EVALUATING THE RESPONSE TO THE NEOADJUVANT THERAPY FOR LOCALLY ADVANCED RECTAL CANCERS

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ABSTRACT

Introduction: Colcorectal cancers are the most important causes of the morbidity and mortality in the world. After only the surgical treatment, local recurrence occurs at rates ranging 5-50% and because of the difficulties with there laps therapy, the search of the adjuvant therapy has emerged. We aimed to assess the relationship between pre-neo adjuvant therapy CEA levels and response measures to neoadjuvant therapy and tumor regression degrees established in histopathologic examination.

Materials and Methods: A total of 138 patients whose data were accessed completely were enrolled in study. According to the CRT protocol, with the radiotherapy, intravenous 5-FU 225mg/m2/g of plant (5 days per week) was applied by continuous infusion in all patients. After 6-8 weeks from the neoadjuvant therapy. All patients underwent radical resection with TME technique. If pathology specimen had no tumor cells- pT0N0- ypTY called complete response, N stage regression called partial response (KY), T stage regression called TG. If there was not any regression was called '' no response ''. In statistical analysis SPSS for Windows version 15.0 was used.

Results: Clinical characteristics of the 138 patients, included in the study, evaluated, 49 patients (35.5%) were female and 89 patients (64.5%) were male. Patients' mean age was 58 ± 13 years (range, 21-87).

Conclusion: According to our study, Wheeler Regression Score is not seen as an influential factor to evaluate the response to the neoadjuvant treatment. As a result, patients with preoperative ≤ 5 ng / ml CEA value, are more likely to respond to neoadjuvant therapy.

INTRODUCTION

Colorectal cancers are the most important causes of morbidity and mortality in the world. Surgery is the primary treatment modality. Total mesorectal excision (TME)'s participation in the surgical procedure with the improvement in terms of local disease control although local recurrence rates as high as 10-30% (1, 2).

After only the surgical treatment, local recurrence occurs at rates ranging from 5-50% and because of the difficulties with the relaps therapy, the search for adjuvant therapy has emerged (3, 4, 5, 6). In studies conducted in patients with stage II and III rectal cancer adjuvant chemoradiotherapy (CRT) applications has shown positive effects on local disease control (7, 8, 9, 10). However, the debate about the time of treatment is still ongoing. After neoadjuvant therapy in patients with carcinoma of the rectum up to 30% pathologic complete response (ypty) is seen (11). In a limited response observed in a subset of patients and in others there are resistance to CRT. Before the CRT protocol will be implemented, the prediction of response to therapy, will have great advantages. Serum carcinoembryonic antigen (CEA), especially in colorectal malignancies, because of the reliability and low cost, has found wide use area. A lot of studies is known about the CEA levels measured before treatment in predicting prognosis, postoperative follow-up series of CEA is also decisive for the detection of local recurrence (12).

Pathological findings in patients undergoing CRT protocol are classified according to the avaliable scoring system. Mandart defined by the scoring system consisting of five degrees, locating Wheeler published in 2002 and consists of three degrees of pathologists grading studies are also used in systems that provide standardization (13). In our study we, in patients who received the diagnosis of advanced-stage local cancer and were decided to undergo neoadjuvant chemoradiotherapy, aimed to assess the relationship between pre-neoadjuvant therapy CEA levels and response measures to neoadjuvant therapy and tumor regression degrees established in histopathologic examination and to reveal those factors

which can be used in predictting the response to neoadjuvant therapy.

MATERIALS AND METHODS

Patients who received the diagnose of advanced-phase local cancer and were followed up in Dokuz Eylul University Hospital between 1993 and 2009 and whose data were recorded retrospectively, have been screened in Colorectal Cancer database. A total of 138 patients whose data were accessed completely were enrolled in study. Rectum was considered as 0 and 15 cm from anal verge. Between 0-5 cm is low rectum, between 6-10 cm is middle rectum and between 11-15 cm was classified as upper rectum.

