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Neoadjuvant therapy does not affect lymph node ratio in rectal cancer

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ABSTRACT

Aims: Recently, lymph-node ratio (LNR) has emerged as a prognostic tool in staging rectal cancer. Studies to date have demonstrated threshold values above and below which survival is differentially altered. Neoadjuvant therapy significantly reduces the number of lymph node retrieved. The aim of the present study was to determine the effect of neoadjuvant therapy on LNR and its prognostic properties.

Methods: Consecutive patients who underwent curative rectal cancer resections in a single institution from 2007 to 2010 were reviewed. LNR was stratified into five subgroups of 0, 0.01–0.17, 0.18–0.41, 0.42–0.69 and 0.7–1.0 based on a previous study. The effect of neoadjuvant therapy on lymph node retrieval, LNR, locoregional (LR) and systemic recurrence (SR), disease-free (DFS) and overall survival (OS) was compared between patients who did (Neoadjuvant) and did not (Surgery Alone) receive neoadjuvant therapy.

Results: Neoadjuvant and Surgery Alone groups were comparable in gender, age and tumour stage. The number of lymph nodes retrieved were significantly lower in the Neoadjuvant group ($p < 0.01$). However, LNR remained similar in both groups ($p = 0.36$). There was no statistical difference in the DFS and OS between the Neoadjuvant and Surgery Alone groups at the various LNR cut off values in patients with AJCC Stage 3 tumours.

Conclusions: LNR ratio remains unaltered despite reduced lymph node retrieval after neoadjuvant therapy in rectal cancer. LNR may therefore be a more reliable prognostic indicator in this subgroup of patients.

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Introduction

Neoadjuvant radiotherapy in conjunction with total mesorectal excision (TME) have been established as the standard treatment modalities in the management of locally advanced rectal cancer.^{1–4} The quality of TME and associated lymph node retrieval have been shown to be of prognostic values and therefore used as surrogate markers of the adequacy of oncological resection. The American Joint Committee on Cancer (AJCC) stated that at least twelve lymph nodes are required for full nodal staging.^{1,2} However, despite this guidance and changes in the processes of pathological assessment, most rectal cancer resections fall short of this recommendation and potentially lead to suboptimal staging.³ Furthermore, neoadjuvant therapy leads to mesorectal fibrosis, which results in a decrease in the mean number of lymph nodes retrieved in a TME specimen.⁴

Lymph node ratio (LNR) has been shown to be a more accurate prognostic tool than nodal status alone in colorectal cancer.⁵ LNR is the ratio of positive lymph nodes to the total lymph nodes resected. Previous studies have demonstrated an inverse relationship between LNR and survival outcomes in colorectal cancer.^{9,10} Rosenberg et al. divided patients into five subgroups using LNR cut off values of 0.0, 0.01–0.17, 0.18–0.41, 0.42–0.69 and 0.70–1.0. In a large population-based study consisting of 27,803 patients, Rosenberg et al. demonstrated that 5-year survival decreased significantly with increasing LNR: LNR = 0 in 71.4%, LNR 0.01 to 0.17 in 52.4%, LNR 0.18 to 0.41 in 33.3%, LNR 0.42 to 0.69 in 19.8%, and LNR > or = 0.70 in 8.3%.

With the more widespread use of neoadjuvant therapy in rectal cancer and its potential impact on lymph node retrieval, no study has assessed the role of LNR in radiotherapy-treated rectal cancer. The primary aim of this study was to assess the impact of neoadjuvant therapy on LNR. The secondary aim was to compare the LNR and its prognostic values in patients with rectal cancer who did (Neoadjuvant) and did not receive neoadjuvant therapy (Surgery Alone).

Methods

This is a comparative observational study of patients undergoing potentially curative surgery for rectal cancer between 2007 and 2010. All pathology was reported by three pathologists and each cancer diagnosis was discussed at the multidisciplinary conference. Patient and tumour characteristics were recorded alongside survival outcomes.

Patients with locally advanced tumour (i.e. T3 or T4, or node positivity or threatened circumferential resection margins) were considered for neoadjuvant chemoradiotherapy. Long course neoadjuvant therapy consisted of 45–50 Gy of radiation and concurrent 5-Fluorouracil chemotherapy. Surgical resections were performed approximately eight weeks after the completion of neoadjuvant therapy.

Locoregional recurrence (LR) was defined as clinical, radiological or pathological evidence of recurrent rectal cancer in the soft or bony tissues of the pelvis at least three months following curative resection^{6,7}. Systemic recurrence

(SR) was defined as the development of metastatic disease at a site distant to the primary cancer. Disease-free survival (DFS) was defined as the time from surgery to the development of local or systemic recurrence or death. Overall survival (OS) was defined as the time from surgery to death of any cause.

LNR cut off values described by Rosenberg et al. were adopted in this study.^{5,8} To date, these remain the only published statistically-derived cut off values with prognostic significance.

Statistical analysis was performed using SPSS 15. Chi-Square analysis was performed to compare categorical data. Student t test was used to compare continuous data. Kaplan–Meier estimates (KM) were generated and plotted for each outcome measure and differences were compared using the LogRank test. A *p* value of less than 0.05 was considered significant.

Results

Patients

In total, 153 patients underwent curative resection for rectal cancer during the study period. Of these, 56 (36.6%) received neoadjuvant therapy. The Surgery Alone cohort displayed more advanced T (*p* = 0.020) and overall AJCC stage (*p* = 0.034). Patient and tumour characteristics are summarised in [Table 1](#).

Lymph node retrieval

There was a significant difference in the average number of lymph nodes retrieved from the Neoadjuvant cohort as compared with the Surgery Alone cohort (6.68 ± 4.74 vs 11.54 ± 6.44 , *p* < 0.010). However, there was no difference in the number of positive tumour-involved lymph nodes between the two cohorts (1.02 ± 3.05 vs 1.73 ± 2.79 , *p* = 0.152).

Lymph node ratio (LNR)

There was no difference in the average LNR between the Neoadjuvant and Surgery Alone cohort (0.122 ± 0.24 vs 0.161 ± 0.23 , *p* = 0.361). When only lymph node positive cancers (stage III) were analysed, therefore considering tumours with LNR of greater than zero, the LNR did not differ significantly between the Neoadjuvant and Surgery Alone cohorts (0.341 ± 0.298 vs 0.334 ± 0.246 , *p* = 0.933).

Prognostic value of LNR

Using the cut off values described by Rosenberg et al., LNR was not predictive of disease-free or overall survival in both cohorts ([Tables 2 and 3](#)).

Discussion

Our results demonstrate that, although there is a reduction in the number of lymph nodes retrieved at time of surgery between patients who underwent neoadjuvant therapy and

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