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Endoscopic assessment of tumor regression after preoperative chemoradiotherapy as a prognostic marker in locally advanced rectal cancer

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ABSTRACT

Purpose: This study was designed to evaluate tumor regression endoscopic criteria for predicting the post-chemoradiotherapy (CRT) prognosis of patients with locally advanced rectal cancer.
Material and methods: A total of 425 patients with rectal cancer who received radical surgery after CRT were included in this study. All patients were divided into two groups according to post-CRT preoperative endoscopic findings: 1) good response (E-GR): scar, telangiectasia, or erythema; 2) minimal or no response (E-MR): nodules, ulcers, strictures, or remnant tumor. Cox proportional hazard models were used to analyze the effect of preoperative clinicopathological variables on disease-free survival (DFS) and overall survival (OS).
Results: The independent prognostic factors for DFS were tumor location less than 5 cm from anal verge (hazard ratio [HR] 1.92, 95% confidence interval [CI] 1.27 to 2.88), pre-CRT carcinoembryonic antigen (CEA) > 5 ng/mL (HR 2.10, 95% CI 1.41 to 3.14), histologic high grade (HR 2.96, 95% CI 1.51 to 5.81), and E-GR (HR 0.26, 95% CI 0.08 to 0.83). The independent prognostic factors for OS were age over 65 years, tumor location, pre-CRT CEA, histologic grade, and E-GR (HR 0.13, 95% CI 0.02 to 0.99).
Conclusions: Post-CRT endoscopic findings were predictors of prognosis in patients with rectal cancer. If endoscopic findings are simultaneously used with certain preoperative prognostic factors, rectal cancer patients will potentially have more treatment options.

1. Introduction

Preoperative chemoradiotherapy (CRT) is widely used as a standard treatment for locally advanced rectal cancer. Accurate classification of ypT, ypN, and tumor regression grade (TRG) after preoperative CRT predicts a patient's prognosis [1–3]. Recently, magnetic resonance imaging (MRI) has been reported to be an effective tool for assessing TRG and volume reduction rate after preoperative CRT [4–8]. However, a standardized MRI protocol for post-CRT assessment has yet to be developed and remains controversial in predicting pathological response [9,10].

In addition, a set of clinical trials evaluating the quality-of-life after radical surgery of rectal cancer has applied post-CRT local resection or deferring surgery [11–15]. Such organ-preserving strategies have been considered because there is no difference between radical surgery and organ preservation in the overall survival of patients with a good prognosis [16–18]. Therefore, information that can be used to predict a patient's post-CRT prognosis would be helpful in the selection of various treatment options.

Using post-CRT endoscopic data from previous studies, our group has developed diagnostic criteria to predict pathologic tumor response [19]. However, its use as a surrogate marker is still controversial because the pathologic tumor response, including complete remission after CRT (ypCR), does not accurately reflect the patient's prognosis [9]. In this study, we evaluated the endoscopic criteria to determine if it can be used to predict the post-CRT prognosis of patients with locally advanced rectal cancer.

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2. Materials and methods

2.1. Patient enrollment

The records of 425 patients with rectal cancer who underwent preoperative CRT followed by radical surgery, from 2004 to 2013 at the National Cancer Center, were included in this study. Cases without endoscopy, surgical, or follow-up results were excluded. Patients with preoperative treatment by oxaliplatin or irinotecan were also excluded. All tumors were located in the mid- or distal rectum with no distant metastasis and clinically diagnosed as T3, T4 or with lymph node positivity. This study was approved by the Institutional Review Board of the National Cancer Center (NCC2017-0039).

2.2. Treatments

According to our institution's standard treatment protocol, all patients received 45 Gy pelvic radiation therapy in 25 fractions followed by a 5.4 Gy boost in three fractions. On the first day of pelvic radiotherapy, preoperative chemotherapy began. The standard chemotherapy protocol consisted of 5-fluouracil(FU)-based regimens including 5-FU/leucovorin or capecitabine or tegafur/uracil. Surgical resection was performed six to eight weeks after the last administration of CRT. All enrolled patients underwent radical surgery with total mesorectal excision, including anterior resection, abdominoperineal resection, or lymph node dissection. Lateral pelvic lymph node dissection was also performed when persistent pelvic node observed after CRT.