Treatment planning was evaluated in Dokuz Eylul Colon and Rectal Cancer group according to the patients' physical examination, complete blood counts, colonoscopy, the flexible sigmoidoscopy the thoracoabdominal computed tomography (CT) and endorectal" coil" and / or pelvic superficial" phased array" magnetic resonance imaging.

Patients operations materials were evaluated according to the College of American Pathologists (CAP) criterias in DokuzEylul University Department of Pathology. When assessing the degree of tumor regression in patients, three-stage regression classification system (Wheeler scoring system) (13) was used (Table 1).

Table 1 Wheeler Regression Score

Wheeler Regression Score
TRG I : Sterilization or adenocarcinoma focus and increased fibrozis at only a small microscopic area
TRG II : Increased fibrozis and macroscopic disease
TRG III: Little or no fibrozis / significant macroscopic disease

Neoadjuvant Chemoradiotherapy

According to the CRT protocol, with the radiotherapy, intravenous 5-FU 225mg/m2/g of plant (5 days per week) was applied by continuous infusion in All patients. Patients were evaluated by physical examination, Karnofsky performance status, hematological and biochemical parameters in weekly. Preoperative radiotherapy was applied as a dose of 45-50 Gy at 1.8-2.0 Gy in fractions for 20-25 days while using high energy (6-23 MV) X rays.

Surgical Technique

Timing of surgery was after 6-8 weeks from the neoadjuvant therapy. All patients underwent radical resection with TME technique. During the surgery, if we could not walk down to at least 2 cm distal from the tumor to ensure negative surgical

Assessment of Response to Neoadjuvant Therapy

Assessing the response to the neoadjuvant therapy of patients was performed by comparison of clinical and pathological stages. If Pathology specimen had no tumor cells- pT0N0-ypTY, N stage regression called partial response (KY), T stage regression called TG. İf there was not any regression was called '' no response ''. In statistical analysis SPSS for Windows version 15.0 was used

RESULTS

Clinical characteristics of the 138 patients included in the study, are shown at the table 2. Patients' mean age was 58 ± 13 years (range, 21-87).Working within the histological distribution of the tumors, 117 patients (84.8%) were detected adenocarcinoma, 21 patients (15.2%) pathology was found, mucinous, signet ring cell or medullary carcinoma. Sphincter protective surgery applied 83 patients (60.1%) while 55 (39.9%) patients were made to the APR.

Table 2 Clinical findings of the patients

Clinical Findings			
Gender	Female 49 (35.5%)	Male 89 (65.5%)	
Age	≤65 96 (69.6%)	>65 42 (30.4%)	
Tumor Stage	Stage II 24 (17.4%)	Stage III 114 (82.6%)	
CEA Levels	≤5 74 (53.6%)	>5 64 (46.4%)	
Tumor Location	Upper 15 (10.8%)	Middle 31 (22.5%)	Lower 92 (66.7%)
Tumor Regression Grade	TRG I 39 (28.2%)	TRG II 70 (50.7%)	TRG III 29 (21.1%)

Response to Neoadjuvant Therapy

Considering the response to the neoadjuvant therapy, In 8 patients had (5.8%) pathological completrespons, in 106 patients (76.8%) had partial response, in 24 patients (17.4%) there was no response to neoadjuvant therapy. Before the neoadjuvant therapy, 114 patients were stage III, after the neoadjuvant CRT, number of the stage III patients were found 41.

Before neoadjuvant therapy, CEA values of the patients were with an average 11.1 ± 23.6 ng / ml (Rate 0.32-202ng/ml). CEA value's upper limit was taken as 5ng/ml. According to the classification, 74 patients' (53.6%) CEA level were ≤ 5 ng / ml. 64 patients' (46.4%) CEA levels were found > 5 ng / ml.

