Original Article

Lower lymph node yield following neoadjuvant therapy for rectal cancer has no clinical significance

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Background: Obtaining 12 lymph nodes following resection for rectal cancer is an important prognostic marker. However, patients who have received neoadjuvant therapy are known to have a lower lymph node yield. We conducted this study to determine the clinical significance of evaluating <12 versus ≥12 lymph nodes in individuals who underwent surgery following neoadjuvant therapy for rectal cancer.

Methods: A retrospective analysis of all patients who received neoadjuvant therapy for locally advanced rectal cancer between January 2008 and December 2014 followed by proctectomy was conducted.

Results: In total, 217 patients were treated for rectal cancer. Mean follow-up was 23.4 (interquartile range, 9–40.5) months. Sixty-three (29.0%) patients received neoadjuvant therapy. There was a statistically significant difference in the number of patients with <12 lymph node yield between those who received neoadjuvant therapy and those who did not (27.0% *vs.* 9.1%, P=0.001). Amongst the 63 patients who received neoadjuvant therapy, lymph node yield of ≥12 was not associated with a statistically significant difference in time to recurrence [hazard ratio (HR) 0.17; 95% confidence interval (CI), 0.01–2.01, P=0.160] or time to death (HR 1.07; 0.15–7.90, P=0.946). Kaplan-Meier curves also did not show any significant difference between those with <12 lymph nodes and those with ≥12 lymph nodes in terms of recurrence and death (P=0.203 and P=0.762 respectively).

Conclusions: Although neoadjuvant therapy reduces the lymph node yield during surgery for locally advanced rectal cancer, this has no significance on the overall survival of the patient.

Keywords: Rectal cancer; neoadjuvant therapy; lymph node yield; prognosis; staging

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Introduction

A minimum yield of 12 lymph nodes following resection of colorectal cancer is often "mandatory" for accurate nodal staging as lymph node status has been shown to be a major prognostic factor for oncological outcomes (1). Interestingly, neoadjuvant chemoradiotherapy administered for locally advanced rectal cancer has however been associated with a considerable reduction in the lymph node yield following resection (2,3).

The implications of this lower lymph node yield continue to be debated in the literature. There are authors who have suggested that efforts should be made to ensure that a minimum of 12 lymph nodes are retrieved from the resection specimen to maintain the validity of node negative disease (4,5), while other authors have proposed that a reduction in lymph node yield implies better prognosis for the patient and that this minimum number of 12 lymph nodes is not necessary. Gurawalia *et al.* showed

Table 1 Comparison of lymph node yield

Determinants	Neoadjuvant (n=63)	No neoadjuvant (n=154)	P value
Lymph node yield, mean ± SD	14.5±6.1	17.3±5.6	0.002
Lymph node yield <12 (%)	17 (27.0)	14 (9.1)	0.001

SD, standard deviation.

that pathological complete response (PCR) rates were significantly higher in patients with less than 12 lymph nodes harvested compared with those who had at least 12 (40% *vs.* 26%, P<0.05) (6). Similarly, disease-free survival (DFS) has been shown to be better in patients who yielded less than 12 lymph nodes (7).

We therefore performed this study to determine if harvesting a minimum of 12 lymph nodes after surgical resection for rectal cancer following neoadjuvant chemoradiotherapy affected oncologic outcomes.

Methods

A retrospective study of all patients who were treated for rectal cancer in our institution from January 2008 to December 2014 was performed. Rectal cancer was defined as adenocarcinomas located within 15 cm from the anal verge (5). All patients were staged according to the 6th or 7th editions of the AJCC manual for rectal cancer, depending on the most recent edition present at time of diagnosis (8). Patients were excluded if they had metastatic disease (M1), or had a history of familial colorectal cancer syndromes. It is our institutional practice to discuss all new cases of rectal cancer in our multidisciplinary tumour board meeting which are represented by surgical, medical, radiation oncologists, as well as pathologists and radiologists. Neoadjuvant chemoradiotherapy is typically recommended in locally advanced mid to lower rectal cancers that are T3, positive nodal status, threatened circumferential radial margin on pre-operative magnetic resonance imaging (MRI).

