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Clinical predictive factors associated with pathologic complete response in locally advanced rectal cancer

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ABSTRACT

Objective: In this study, our aim was to identify the main predictive factors associated with pathologic complete response (pCR) to neoadjuvantchemoradiotherapy (nCRT) in patients with locally advanced rectal cancer.
Methods: The patients who had locally advanced rectal cancer and underwent a long-course nCRT, followed by curative surgery between January 2009 and December 2015 at two-center were included. The clinical factors associated with pCR or non-pCR were analyzed by Logistic regression.
Results: Two hundred and three patients were included in this study. Forty-six patients (22.7%) had pCR and 157 patients (77.3%) had non-pCR. In the univariate analysis, no smoking history, clinically negative lymp node (cN-), well-differentiated tumor, tumor size of ≤5 cm, pre-nCRT CEA level of ≤5 (ng/mL) and median interval to surgery>8 week were associated with an increased rate of pCR. No smoking history [odds ratio (OR) = 3.382, P = .008], endoscopic tumor size of ≤5 [OR = 2.608, P = .03], cN- [OR = 3.800, P = *.002*], well-differentiated tumor [OR = 3.566, P = *.002*], median interval to surgery of >8 week [OR = 2.981, P = .014], and pre-nCRT CEA level of ≤5 (ng/mL) [OR = 3.067, P = .008] were determined to be independent predictive factors of pCR with logistic regression model analysis.
Conclusion: No smoking history, cN-, tumor size of ≤5 cm, well-differentiated tumor, pre-nCRT CEA level of ≤5 (ng/mL) and median interval to surgery of >8 weeks were independent clinical predictors for pCR in rectal cancer patients treated with long course of nCRT. This factors may help clinicians predict the prognosis of patients and develop proper treatment approach.

1. Introduction

Today, neoadjuvant chemoradiotherapy (nCRT) has become the standard option in the therapy of patients with locally advanced rectal cancer. nCRT also has higher rates of sphincter sparing surgery with lower local recurrence incidents.[1–4] The results regarding surgery and prognosis varies depend on the response to nCRT. Meta-analyses reported better prolonged clinical outcomes in patients with pathological complete response (pCR) after nCRT, in comparison with the patients without pathologic complete response (non-pCR).[5]

In patients with rectal cancer, it is known that up to 15–20% of pCR is obtained after neoadjuvant chemoradiotherapy, however some patients only respond partially or some develop resistance to chemoradiotherapy.[6] Therefore in some cases, chemoradiotherapy is performed for the patients who will not benefit as desired. It would be provide a great advantage if there were some methods to predict the response of patients before chemoradiation protocol. For this reason, pCR that associated with better outcomes has been drawn a great interest. In previous studies, factors such as tumor size, carcinoembryogenic antigen (CEA) levels have been reported to be of predictive value to pCR follow in nCRT.[7–9] However, there is still a lack of consensus on the predictive factors of pCR.

We aimed to determine the clinical factors and treatment

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parameters predictive of pCR after nCRT in the patients with locally advanced rectal cancer.

2. Material and methods

Two hundred and seventy-nine patients with locally advanced rectal cancer who had nCRT between January 2009 and December 2015 in two-center were evaluated retrospectively. Patients were recruited in the study according to the following criteria: 1- Pathologically proven rectal adenocarcinoma, 2- Localized tumor within the first 15 cm from anal verge, 3- Clinical stage both II or III, 4- Patients without distant metastasis, 5-Curative surgery following nCRT. Patients who did not have surgery following neo-adjuvant treatment or patients who were lost to follow up were excluded (n = 76). Besides, patients with a second primary malignancy, patients with hereditary colon cancer or patients who had endoscopic surgery were excluded from the study.

All patients were histopathologically diagnosed with adenocarcinoma. Pelvic magnetic resonance imaging, abdominopelvic computerized tomography, transrectal ultrasonography, or various combinations of these options were used for the clinical staging before nCRT. Surgery specimen and lymph nodes without viable tumor cells were defined as pCR and those with viable cells were defined as non-pCR, respectively.

Radiotherapy was performed to primary tumor site and perirectal metastatic lymph nodes in 42–54 Gy dose range, as 1.8–2 Gy fractions, five days a week for 30–35 days. Patients had one out of two different chemotherapy regimens simultaneously with radiotherapy: 225 mg/m^2/day of 5-Fluorouracyl (5 days a week) was introduced through central venous catheter with a pomp; 825 mg/m^2 oral capecitabine (2 times a day) was performed the whole week during the radiotherapy period. All patients had total mesorectal excision as the surgical procedure. Adjuvant FOLFOX chemotherapy (folinic acid, 5-flurouracyl, oxaliplatin) regimen was introduced in 3–6th weeks following the surgery.

