

Clinical Science

Metastatic lymph node ratio in stage III rectal carcinoma is a valuable prognostic factor even with less than 12 lymph nodes retrieved: a prospective study



Khaled M. Madbouly, M.D., Ph.D., M.R.C.S.(Glasg.)*, Khaled S. Abbas, M.D., Ph.D., Ahmed M. Hussein, M.Ch., Dr.Ch.

Department of Surgery, University of Alexandria, El Raml Station, Alexandria 21321, Egypt

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Rectal cancer;
Recurrence

Abstract

BACKGROUND: The aim of this study was to assess the prognostic value of metastatic lymph node (LN) ratio (MLNR) in stage III rectal cancer and whether this prognostic value remains significant when <12 LNs are retrieved.

METHODS: This prospective study included 115 patients with stage III rectal cancer from 2006 to 2010. All patients underwent neoadjuvant long-course chemoradiation, curative resection, and postoperative adjuvant therapy (5-fluorouracil and leucovorin). Data collected included demographics, tumor pathology, tumor-node-metastasis staging, number of LNs retrieved, MLNR, recurrence, and mortality.

RESULTS: The mean number of examined LNs was 12.1, and the mean number of metastatic LNs was 3.5 (range, 1 to 19). The mean MLNR was .37 (range, 0 to 1.00). The mean duration of follow-up was 37 months (range, 24 to 63). Forty patients died during the follow-up period (overall mortality, 34.8%), only 31 because of cancer (cancer-specific mortality, 27%). Univariate analysis revealed that ypN stage, lymphovascular invasion, and follow-up duration were significantly associated with increased recurrence and decreased survival. Number of positive nodes and ypT stage significantly affected recurrence, with no effect on overall survival. Multivariate analysis proved that MLNR was the only independent risk factor for both mortality and recurrence. Prognostic capability was not affected by having <12 nodes retrieved. The best sensitivity and specificity of MLNR as a prognostic factor for both tumor recurrence and overall survival were achieved at a cutoff value of .375.

CONCLUSIONS: MLNR is an independent prognostic factor for recurrence and survival after the resection of stage III rectal cancer, with high sensitivity and specificity in patients who received neoadjuvant chemoradiation and postoperative chemotherapy. The total number of LN retrieved did not affect the prognostic value of MLNR even if <12.

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* Corresponding author. Tel.: +20-1002033676; fax: +203 4802375.

E-mail address: khaled.madbouly@alexmed.edu.eg

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Rectal cancer remains a challenge to surgeons and oncologists. The use of neoadjuvant chemoradiation therapy (CRT), total mesorectal excision, and new generations of chemotherapeutic agents has improved recurrence and survival. However, local and systemic recurrence remains high.^{1,2} Distant metastases occur in 25% to 30% of patients at 5 year

follow-up.³ The principal target of a cancer staging system is its ability to provide an accurate prognosis and to guide appropriate clinical decisions regarding postoperative management and follow-up.⁴ Currently, the most widely used staging system is the tumor-node-metastasis (TNM) classification system. The TNM staging system classifies patients into prognostic groups according to the depth of the primary tumor, the presence of regional lymph node (LN) metastases, and evidence of distant metastatic spread.^{5,6} The greater the number of positive LNs retrieved, the higher the stage and the worse the prognosis. There have been several recommendations for the minimum number of LNs to be found when dissecting colon or rectal specimens. The current guidelines established by the American Joint Committee on Cancer recommend the assessment of ≥ 12 nodes for accurate staging.⁷

Despite the efforts of surgeons and pathologists, several factors could influence LN retrieval, such as age >60 years, obesity, female sex, small tumor size, poor differentiation grade, the absence of a lymphoid reaction, and neoadjuvant CRT.^{8,9} Neoadjuvant CRT has been shown to result in significant decreases in both the size and number of LNs available for examination after resection.¹⁰ Hence, looking for a new method that can overcome the problem of overall LN retrieval was essential. Many studies have shown that metastatic LN ratio (MLNR) can be considered a prognostic factor in colon cancer. However, the evidence is still limited in rectal cancer.^{11,12}

All studies on the role of MLNR in rectal cancer as a prognostic factor were retrospective and mostly combined colon and rectal cancer in the analyses.^{13–15} Moreover, some studies included both patients who received preoperative neoadjuvant CRT and others who did not.¹⁴ Other studies included only patients with >12 LNs retrieved^{11,12}; thus, bias in patient selection could have affected the results.