Further analysis was then conducted on patients who had received neoadjuvant chemoradiotherapy. Patients who had less than 12 lymph nodes harvested were compared to those who had 12 or more lymph nodes harvested. Patient characteristics such as gender, ethnicity, age, and the presence of comorbidities were compared between these two groups. Disease characteristics including mean carcinoembryonic antigen (CEA) values, T-staging, tumour grade, presence of lymphovascular invasion, mucinous histology, extent of resection, as well as whether the patient received adjuvant chemotherapy were also compared. Univariable comparisons of categorical data between groups were performed by Chi-square test, while continuous data were analysed by Student's *t*-test. Statistical analysis was performed using Stata software, version 14 (StataCorp, College Station, TX, USA).

All patients were followed up at the outpatient surgical clinic and in concordance to guidelines by American Gastroenterology Association (9). All patients received regular history and physical examination, as well as endoscopic and radiological investigations as needed to identify recurrences. Oncologic endpoints of recurrence and survival were then analysed. Overall survival and recurrence outcomes were analysed by the Kaplan-Meier method, whilst recurrence and disease-free survival (DFS) were analysed by multivariate Cox regression. The study was approved by the National Healthcare Group Domain Specific Review Board (NHG DSRB). NHG DSRB reference number 2015/00842 and informed consent was taken from all patients.

Results

Between January 2008 and December 2014, there were 217 patients who underwent surgical resection for rectal cancer. Out of this, 63 (29.0%) had received neoadjuvant therapy prior to surgical resection. Seventeen (27.0%) patients from the neoadjuvant therapy group had less than twelve lymph nodes in the final resection specimen compared to 14 (9.1%) patients (P=0.001) who did not receive neoadjuvant chemotherapy. Mean lymph node yield was also significantly less amongst patients who had received neoadjuvant therapy compared with those who did not (14.5±6.1 *vs.* 17.3±5.6, P=0.002) (*Table 1*).

Further analysis was conducted on the group of patients who received neoadjuvant therapy. Patient and disease characteristics were compared between lymph node yields of less than 12 lymph nodes and lymph node yields of 12 and more lymph nodes (*Table 2*). Gender (male sex: 58.8% *vs.* 71.7%, P=0.328), ethnicity, mean age (57.7±7.3 *vs.*

Table 2 Comparison of patient and disease characteristics amongst patients who received neoadjuvant therapy

Determinants	LN <12 (n=17)	LN ≥12 (n=46)	P value
Gender, (%)			
Male	10 (58.8)	33 (71.7)	0.328
Age, mean (± SD)	57.7 (±7.3)	59.2 (±9.9)	0.574
Comorbidities, (%)			
Hypertension	6 (35.3)	27 (58.7)	0.099
DM	2 (11.8)	11 (23.9)	0.290
IHD	3 (17.7)	2 (4.4)	0.083
Stroke	0	1 (2.2)	0.540
CEA (ng/mL), mean (± SD)	6.2 (8.0)	6.0 (11.4)	0.961
T-staging			
T1	1 (5.9)	3 (6.5)	
T2	7 (41.2)	11 (23.9)	
T3	7 (41.2)	29 (63.0)	
T4	2 (11.8)	3 (6.5)	0.428
Grade			
Well	4 (23.5)	5 (10.9)	
Moderate	11 (64.7)	36 (78.3)	
Poor	2 (11.8)	5 (10.9)	0.426
Lymphovascular invasion	2 (11.8)	2 (4.4)	0.284
Mucinous histology	1 (5.9)	7 (15.2)	0.323
Extent of resection			
R0	14 (82.4)	42 (91.3)	
R1	3 (17.7)	4 (8.7)	
R2	0	0	0.316
Adjuvant chemotherapy	9 (52.9)	21 (45.7)	0.607

LN, lymph node; DM, diabetes mellitus; IHD, ischemic heart disease; CEA, carcinoembryonic antigen; SD, standard deviation.

