Histopathological Changes of Neoadjuvant Chemoradiation and Relation with the Pre-Treatment Tumor Stage in Rectal Carcinoma

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ABSTRACT

Objective: Neoadjuvant chemoradiotherapy has considered one of the standard treatment modalities for locally advanced rectal cancers. Chemoradiotherapy has a variety of different effects and responses on tumor, tumor bed and peritumoral tissues. The purpose of the present study was to evaluate the stromal responses in tumor bed between the different treatment modalities and different clinical T stages.

Methods: Fifty-seven consecutive patients with median age of 62.4 years were treated for rectal adenocarcinoma between January 2005 and July 2012 in Uludağ University Medical Faculty. Twenty-three of the patients were treated with neoadjuvant chemoradiation therapy and following surgery, 34 patients treated with surgery only.

Results: When we compared the stromal responses in the tumor bed between the two different treatment modalities, the amount of fibrosis and intensity of inflammatory cell infiltration were found considerably marked. The existence of calcification, hemosiderin-laden macrophages and mucin lakes were found also significant marked. There was no difference found in between the patients with different clinical stages which were received neoadjuvant CRT.

Conclusion: The stromal response in the tumor bed increases with the neoadjuvant chemoradiotherapy but the excess of the response doesn’t have any relation with the clinical T stage.

Key Words: Rectum, adenocarcinoma, neoadjuvant chemoradiotherapy, stromal response, tumor bed, T stage

ÖZET


Sonuç: Tümör yatağındaki stromal cevap neoadjuvant kemoradyoterapi ile artış göstermektedir ancak bu artışın yanıtın tümör evresi ile ilişkili saptanamamıştır.

Anahtar Sözcükler: Rektum, adenokarsinom, neoadjuvant kemoradyoterapi, stromal yanıt, T evresi, tümör yatağı

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INTRODUCTION

Rectal cancer is the third most frequent malignancy in males and second in females, accounting for about 1.2 million new cases per year worldwide (1). Neoadjuvant treatment has become the standard of care for locally advanced gastrointestinal tumors (2). The modern treatment of rectal cancer needs a multidisciplinary approach and a cooperative effort between the medical departments (3). Based on the randomized clinical trials, neoadjuvant chemoradiotherapy (CRT) followed by surgery is established as the standard treatment in locally advanced rectal tumor including clinically T3/T4 and/or clinically node positive stage cancers (4). It has been demonstrated in several studies, however, that clinical outcome depends not only on the initial stage of the tumor, but also on the CRT-induced tumor response which varies among individual patients (1). The purpose of the neoadjuvant CRT are both downsizing and downstaging the tumor. Downsizing the tumor facilitates the surgical resection, enables sphincter-preserving procedure and improve local control (5).

A growing body of evidence indicates that pathological response to neoadjuvant treatment can be measured with the histopathological tumor regression grade (TRG) (6). Rectal cancers that respond to neoadjuvant treatment undergo significant changes, which may result in complete disappearance of carcinoma cells and replacement of the tumor by fibrous or fibroinflammatory tissue (7).

Neoadjuvant chemoradiation therapy in rectal cancer is associated with significant tumor response and downstaging. Several systems for tumor response have been advocated (8,9), and a modified Ryan scheme is suggested, which has been shown to provide good inter-observer reproducibility provide prognostic significance (10).

According to the CAP protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum, the tumor regression score (TRS) was established as follows: Score 0: No viable cancer cells (complete response), Score 1: Single cells or rare small groups of cancer cells (near complete response), Score 2: Residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells (partial response), Score 3: Extensive residual cancer with no evident tumor regression (poor or no response) (11).

The aim of this study is to find out the stromal responses in the tumor bed between the different treatment modalities and between the different clinical T stages.

MATERIALS and METHODS

Patients

A total of 57 consecutive patients were treated for rectal adenocarcinoma between January 2005 and July 2012 at Uludağ University. The patients were selected retrospectively from the pathology archive. The mean age of 57 patients was 62.4±12.2 (range, 28-81 years). Pre-treatment workup consisted of digital rectal examination, rectosigmoidoscopy, biopsy, abdominopelvic computed tomography and chest X-ray. All the 57 patients were categorized according to the pre-treatment clinical T stage.

Twenty-three of the patients were treated with pre-operative CRT and surgery, while the remaining 34 patients treated with surgery only. In all patients which treated with neoadjuvant CRT, 3D planned conformal radiotherapy was carried out with belly board. Primary tumor as well as lymph nodes at risk was covered and received 45 Gy in 25 fractions over a period of 5 weeks. As a concomitant chemotherapy 500 mg/m² 5-flourourasil continuous infusion was administered. Surgical resection was performed 6-9 weeks after the completion of the CRT. The main demographic data of all patients is given in Table 1. The remaining 34 patients treated with surgery only had chosen as a control group.

Histopathological evaluation

Pathological response to neoadjuvant CRT in the tumor bed was determined by histopathological evaluation of resected specimens. Evaluation of the TRS, modified Ryan scheme was used. To assess the stromal responses in tumor bed, we evaluated fibrosis and inflammatory cell infiltration around the tumor islands and within the tumor bed. Intensity of fibrosis (Figure 1) and presence of inflammatory cells (Figure 2) were classified as low (Grade 1), intermediate (Grade 2), and high (Grade 3). While evaluating the inflammatory cells, we counted both the lymphocytes and the polymorphonuclear leukocytes. Other variables that we noted while evaluating the changes in the tumor bed were occurrence of calcification, hemosiderin-laden macrophages, and mucin lakes.
Low anterior resection or very low anterior resection were performed to all patients. There were 23 patients treated with neoadjuvant CRT and surgery (Group 1), while other 34 patients treated with surgery only (Group 2). Patients clinically staged before treatment. In Group 1, 4 patients were found cT4, 15 cT3, 4 patients cT2, respectively. In Group 2, 7 patients were found cT4, 21 patients cT3, 6 patients cT2, respectively. Pathological evaluation of the rectum resections, response to neoadjuvant CRT revealed complete response (TRS 0) in 4, near complete response (TRS 1) in 7, partial response (TRS 2) in 8 and, poor or no response (TRS 3) in 4 of 23 patients.

As shown in Table 2, the intensity of fibrosis and inflammatory cell infiltration in the tumor bed were found significantly marked in Group 1 (p<0.01). The occurrence of calcification, hemosiderin-laden macrophages and mucin lakes in the tumor bed were also found significantly distinctive in Group 1 (p<0.01).

We evaluated the same variables between different clinical T stages in Group 1. There were no differences found in stromal responses between different clinical stages (Table 3).
Although the stromal changes were significantly different between Group 1 and Group 2, there was not any difference in stromal responses between the neoadjuvant CRT received cT2, cT3, and cT4 stages.

**CONCLUSION**

Neoadjuvant chemoradiation therapy makes a stromal response in tumor bed by fibrosis, inflammatory cell infiltration, and accumulation of hemosiderin-laden macrophages. These changes occur in every tumor bed constantly and independently from the clinical/pathological T stage according to our study.

**Conflict of interest**

No conflict of interest was declared by the authors.

**REFERENCES**