stage is shown in Table 1. All the tumours were adenocarcinomas and most of them were well or moderately differentiated (82%). Of the patients with a known pT stage, there was a predominance of T3 tumours (47%). There was no difference in tumours in the distribution of the rectum. The time elapsed between the completion of the CRT and the surgery ranged between 1 and 20 weeks with a mean of 8 weeks.

Table 1. *Clinicopathological features of patients.*

Age	SURG	NEO	Total
<50	1	3	4
>50	41	48	89
Gender			
Male	29	31	60
Female	13	20	33
Tumour site			
Upper	28	6	34
Middle	9	21	30
Lower	3	26	29
Grade			
Well/moderate	38	39	77
Poor	3	1	4
T stage			
T1	3	3	6
T2	3	11	14
T3	22	22	44
T4	11	6	17

3.1. Neoadjuvant Therapy and Lymph Node Yield

We looked at the number of lymph nodes removed with the specimens. The mean number in the SURG group was 21 (range 9-37). The mean number in preoperative CRT (NEO) was 16 (range 3-28) ($p<0.05$). Figure 1. The number of lymph nodes required for adequate staging being 12, only 85% (40/47) of patients receiving neoadjuvant therapy had this amount, in comparison to 98% (41/42) for those having no preoperative therapy ($p < 0.03$), indicating that a higher proportion of patients who received neoadjuvant CRT would be considered as having inappropriate staging.

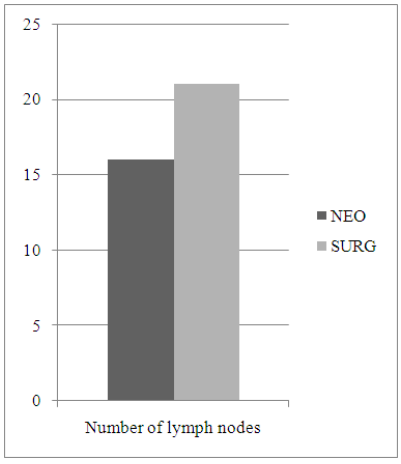

Figure 1. *Analysis of patients that underwent surgery vs neoadjuvant chemoradiotherapy and the lymph nodes harvested. P<0.05.*

3.2. Other Factors

Multivariate analysis of the data also showed a significant association with lower rectal tumours and

female sex on the number of lymph nodes harvested. Patient age, tumour grade, T stage and type of surgery (APR vs. LAR) had no bearing. Table 2.

Table 2. *Association between total nodes and predictors.*

Variable	P value
Age	NS
Gender	0.03
Surgery type	NS
Neoadjuvant chemo	0.03
Lower rectal tumour	0.02
T stage	NS

There was no difference in the length of stay in days between groups (NEO9.37±1.2 vs. SURG 8.3±1.3). Examination of pathology reports revealed that all patients in the NEO group had more nodes with metastatic disease compared to the SURG group (23 vs 18, $p<0.05$). When comparing patients between groups that underwent APR, the total number of lymph nodes resected was similar between groups (NEO 16 vs. SURG 18, p=0.2)

6 pts of CRT had complete response (12.5%). 14 of 23 MRI staging reports matched with final histology in terms of response to CRT and 7 conflicted with final histology. 19 out of 48 patients showed response to CRT (40%). Quality of TME (rectal tumours) i.e. on mesorectal fascia (R0), within mesorectum (R1), or reaching muscularis (R2) was available in 45 patients of NEO group (R0- 35, R1/2 10), and 41 of SURG group (R0-34, R1/2-7). Restaging MRI was done in 23 out of 51 (45%). Tumour regression grade following preop chemoradiotherapy was known in 23 patients. 6 patients with no residual tumor, 12 patients with microscopic residual tumour and 5 with macroscopic residual tumor in the specimen. Extramural venous spread was shown in 27 of surgery group as opposed to 18 of NEO group.

3.3. Survival Analysis

The Kaplan–Meier survival curves failed to demonstrate a survival advantage in the NEO group. Figure 2.

