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Long-term prognostic value of mesorectal grading after neoadjuvant chemoradiotherapy for rectal cancer

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Mesorectal grade;
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Abstract

BACKGROUND: Mesorectal grading was reported to be a valuable prognostic factor in rectal cancer surgery. Previous studies were retrospective, and had short follow-up.

OBJECTIVE: To assess the long-term influence of total mesorectal excision quality on disease recurrence in mid and low rectal cancer patients who received preoperative neoadjuvant chemoradiotherapy (CRT) and postoperative chemotherapy.

METHODS: One hundred twenty-one patients with rectal cancer had either low anterior resection or abdominoperineal resection. All patients received neoadjuvant CRT and postoperative chemotherapy. Main outcome measures included TNM staging, involvement of the circumferential resection margin (ICRM), mesorectal grading, local and systemic recurrences were recorded.

RESULTS: Follow-up was done for at least 5 years or up to disease recurrence whatever comes first. Mean follow-up time was 59.4 months. Twenty-nine patients had abdominoperineal resection and 92 had low anterior resection. About 7.5% had positive CRM which was significantly correlated with mesorectal grading. Grade 3 mesorectal specimens were obtained in approximately 60% of patients, 27% had grade 2, and only 13% had grade 1 (poor) mesorectal specimens. Poorer mesorectal grading increased with APR and lower rectal tumors. Recurrences occurred in 20% of patients (40% in the first 2 years, 32% in the 3rd year, and 28% in the 4th and 5th years); factors affecting recurrence included lymphovascular invasion, ICRM, and N stage. Mesorectal grading was not a valuable prognostic factor for recurrence unless it resulted in ICRM. Recurrences occurred earlier with poorer mesorectal grade, yet this was not statistically significant.

CONCLUSIONS: Mesorectal grading is a pathologic description that reflects the quality of surgery. However, in patients who received neoadjuvant CRT and postoperative chemotherapy, grading had no long-term prognostic value regarding recurrences unless it resulted in ICRM.

Tumors in the middle and lower thirds of rectum have always been a challenge in their management in terms of a higher local recurrence rate compared to upper rectal cancers.[1] Radical resection with total mesorectal excision (TME) has become the gold standard of treatment of these tumors. TME was introduced to avoid the unacceptably high local recurrence rates (30% to 40%) associated with the conventional techniques.[2] Differences in outcomes after TME have

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been observed in different trials.[3–5] Local recurrence is attributed to both surgery-related (technical) and tumor-related (biologic) factors. The stage of the tumor at presentation, pathologic type are the most important tumor-related factors influencing recurrence, while technical factors are directly related to the quality of surgery.[6] Currently, there are two important parameters that can assess the surgical quality: First one is the involvement of the circumferential resection margin (ICRM) which prognostic importance was proved in many publications.[7–10] The second is the adequacy of excision of the mesorectal envelope consisting of all the lymphatics, lymph node, and neural tissue around the rectum; the concept that was proposed by Nagtegaal et al[11] as mesorectal grading. Analyses investigating the relationship between oncological outcomes, mesorectal grading and/or CRM status have, however, yielded different results.[12]

The use of neoadjuvant chemoradiotherapy (CRT) is now a part of the standard treatment of locally advanced middle and low rectal tumors. It has been proved that it is more effective than postoperative chemotherapy in preventing tumor recurrence.[13] Previous studies regarding prognostic value of mesorectal grading were done either on patients operated upon before the era of neoadjuvant CRT, used preoperative short course radiotherapy, or had mixed population of different types of adjuvant treatment.[11,12,14] Moreover, all of them were retrospective with short follow-up.

Up till now, there is no publication that assesses the prognostic value of mesorectal grading in patients who had neoadjuvant CRT and postoperative chemotherapy.

The aim of this study was to answer these key questions: Is the prospective mesorectal grading an independent prognostic factor for local or systemic recurrence? Does preoperative neoadjuvant CRT with postoperative chemotherapy compensate a poor mesorectal quality?

Specific Aims

The aim of this study was to assess the long-term influence of quality of TME on disease recurrence in middle and lower third rectal cancer patients who received preoperative neoadjuvant CRT and postoperative chemotherapy.

Patients and Methods

This study prospectively included 121 adult patients with rectal adenocarcinoma (within 12 cm above the anal verge) in the period from January 2005 to May 2008. All patients included had T3 or T4 tumors and received preoperative long-course neoadjuvant CRT.

Patients were excluded if they had recurrent cancer, mucoid carcinoma, distant, or peritoneal metastasis. The study was performed after approval of the Alexandria University Ethical Committee and informed consent was obtained from each patient before undergoing preoperative CRT.

Preoperative evaluation was done by clinical examination, colonoscopy, abdominal computed tomography (CT), and pelvic MRI. Patients were not included if the potential circumferential resection margin was involved in pelvic MRI. Distance of a tumor from anal verge was measured by rigid proctoscopy. CEA and CA19.9 were measured before any therapy for follow-up. All patients received neoadjuvant CRT (45 to 50.4 Gy pelvic irradiation and chemotherapy using 5-FU and leucovorin).

Treatment

Radical surgery with TME was performed 8 to 10 weeks following the completion of the neoadjuvant therapy with curative intent. Patients were operated upon with either low anterior resection (LAR) and proximal diversion or abdominoperineal resection (APR) based upon the distance from the anal verge. All surgeries were performed by 2 experienced surgeons with a volume more than 50 per year for each of them. All patients in this study were done by open surgery.

Gross examinations by the surgeon and an experienced pathologist were performed before formalin fixation and quality of mesorectum was graded according to Quirke's mesorectal grading[11] as follows:

Grade 3 (good). Intact mesorectum with smooth mesorectal surface. No defect deeper than 5 mm. No coning on the specimen. Smooth circumferential resection margins on slicing.

Grade 2 (moderate). Moderate bulk of the mesorectum but there is irregularity in the mesorectal surface. Moderate coning of the specimen toward the distal margin. At no site is the muscularis propria visible with exception of the insertion of the levator muscles. Moderate irregularity of the circumferential resection margin.

Grade 1 (poor). Little bulk of the mesorectum with defects down into the muscularis propria and/or very irregular circumferential resection margin.

All specimens were photographed and the 3 authors reviewed all the photographs while blinded to the operating surgeon for reconfirmation of the mesorectal grade. Staging was done based on the 7th edition of the classification of the American Joint Committee on Cancer.[15]

Adjuvant therapy

Postoperative adjuvant chemotherapy consisted of a bolus of 5-FU (450 mg/m^2) and leucovorin (20 mg/m^2) administered daily for 5 days every 28 days for 6 cycles.

Follow-up

Follow-up was done by abdominal CT, CEA, and CA19.9 every 6 months. Colonoscopy was performed annually. Data collected included demographics, tumor pathology, TNM staging, number of LN retrieved, and recurrences. Recurrence was determined by clinical and radiological examinations followed by histological