59.2±9.9, P=0.574), and presence of comorbidity were not statistically significantly different between both groups. Disease characteristics such as mean CEA levels (6.2 *vs.* 6.0, P=0.961), T-staging, grade, presence of lymphovascular invasion (11.8% *vs.* 4.4%, P=0.284), mucinous histology (5.9% *vs.* 15.2%, P=0.323) extent of resection, as well as administration of adjuvant chemotherapy (52.9% *vs.* 45.7%, P=0.607) were also found to have no statistically significant difference between the 2 groups.

These patients were followed up for a mean of 23.4 (interquartile range, 9–40.5) months. Univariate and multivariate analysis of lymph node yield together with disease variables which included T-staging, histological grade, lymphovascular invasion, extent of resection and administration of adjuvant chemotherapy were conducted for both recurrence as well as overall survival. On multivariate analysis, lymph node yield of more than or equal to 12 was not associated with a statistically significant difference in time to recurrence [hazard ratio (HR) 0.17; 95% confidence interval (CI), 0.01–2.01, P=0.160] (*Table 3*). Multivariate analysis for overall survival could not be performed due to small numbers of patients who were

Table 3 Univariate and multivariate analysis for recurrence

Determinants	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Lymph nodes ≥12	0.30 (0.06–1.61)	0.161	0.17 (0.01–2.01)	0.160
T-staging	0.81 (0.10–6.33)	0.840	1.83 (0.29–11.58)	0.519
Grade	1.36 (0.32–5.77)	0.672	11.91 (0.70–201.67)	0.086
Lymphovascular invasion	1.93 (0.32–11.71)	0.474	2.77 (0.02–377.43)	0.684
Extent of resection	0.69 (0.14–3.53)	0.660	0.07 (0.002–2.09)	0.126
Adjuvant chemotherapy	0.94 (0.58–1.52)	0.796	0.50 (0.16–1.52)	0.221

HR, hazard ratio; CI, confidence interval.

Table 4 Univariate analysis for death

Determinants	Univariate analysis	
	HR (95% CI)	P value
Lymph nodes ≥12	1.07 (0.15–7.90)	0.946
T-staging	1.45 (0.14–14.81)	0.755
Grade	0.45 (0.04–5.24)	0.523
Lymphovascular invasion	0.93 (0.13–6.88)	0.946
Extent of resection	1.42 (0.13–16.04)	0.775
Adjuvant chemotherapy	0.66 (0.26–1.67)	0.381

HR, hazard ratio; CI, confidence interval.

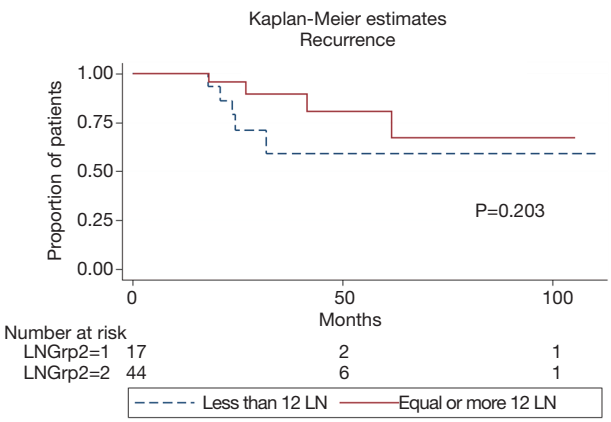

Figure 1 Kaplan-Meier curve for recurrence between LN <12 and LN ≥12. LN, lymph node.