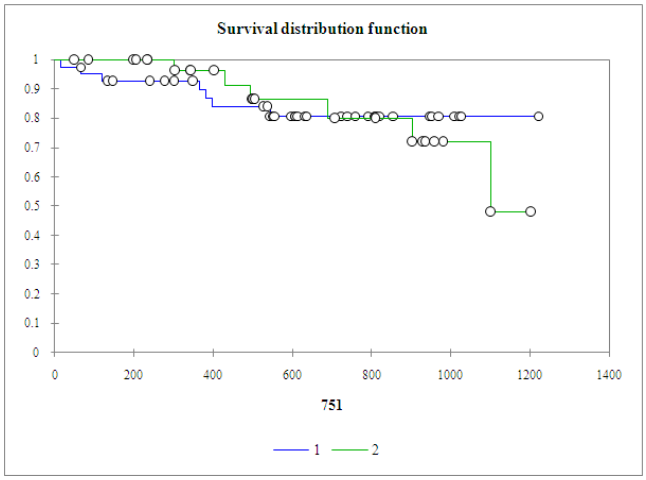

Figure 2. *Survival probabilities (the Kaplan-Meier method) 1- Neoadjuvant group. 2. Surgery group.*

Test of equality of the survival distribution functions (DF = 1):

Statistic	Observed value	Critical value	p-value	alpha
Log-rank	0.000	3.841	0.986	0.050
Wilcoxon	0.456	3.841	0.500	0.050
Tarone-Ware	0.162	3.841	0.687	0.050

4. Discussion

Lymph node harvest in rectal cancer surgery is critical for staging and can impact further interventional decisions, such as adjuvant chemotherapy. A positive lymph node is more likely to be identified if more lymph nodes are examined, and patients with lymph node-negative colorectal cancer, on average, have fewer lymph nodes examined than patients with lymph node-positive disease [16-17].

Studies have demonstrated that chemoradiation significantly decreases the number of lymph nodes retrieved in rectal specimens [12,13,15]. Preoperative chemoradiation can decrease the number of retrieved lymph nodes substantially because of lymph node atrophy, fibrosis, and lymphocyte depletion [18].

This may not be the only factor affecting the number of lymph nodes retrieved. The anatomic site, with lower yield in resected rectal cancer specimens and higher yield in colon cancer specimens,[19-20] other factors, such as tumour location, the extent of surgery, diligent pathologic assessment, histologic grade, and other patient-related factors, can have a significant impact on the number of lymph nodes retrieved [21-24]. Among patients who received preoperative radiation therapy (5 × 5 Gy), more lymph nodes were retrieved after low anterior resection than after abdominoperineal resection [25].

It is also well demonstrated that the fat-clearance techniques for lymph node harvest has a significant impact on the number of lymph nodes examined [26]. It is worth noting that two thirds of metastatic lymph nodes are less that 5 mm in diameter [27]. Those lymph nodes might not be detected if not looked for carefully.

In the present study, the mean number of lymph nodes removed was 18. This compares favorably with other series [20,22,28,29,30]. Age did not have a significant effect on lymph node yield. One study has found higher lymph node yield in younger patients in the past [19]. In our series, female sex was associated with a higher number of lymph nodes. This study also showed an increase in the number of lymph nodes in low rectal cancers as opposed to a previous study [22]. The present study also failed to demonstrate a survival advantage in those who receive neoadjuvant chemoradiotherapy. This could be because the cohort did not have a large sample to be powered enough to show any association.

The type of surgery (APR vs. LAR) had no effect on lymph node yield either. This is possibly due to the lymph node bearing tissues in the mesorectum and the inferior mesenteric artery are removed in a similar manner in both procedures.

In conclusion, preoperative CRT is associated with a reduction in the yield of lymph nodes in rectal cancer surgery. This is mainly related to radiotherapy, which exerts its effects on the lymph nodes. Also factors such as sex and the level of the tumour may affect lymph node yield. All of these factors should be taken into consideration when evaluating the adequacy of lymph node resection in rectal carcinoma. Although high-quality surgery and thorough pathologic examination might improve lymph node yield and provide more accurate staging after preoperative chemoradiation.

The authors declare that they have no conflict of interest.

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