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# Clinical implication of negative conversion of predicted circumferential resection margin status after preoperative chemoradiotherapy for locally advanced rectal cancer

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ABSTRACT

*Objective:* To evaluate the prognostic implication of the negative conversion of predicted circumferential resection margin status before surgery in patients with locally advanced rectal cancer with predicted circumferential resection margin involvement.
*Methods:* Thirty-eight patients (28 men, 10 women; median age, 61 years; age range, 39–80 years) with locally advanced rectal cancer with predicted circumferential resection margin involvement who underwent preoperative chemoradiotherapy followed by radical surgery were analyzed. Involvement of the circumferential resection margin was predicted on the basis of pre- and post-chemoradiotherapy magnetic resonance imaging. The primary endpoints were 3-year local recurrence-free survival and overall survival.
*Results:* The median follow-up time was 41.1 months (range, 13.9–85.2 months). The negative conversion rate of predicted circumferential resection margin status after preoperative chemoradiotherapy was 65.8%. Patients who experienced negative conversion of predicted circumferential resection margin status had a significantly higher 3-year local recurrence-free survival rate (100.0% vs. 76.9%; $P = 0.013$), disease-free survival rate (91.7% vs. 59.3%; $P = 0.023$), and overall survival rate (96.0% vs. 73.8%; $P = 0.016$) than those who had persistent circumferential resection margin involvement.
*Conclusions:* The negative conversion of the predicted circumferential resection margin status as predicted by magnetic resonance imaging will assist in individual risk stratification as a predictive factor for treatment response and survival before surgery. These findings may help physicians determine whether to administer more intense adjuvant chemotherapy or change the surgical plan for patients displaying resistance to preoperative chemoradiotherapy.



## 1. Introduction

Pathological circumferential resection margin (CRM) involvement in rectal cancer is a well-established prognostic factor for local recurrence and overall survival (OS) [1–6]. However, with recent advances in magnetic resonance imaging (MRI) technology, several studies showed that MRI could accurately provide measurements of the distance from the tumor to the mesorectal fascia and have highlighted the importance of assessing clinical CRM status before preoperative chemoradiotherapy (CRT) [7,8]. In general, positive CRM was defined as a <1 mm distance from the tumor to the mesorectal fascia on MRI. According to published data, it has been suggested that MRI-based prediction of CRM status before initiation of preoperative CRT has the correlation with local recurrence and long-term survival [8,9].

Preoperative CRT may allow changing in CRM status by regression of the primary tumor and lymph node metastases. Recently, a subgroup analysis of patients enrolled in the Magnetic Resonance Imaging in Rectal Cancer European Equivalence Study (MERCURY) trial demonstrated that post-treatment MRI prediction of CRM involvement before surgery was important prognostic information regarding the risk of local recurrence [10]. The various changes in CRM status after preoperative CRT may reflect an aspect of biologic heterogeneity of tumor with different radiosensitivity or chemosensitivity that can yield important prognostic information. Therefore, assessment of sensitivity to preoperative CRT is

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essential for tailoring subsequent treatment plans to increase the chance of a cure [11].

We hypothesized that negative conversion of predicted CRM status after preoperative CRT may reflect sensitivity to CRT and would be associated with better prognosis. To our knowledge, the relevance of negative conversion of CRM status in predicting survival outcomes has not been investigated. Thus, the aim of this study to evaluate the prognostic implication of negative conversion of predicted CRM status before surgery in patients with locally advanced rectal cancer with predicted CRM involvement.

## 2. Materials and methods

### 2.1. Patients

A database of patients enrolled from January 2000 to December 2010 was reviewed to select for patients with locally advanced rectal cancer who received preoperative CRT followed by radical surgery. All patients were required to meet the following inclusion criteria: (1) histologically confirmed adenocarcinoma, (2) cT4 or cT3 disease with CRM involvement as assessed by pretreatment MRI, (3) no evidence of distant metastasis, and (4) no prior history of other malignancies except for adequately resected double primary colon cancer or any other cancer with disease-free status for 5 years. A total of 38 patients were selected (28 men and 10 women; median age, 61 years; range, 39–80 years). The tumor was located in the upper third of the rectum in 1 patient (2.6%), the middle third in 23 patients (60.5%), and the lower third in 14 patients (36.8%). This study was performed in accordance with the guidelines of the institutional review board of the Korea University Medical Center, which deemed that informed consent was not required because the study was retrospective in nature.