CEA levels and the regression in T and N stage were examined. The patients with the CEA ≤ 5 ng / ml levels, had significantly higher regression in the T stage (p = 0.004). Similarly, after the neoadjuvant CRT the regression of the tumors in the patients with CEA ≤ 5 levels were higher (p= 0.002) (Table 3)

Table 3 Relationship between the CEA levels and the regression

CEA LEVELS	NO REGRESSION	REGRESSION		NO REGRESSION	REGRESSION
≤5	26 (35.1%)	48 (64.9%)		19 (25.6%)	55 (74.4%)
>5	38 (59.3%).	26 (40.7%)		33 (31.6%)	31 (48.4%)
	64	74		52	86

margins the operation underwent APR. In cases where negative surgical margin provided safely, sphincter-protecting surgery (low anterior resection, very low anterior resection, coloanal anastomosis) was occured. Patients Who had anastomosis were performed protective ileostomy.

When we evaluated the relationship between groups of TRG and CEA, the majority of the 74 patients with CEA ≤ 5 levels had TRG2 (41 patients (55.4%). CEA values of 20 Patients with TRG1 levels were greater than the 5 ng/ml. Similarly CEA values of 15 patients with TRG3 were greater than the 5

ng/ml. However, the relationship between them was not statistically significant (Table 4).

Table 4 Relationship between the CEA levels and the tumor regression grades

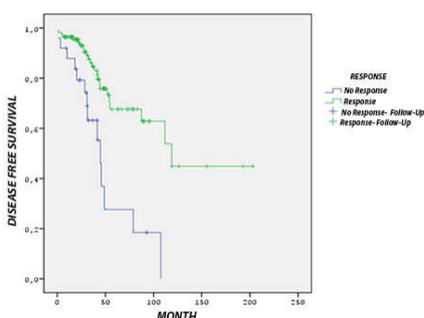| CEA	TRG			TOTAL
	I	II	III	
≤5	19 (25.6%)	41 (55.4%)	14 (19%)	74
>5	20 (30.5%)	29 (43.9%)	15 (25.8%)	64
	39	70	29	138

When the relationship between CEA groups and TRG levels were evaluated, results were not significant. In our series mean follow-up period was 42.6 ± 34.2 months (Rate: 1-203 months). When the patients with positive circumferential resection margins, were excluded, during follow-up of 135 patients who underwent R0 resection, locoregional recurrence rate was 8.1% (11 patients). Evaluating the relationship between loco regional reccurrence and the response to the CRT, recurrence rates with the patients who had a complete or partial response were significantly lower than the patients with no response (p<0.025) Similarly, the average duration of 42.6 months follow-up, 90% percent of 100 patients who survived had a response to the treatment (p<0.001) .

When assessing response to therapy and overall survival, in responding to treatment overall survival was $127.5 + \_13.3$ month. In Patients who did not respond the treatment, overall survive was $50.3 + \_8.7$ months. This relationship between response to the treatment and overall survive was statistically significant (p≤0.001) (Figure 1).
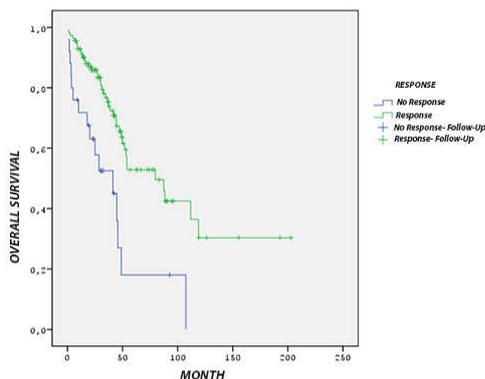
**Figure 1** The relationship between response to the neoadjuvant treatment and overall survival

Patients who had a response to the treatment, disease-free survive was 99.9 ± 11.2 months, in patients who do not response, it was 40.5 ± 8.9 months (p<0.001) (Figure 2).

Figure 2 Disease free survival rates

When analyzed in terms of distant metastases, in 31 patients (22.5%), metastases (liver, lung, bone, brain) have been developed. Perioperative (30 days) mortality rate was 0.72%. (1 patient: myocardenfarctus in postoperative 6th day). In follow-up, 100 (72.5%) patients were right, 38 (27.5%) patients were died. 14 of 100 patients who survived (14%) had distant metastases, 2 patients had loco regional recurrense, in 2 (2%) patients, both distant metastases and locoregional recurrense have developed.