Sex, age, body mass index (BMI), ECOG (Eastern Cooperative Oncology Group) performance score at the time of diagnosis, smoking history, clinical TNM staging, tumor differentiation, the distance between the tumor and the anal verge, endoscopic appearance of the tumor, endoscopic size of the tumor, chemotherapy regimen given with radiotherapy, radiotherapy dosage, interval between the radiotherapy and the surgery, carbohydrate antigen 19-9 (CA 19-9) and CEA levels before the therapy were reported. Moreover, hemoglobin level, trombocyte count, neutrophile/lymphocyte ratio (NLR), thrombocyte/lymphocyte ratio (PLR), lactate dehydrogenase and albumin levels before the nCRT were evaluated. For the NLR and PLR cut-off values were <3 and < 160 as the previous studies suggested, respectively.[10,11]

Rectum was defined as the 0 to 15th cm segment from the anal verge; inferior rectum as the 0–4.99 cm from the anal inlet, midrectum as 5 cm–9.99 cm portion, superior rectum as 10th to 15th cm portion.

2.1. Statistical analysis

Statistical analyses were performed using *'Statistical Package for The Social Sciences'* version 18.0 for Windows (SPSS, Inc, Chicago, IL, USA). The variables were investigated according to the visual (histograms, probability plots) and analytical methods (Kolmogorov Simirnov/Shapiro-Wilk's test) to determine whether they are normally distributed or not. Data was presented as median and range, and categorical variables were presented as the frequency with percentages. Continuous variables were analyzed with the Mann-Whitney U tests. Categorical variables were analyzed using the Chi-square or Fisher exact test, when appropriate. Univariate and multivariate analyses (logistic regression and Cox proportional hazard ratio) were performed to identify factors that predict pCR.

3. Results

3.1. Clinicopathologic characteristics

Two hundred and three patients were evaluated in this study. The demographical features and tumor characteristics are shown in Table 1. The median age was 58 (range = 21–85) year and 135 of them were male (%66.5), 68 were female (33.5%). There were one or more comorbid diseases in 56% of the patients, and hypertension and diabetes mellitus were most frequent comorbidities. 49% patients had clinical stage 3 and 51% had clinical stage 2 disease. Moderately differentiated adenocarcinoma was the most common histopathological subtype (54%). The median distance from anal verge to the tumor was 6 cm (range = 1–15). The median endoscopic diameter of the tumor was 5 cm (range = 1–12) and most of them (66%) had ulcerovegetan appearance. The median radiation dose was 50 Gy (range = 42–54 Gy). Concomitant to radiotherapy, 20 patients (10%) were treated with oral capecitabine alone, and 183 (90%) patients were treated with 5-fluorouracil alone, respectively. Median interval between the chemoradiotherapy and surgery was 58 days (range = 19–120 days).

3.2. Pathologic and non-pathologic complete response

Pathological complete response achieved in 46 out of 203 patients (22.7%) whereas 157 patients (77.3%) did not achieved. Clinical and pathological variables were compared between non-pCR and the pCR group. Sex, age, BMI, ECOG performance score, the distance between the tumor and the anal verge, comorbidities, endoscopic appearance of the tumor, radiotherapy dose and the applied surgical procedure were similar between the pCR and non-PCR groups. Former or current smoker patients were higher in number in non-PCR group (p = .009). Well-differentiated adenocarcinoma was the most common histopathological subtype (50%) in pCR group, whereas in non-pCR group moderately differentiated adenocarcinoma was the most common subtype (62%). Clinical stage 2 and negative lymph nodes were more common in pCR group in comparison with non-pCR (p < .001). Median pretreatment CA 19-9 and CEA levels were reported to be lower in pCR patients and median CA 19-9 and CEA levels were within normal ranges in both groups (p = .003, p = .03, respectively). Median tumor size was larger in the non-pCR group (5 vs 5.2 cm). The median interval between completion of the nCRT and the surgery was longer in the pCR group (62.5 vs 54 days).

3.3. Univariate and multivariate logistic regression analysis

Patients were analyzed separately for categorical parameters for both univariate and multivariate logistic regression analysis. The distance between the tumor and the anal verge were categorized into 3 groups: superior (10–15 cm), middle (5–9.99 cm) and inferior (<5 cm). Since the median time interval between completion of nCRT and surgery was 58 days, 8 weeks was used as the median interval to surgery parameter for the analysis.

Broad univariate analysis was performed using approximately 22 parameters (Table 2). In the univariate analysis, No smoking history, clinically negative lymp node (cN-), well-differentiated tumor, tumor size of ≤5 cm, pre-nCRT CEA level of ≤5 (ng/mL) and median interval to surgery>8 week were associated with an increased rate of pCR.

Multivariate logistic regression analysis revealed that no smoking history (p = .008), cN- (p = .002), endoscopic tumor size of

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