### 2.2. Treatments

Radiation therapy was administered to the whole pelvis at a total dose of 50.4 Gy in 28 fractions with concurrent fluoropyrimidine-based chemotherapy. Conventional or three-dimensional treatment planning using three- or four-field techniques was used. Chemotherapy with 5-fluorouracil ($n = 31$, 82%), tegafur-uracil ($n = 4$, 11%), or capecitabine ($n = 3$, 8%) was administered concurrently with radiation therapy. The median duration of CRT was 39 days (range, 37–54 days). After completion of preoperative CRT, low anterior resection ($n = 31$, 81.6%) or abdominoperineal resection ($n = 7$, 18.4%) was performed. The median time interval from CRT to surgery was 43 days (range, 29–108 days). Thirty-two patients (84%) received adjuvant chemotherapy comprising a fluoropyrimidine-based regimen ($n = 15$, 39%) or an oxaliplatin-based regimen ($n = 17$, 45%). The chemotherapeutic regimens, both preoperative and postoperative, were selected for each patient according to the discretion of the attending medical oncologist.

### 2.3. Evaluation

Clinical staging of rectal cancers is mainly accomplished through a standard pretreatment workup that includes taking of medical history, physical examination, complete blood count evaluation, biochemical profiles, determination of the serum carcinoembryonic antigen level, and endoscopy. In addition, imaging studies such as computed tomography (CT), MRI, transrectal ultrasonography, or $^{18}$F-fluorodeoxyglucose positron emission tomography are also performed.

MRI was performed approximately 1 week before surgery, and radiographic response was evaluated to predict CRM involvement. All MR images were reviewed by two radiologists with decisions reached by consensus. CRM involvement was defined as a distance of <1 mm from the circumference margin [1,10]. Clinically positive lymph node involvement was defined as a lymph node >5 mm in the short-axis diameter observed by CT or MRI. All tumors were

**Table 1**
Patient and tumor characteristics.

| Characteristic | Number of patients (%) |
|---|---|
| Age (years) | |
| Median (range) | 61 (39–80) |
| Gender | |
| Male | 28 (73.7) |
| Female | 10 (26.3) |
| ECOG performance status | |
| 1 | 36 (94.7) |
| 2 | 2 (5.3) |
| Distance from anal verge (cm) | |
| Median (range) | 5.0 (0.0–10.0) |
| Clinical stage | |
| IIIB | 22 (57.9) |
| IIIC | 16 (42.1) |
| cT classification | |
| 3 | 25 (65.8) |
| 4 | 13 (34.2) |
| cN classification | |
| 1a | 4 (10.5) |
| 1b | 9 (23.7) |
| 2a | 17 (44.7) |
| 2b | 8 (21.1) |
| Differentiation | |
| Well | 18 (47.4) |
| Moderate | 19 (50.0) |
| Unknown | 1 (2.6) |
| Tumor length (cm) | |
| Median (range) | 6.0 (3.0–10.0) |
| Serum CEA (ng/ml), initial | |
| Median (range) | 2.2 (0.5–44.9) |
| Serum CEA (ng/ml), post-CRT | |
| Median (range) | 1.2 (0.3–15.0) |

*Abbreviations*: ECOG: Eastern Cooperative Oncology Group; CEA: carcinoembryonic antigen; CRT: chemoradiotherapy; "c" prefix: clinical assessment data.
Values are numbers (percentage) unless otherwise noted.

**Table 2**
Pathological tumor characteristics.

| Characteristic | Number of patients (%) |
|---|---|
| Pathologic stage | |
| 0 | 2 (5.3) |
| I | 6 (15.8) |
| IIA | 11 (28.9) |
| IIB | 8 (21.1) |
| IIC | 3 (7.9) |
| IIIA | 2 (5.3) |
| IIIB | 6 (15.8) |
| ypT classification | |
| 0 | 3 (7.9) |
| 1 | 1 (2.6) |
| 2 | 6 (15.8) |
| 3 | 24 (63.2) |
| 4 | 4 (10.5) |
| ypN classification | |
| 0 | 29 (76.3) |
| 1a | 3 (7.9) |
| 1b | 4 (10.5) |
| 2a | 2 (5.3) |
| Downstaging | |
| Yes | 30 (78.9) |
| No | 8 (21.1) |
| Pathologic CRM | |
| Positive | 3 (7.9) |
| Negative | 35 (92) |

*Abbreviations*: CRM: circumferential resection margin; "yp" prefix: pathological data following preoperative chemoradiotherapy.
Values are numbers (percentage) unless otherwise noted.