Patients median survive time was 109.9 ± 11.6 months. In our serie the estimated 1-year survival was 94.9%, 3-years survival was 80.4% and estimated 5-years survival was 60.4%. Overall survival curves are shown in figure 3.
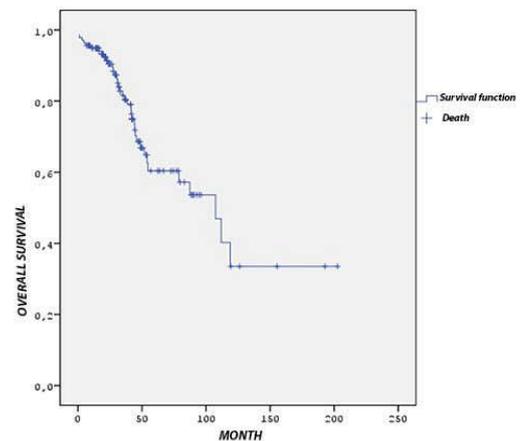
Figure 3 Overall survival rates

CONCLUSION

In patients with locally advanced rectal cancer, when it is compared with the preoperative RT or preoperative chemoradiotherapy, with surgery alone or surgery followed by adjuvant RT ± chemo, local control seems to be better in the group of preoperative RT or preoperative chemo radiotherapy (14). With these advantages chemoradiotherapy for locally advanced rectal cancer patients has become a standard part of a multimodal treatment. But it is still controversial that the neoadjuvant chemoradiotherapy, have a detrimental effect on life expectancy or not (14, 15). Also in all patients respond was not the same extent. Complete pathological response is seen in some patients (4-30%). In partial responses observe in some patients and in a group of patients, resistance is determined to the CRT (16).

Maybe to predict the patients response to neoadjuvant CRT will lead to changes in the treatment plan. Perhaps identification of patients with CRT-resistant, will avoid any unnecessary CRT to the patients. As a result adverse effects of the neoadjuvant treatment would be hampered at least a group of patients. Imaging methods can also be used to assess tumor response to CRT. However, the degree of accuracy is limited.

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Because the fibrosis, caused by the tumor itself or caused by the neoadjuvant therapy, precludes accurate assessment (17).

The Majority of the studies, that predict the CRT respond, concentrated on tumor suppressor genes (p53, p21), apoptotic factors (Bcl2, Bax), epidermal growth factor, cyclooxygenase 2 (COX2) and survivin gene (18). Comparing with these biomarkers, CEA has some advantages like being cheaper, to be measured easily and more familiar to the clinicians. In many studies was focused on determining CEA levels before treatment to predict response to the CRT (19). Park and his colleagues' study, at the patients with pre-treatment CEA> 5, poor response was reported (11). In our study, to evaluate the response to the neoadjuvant therapy, stage regression (T or N stage regression) and TRG classification were used. Stage regression was found at the 74.4% of patients (55 of 74 patients) with CEA $\leq$ 5 ng / ml (p=0.002). On the other hand there was no significant relationship between CEA and TRG. In our study, T stage regression in patients with pre-treatment CEA level $\leq$ 5 ng / ml, was significantly greater. N stage regression was greater in the group of patients with CEA$\leq$5 levels. But it was not significant (p=0.06).

In a study of Moreno and his colleagues, prognostic limit for the CEA have been reported as 2.5 ng / ml (20).To assessment of the chemoradiotherapy response, there are some prognostic studies about the effects of TRG on local reccurrense and desease- free survive (21, 22). The first grading system was performed to assess the regression in patients with esophageal cancer defined by Mandart (23). In our study, 3 grade regression sysytem, which is similar to the Ryan Regression System, (24) was used. And at this grading system, fallibility is lower. In studies, pathologic complete response after neoadjuvant CRT rate is reported as 4-30% (11). In our study, eight (5.8%) patients had pathologic complete response and it is consistent with the literature. These 8 patients' regression stages were grade 1.