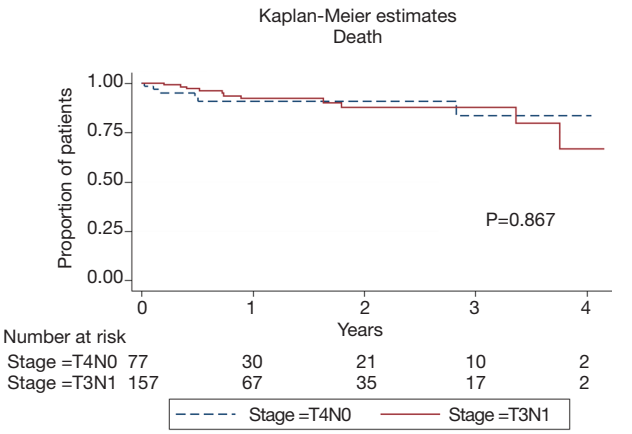

Figure 2 Kaplan-Meier curve for death between LN <12 and LN ≥12. LN, lymph node.

deceased in our population. However, on univariate analysis, we noted that there was also no statistically significant difference in time to death with a lymph node yield of more than or equal to 12 lymph nodes (HR 1.07; 95% CI, 0.15–7.90, P=0.946) (*Table 4*). Kaplan-Meier curves for recurrence and death comparing lymph node yields of less than twelve and more than or equal to twelve were also performed and both were found to not be statistically significantly different (recurrence: P=0.203; death: P=0.867) (*Figures 1,2*).

Discussion

Our results confirm that whilst there is a reduced lymph node yield amongst rectal cancer patients who have received neoadjuvant chemotherapy, but yet this reduced lymph node yield did not lead to any difference in the subsequent oncological outcomes. To note, there were no intrinsic patient or disease characteristics which may have led to the differences in the lymph node yields. Multivariate analysis of time to disease recurrence further showed that even when

controlling for the various histopathological determinants, there was no statistically significant difference in the time to recurrence.

The results from our findings add further weight to the literature that achieving 12 lymph nodes for accurate staging following neoadjuvant chemoradiotherapy for locally advanced rectal cancer may not be required. In fact, the presence of fewer lymph nodes in the final resection specimen following neoadjuvant therapy could imply improved response leading to better tumour regression, and possibly better long-term oncologic results (10). Studies have demonstrated a lower lymph node yield and PCR in the rectum following neoadjuvant therapy (11,12). It was postulated that improved tumour response towards neoadjuvant therapy leads to both reduction in the burden of disease in the lymph nodes as well as at the primary tumour site.

Confusion in the requirement to retrieve at least 12 lymph nodes exists primarily because there is no concession to this requirement in rectal cancer patients who have received neoadjuvant therapy. As such, many authors have proposed novel methods to increase lymph node yield during the surgical phase (13), or post-operatively during pathological analysis (14,15). Our findings therefore suggest that such a requirement is not necessary in the accurate staging and prognostication of rectal cancer. This would reduce the burden and need to artificially maximise the retrieval of lymph nodes from the surgical specimen using adjunctive techniques. Besides, in an oncological resection for rectal cancer, the higher number of lymph nodes that are harvested could have originated in proximity to the inferior mesenteric artery from a wider area of resection rather than from the mesorectum.

Limitations to our study included the small sample size and the retrospective study design which, as discussed, precluded multivariate analysis of overall survival in our patient groups. Although this raises the risk of committing a type two error in the final analysis of our results, our findings do concur with a large body of literature which has suggested similar results. We also noted that owing to the retrospective nature of our study that differences in surgical as well as histopathological techniques may have contributed to differences in lymph node harvesting.

Conclusions

Although lymph node yield is reduced in rectal cancer patients who have received neoadjuvant therapy, our findings suggest that this exhibits no impact on oncologic outcomes. The requirement to harvest at least 12 lymph nodes for accurate staging in rectal cancers following neoadjuvant chemoradiotherapy need to be explored in future studies.

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Footnote

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

Ethical Statement: The study was approved by the National Healthcare Group Domain Specific Review Board (NHG DSRB). NHG DSRB reference number 2015/00842 and informed consent was taken from all patients.

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