Many questions remain unanswered: To what extent can MLNR be considered a reliable prognostic indicator in middle-third and lower-third rectal cancer after neoadjuvant CRT? What is the effect of LN yield <12 on the prognostic capability of MLNR? Finally, which MLNR cutoff values have the best discriminative power in these patients?

The aim of this study was to assess the prognostic value of MLNR in patients with stage III middle and low rectal cancer who received neoadjuvant CRT and whether this prognostic value remains significant when <12 LNs are retrieved.

Methods

Consecutive adult patients undergoing radical surgery for rectal cancer with curative intent were screened for eligibility for the study. Patients were enrolled prospectively during the period from May 2006 through May 2010.

Patients were included if they had histologically confirmed adenocarcinoma of the middle or distal rectum (<12 cm above the anal verge). Patients included in the study had surgically resectable T3 or T4 tumor with stages N1 or N2 and M0. Patients were excluded if they had recurrent cancer, intestinal obstruction, peritoneal deposits, malignant ascites, malnutrition, mucoid carcinoma, or an American Society of Anesthesiologists score >2 . For this study, 227 patients were evaluated; only 182 met the inclusion criteria. Of these, 13 refused to be enrolled in the study, and 12 had involved circumferential resection margins. Of the 157 patients who underwent surgery, we excluded 42 patients; 20 refused to receive postoperative chemotherapy, 13 refused to undergo follow-up procedures such as computed tomography or colonoscopy, and 9 were lost to follow-up because they left the country (Fig. 1). The study was performed on the remaining 115 patients in accordance with the guidelines of Alexandria University's ethics committee, which approved the study protocol, and informed consent was obtained from each patient before performing neoadjuvant CRT.

Preoperative evaluation of the patients was done by clinical examination, colonoscopy, abdominal computed tomography, and pelvic magnetic resonance imaging. Carcinoembryonic antigen and carbohydrate antigen 19.9 were measured before any therapy. The location of the tumor was defined as the distance between the distal margin of the tumor and the anal verge, measured by digital examination and rigid proctoscopy. All patients received neoadjuvant CRT (45 to 50.4 Gy and chemotherapy using 5-fluorouracil and leucovorin).

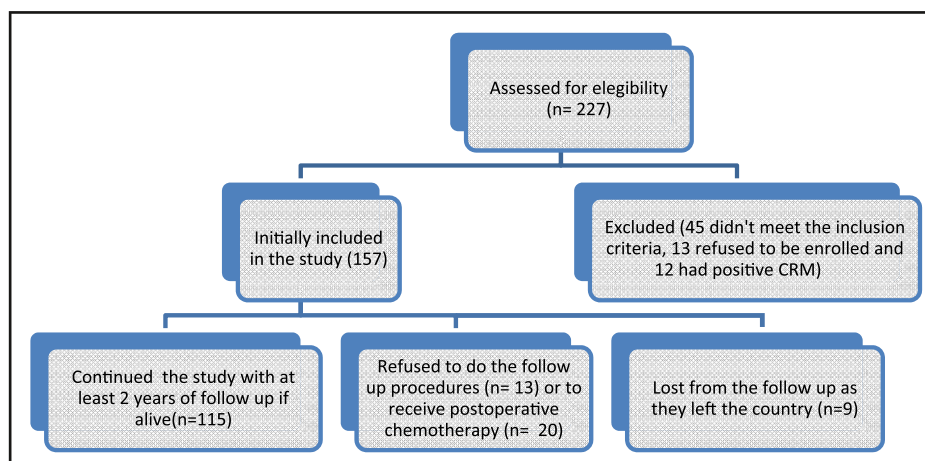


Figure 1 Consolidated Standards of Reporting Trials flowchart.

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