In this study, to determine the response to the neoadjuvant therapy, we used stage regression and Wheeler Regression Grade scale. Stage regression was associated but wheeler regression grade was not. Partial or complete response to the chemoradiotherapy with 27 of 114 patients (23.6%) were TRG1, 61 (53.6%) were TRG2, 26 (22.8%) were TRG3. But there was not any significant relationship between them (p=0.053). In parallel to the study of Ryan *et al*, in our study we did not find any significant relationship between survival and TRG. However, at the study of Shia *et al*, in patients who had a complete or near complete response, there was a significant relationship between TRG and survival (25).

In our study, according to the TRG, patients were grouped in two groups. One of them was TRG1--good response, the other was TRG2-3--poor response. There was not any significant relationship between T and N stage regression and TRG groups. But in the group of patients who had poor response, stage regression was significantly greater. This inverse relationship might be due to the small numbers of patients who had a good response (TRG1) to the treatment. Similar to our study, in the literature, a study has been reported by Benzoni *et al* with 55 months follow up.

In this study, the World Health Organization's age limit of 65 years was taken. There was not any significant relationship between age groups and CRT response, T stage regression, N stage regression. But in our study similar to the JunZhong Lin

*et al*l's , the response to the CRT was better in the patients who were over 50 years old (p=0.054). Similarly it has been reported that in a study of Moral *et al*, CRT response was better in a group of patients who were over 60 years old (26). Similar to the literature, we identified that the number of the male patients were more than the females (27). We did not find any significant relationship between age-gender and local reccurrence-median survival, like to the literature (28). Sauer *et al* (29) reported that preoperative CRT increases the chances of sphincter-sparing surgery. Acccording to a systemic review by Bujko *et al*, it was reported that after neoadjuvant CRT, tumor shrinkage or complete response did not provide significantly increase rate of sphincter spare surgery (30). In our study, the was not any significant relationship between the response to the CRT and sphincter spare surgery too. There wasn't any evidence about that the T stage or N stage regression increases the feasibility of sphincter spare surgery. In our study, we identified a significant relationship with the localization of the tumor and the performed surgery (p<0.001). Sphincter spare surgery was performed much more at the patients who had upper and middle rectum tumor.

In light of these findings, we believe that most important factors about the feasibility of sphincter spare surgery are surgeon's preference, surgical technique, and tumor localization. After neoadjuvant CRT, even if the shrinkage of the tumor size, distal border of tumor may not be change and in order to provide the clear margin APR can be preferred.

117 of the patients (84.8%) in the study were adenocarcinomas. Tumor histological distribution of patients was consistent with the literature. There was not any significant relationship between histological type and locoregional recurrence, distant metastasis and survival.

In the literature, there are many articles about that the neoadjuvant CRT increases the local control of the tumor and resectability of the tumor especially in the distal located tumors. In our study, locoregional reccurrens was less in the patients who had complete or partial response, than the patients who had no response (5.4%, 20.8%). and it was statistically significant (p=0.025). In the patients who had no response, there was not any stage regression and it was statistically significant (p<0.001). The mean survival was better in the patients who had response to the treatment according to the not responding patients. (in order : 99.9±11.2 months; 40.5±8.9 months) (p<0.001).

Applying the neoadjuvant CRT to every patients who had locally advanced rectum cancer, is still being debated. Can it cause over treatment or not?. Even in the same group of patients with the same clinicopathological characteristics, there can be different levels of response and it shows that to evaluate the response we need different markers. In our study, we detected that in the patients with locally advanced rectal tumors, neoadjuvant CRT contrubuted to the tumor regression. We showed that CEA values before treatment (with a limit of 5 ng), could be used to predict the T stage regression and stage regression. In the other studies, there are different cut off values for CEA levels. It shows that different factors should be investigated next to CEA values.

According to our study, Wheeler Regression Score is not seen as an influential factor to evaluate the response to the neoadjuvant treatment. Investigation of different regression scores, may be useful in assessing the response. In the light of findings, it is observed that tumor location is the most

important factor to make sphincter protective surgery. As a result, patients with preoperative ≤ 5 ng / ml CEA value, are more likely to respond to neoadjuvant therapy. We all authors have no conflicts of interest to report.

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