2.3. Endoscopic assessment

All patients underwent two endoscopic examinations: before CRT and immediately before radical operation. Based on our previous study [19], the results were classified into two groups: endoscopic findings for good response (E-GR) and endoscopic findings for minimal or no response (E-MR). E-GR was recorded as follows: (1) scarring (the flat and white mucosa with fibrotic changes); (2) telangiectasia (scarring surrounded by small blood vessels); and (3) erythema (scarring or erosion with peripheral erythematous mucosal changes). E-MR was recorded as follows: (1) nodules (no definite tumor, but small, residual mucosal lump); (2) ulcers (any residual ulceration with a necrotic or regenerative bed); (3) strictures (luminal narrowing with over 50% reduction in luminal diameter); and (4) remnant tumor (definite residual tumor with or without ulceration) (Fig. 1).

2.4. Pathologic assessment

Each specimen was fixed in 10% formalin and cut to a thickness of 4 mm continuously to prepare a slide. Histologic grade was classified into two groups: low grade (well or moderately differentiated) and high grade (poorly differentiated, mucinous or signet ring cell carcinoma). Specimen response to preoperative CRT was evaluated according to the TRG system proposed by Dworak et al. [20]. Tumor degeneration was graded as follows: Grade 0, no regression; Grade 1, dominant tumor mass with obvious fibrosis and/or vasculopathy (minimal regression); Grade 2, dominant fibrotic changes with some obvious tumor cells or groups of cells

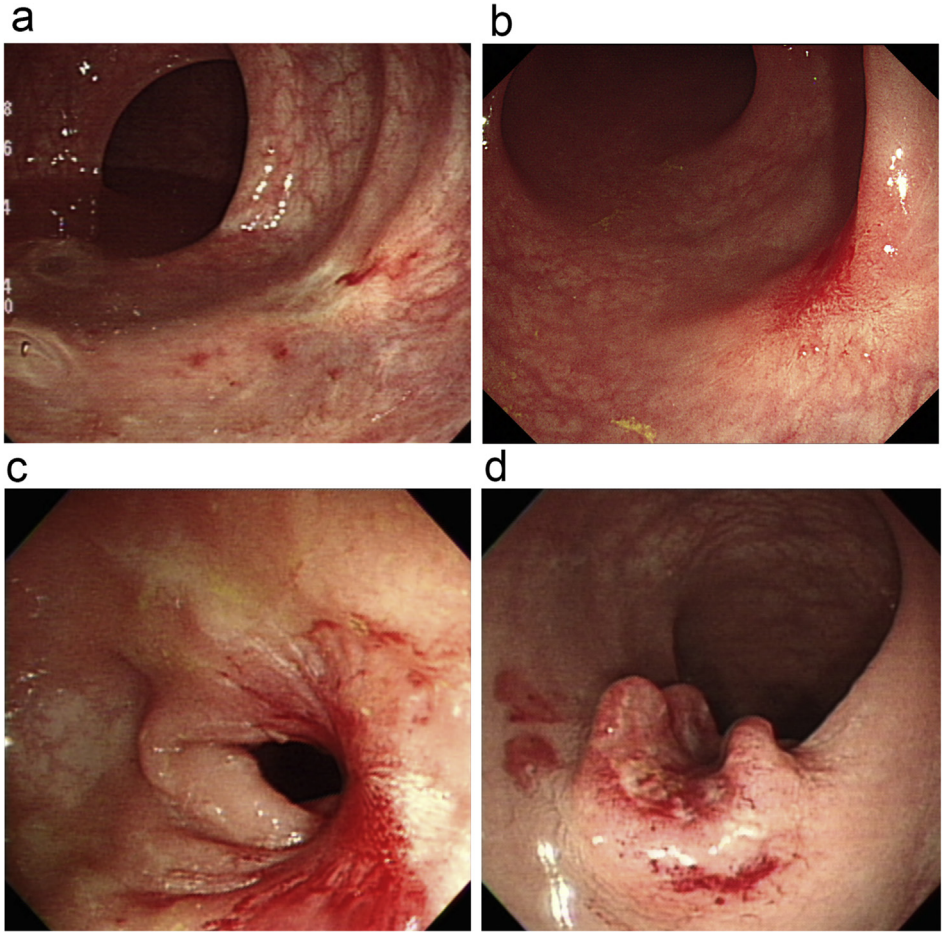

Fig. 1. Endoscopic findings after chemoradiation. A) scarring, B) erythema, C) stricture, D) remnant tumors.