

Predictors of sensitivity to preoperative chemoradiotherapy of rectal adenocarcinoma

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ABSTRACT

Objectives. The purpose of the study was to identify predictive factors of tumor response to preoperative chemoradiotherapy for rectal adenocarcinoma.

Methods. Ninety-eight patients with nonmetastatic rectal adenocarcinoma received preoperative concurrent chemoradiotherapy and underwent mesorectal excision. After treatment, tumor response according to tumor regression grade were evaluated. The correlation of clinicopathologic factors to tumor response was analyzed.

Results. The results from a univariate analysis indicated that pretreatment carcinoembryonic antigen level ≤ 3.0 ng/ml ($P = 0.002$), non-fixed tumor ($P = 0.001$), and tumor circumferential extent $\leq 50\%$ ($P = 0.001$) were associated significantly with a good tumor response. They also indicated that pretreatment positive lymph nodes ($P = 0.032$) were associated significantly with a poor tumor response. In multivariate analysis, the results indicated that pretreatment carcinoembryonic antigen level (hazard ratio, 2.930; $P = 0.003$), tumor mobility (hazard ratio, 2.651; $P = 0.002$) and circumferential extent of tumor (hazard ratio, 2.394; $P = 0.019$) independently predicted a good pathologic response rate. Pretreatment positive lymph nodes were not significantly associated with a good response (hazard ratio, 0.361; $P = 0.191$).

Conclusions. Pretreatment carcinoembryonic antigen level, tumor mobility and circumferential extent of tumor may be helpful in predicting responsiveness in rectal adenocarcinoma to preoperative chemoradiotherapy, although the results should be confirmed in larger, more homogeneous studies.

Introduction

Preoperative chemoradiotherapy (CRT) is the current standard treatment for locally advanced rectal cancer¹⁻⁵. Preoperative CRT for locally advanced rectal cancer has several potential advantages, including decrease in tumor volume, introduction of down-staging, increase in the possibility of R0 resection, reduction in radiation-induced toxicity, enhanced probability of anal-sphincter preservation by shrinking large distal tumors, and reduction in local recurrence⁶⁻⁹. Neoadjuvant therapy for adenocarcinoma of the rectum is well tolerated and can produce substantial down-staging and a high curative resection rate, although toxicity during neoadjuvant therapy is greater than for radiation alone¹⁰.

A Swedish rectal cancer trial demonstrated that a short-term regimen of high-dose preoperative radiotherapy reduces local recurrence rates and improves survival among patients with resectable rectal cancer¹¹. A retrospective study showed that preoperative radiation is an effective and safe adjunct to surgery in the treatment of rectal cancer and that its use can lead to improved survival rates¹². However, the response of individual tumors to adjuvant therapies is not uniform. Most patients benefit from preoperative CRT, and thus, a small proportion of a patient population is less likely to respond to the treatment. In order to offer patients individual therapy, it

Key words: preoperative chemoradiation, rectal cancer, tumor response.

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Received June 9, 2010;
accepted August 3, 2011.

could be important to identify predictive factors of cancer response to preoperative CRT.

However, preoperative CRT is administered to all clinically indicated patients at present, since no apparent factors predicting tumor response have been identified as yet. Some current studies have found that clinicopathologic factors are correlated to tumor response. Knowledge of such factors may be useful to clinicians and patients for predicting treatment outcomes and, hence, for making treatment decisions. The outcome of research remains controversial. Hence, we performed the present study to identify factors that predict tumor response in patients with rectal cancer who have received preoperative CRT followed by mesorectal excision.

Materials and methods

Patient selection

Between August 2004 and June 2009, 98 consecutive patients with rectal adenocarcinoma entered the study, and informed written consent was obtained from each patient. The study was approved by the Ethics Committee of Shandong Tumor Hospital. All patients underwent flexible endoscopy with rectal biopsy, complete blood count, biochemical profile, and serum carcinoembryonic antigen (CEA) level tests. Chest X-ray, abdominal and pelvic computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) scanning and PET combined with CT and/or endoscopic ultrasonography (EUS) were performed to exclude TNM stage I and IV tumors. Complete blood count, urinalysis, liver-function tests and chest X-ray were all normal in the patients. Some pretreatment clinicopathologic factors were assessed by flexible endoscopy and/or digital rectal examination (DRE).

Tumor size was determined based on the length of the tumor, as assessed by rigid proctoscopy, flexible endoscopy, and/or DRE. The distance of the inferior aspect of the tumor from the anal verge and the percentage of rectal lumen circumference involved by the tumor also were determined by rigid proctoscopy, flexible endoscopy, and/or DRE. A fixed tumor means that it is attached to surrounding tissue. A non-fixed tumor means that there is preserved mobility in at least one direction at DRE. DRE was carried out for the study by an expert physician.

The 6th edition of the American Joint Committee on Cancer TNM system was used for staging¹³. Clinical stage was based on the findings of EUS, MRI and CT scans. The criteria used for the definition of nodal involvement were as follows: 1) lymph nodes >8 mm in diameter defined as malignant on CT, MRI and EUS^{14,15}; 2) the presence of mixed signal intensity within the lymph

nodes on MRI and/or irregularity of the borders of the lymph nodes for capsular penetration¹⁶.

Endoscopic ultrasound was performed in 68 patients (70%), MRI in 20 patients (20%), and CT scans in 10 patients (10%). Blood was collected by venipuncture and serum samples were obtained after clotting and centrifugation; the samples were then stored at -80 °C. Serum levels of CEA and CA19-9 were measured by immunoradiometric assays (Boehringer-Mannheim GmbH, Mannheim, Germany). The cutoff points were at 3.0 ng/ml of CEA and 35 U/L of CA19-9, according to the 95% confidence intervals of non-cancer Chinese patients.

Treatment

Ninety-eight patients received preoperative radiation therapy with concurrent chemotherapy followed by mesorectal excision. All patients underwent CT simulation for three-dimensional conformal radiotherapy planning and the three-field technique (one posterior field and two lateral fields). The clinical target volume of the preoperative radiation therapy consisted of the primary tumor, the mesentery including vascular supply, and the perirectal, presacral and internal iliac nodes (up to the S1/S2 junction). Planning target volume was formed by enlarging 10 to 15 mm on the basis of the clinical target volume. Preoperative radiotherapy was delivered in fractions of 1.8-2.0 Gy, 5 fractions per week, to reach a dose of 40-45 Gy. All patients received concurrent chemotherapy (300 mg/m² 5-fluorouracil, 100 mg/m² oxaliplatin and 100 mg/m² leucovorin) on the first five and last five days of radiotherapy. All patients received a total mesorectal excision (TME) procedure after a long interval of up to 4-6 weeks. Four cycles of bolus fluorouracil (500 mg/m²/d five times weekly, repeated every 4 weeks) were started 4 weeks after surgery.

After radical surgery, all tumor specimens were examined by two pathologists, and the entire tumor plus the surrounding normal rectal wall and mesorectal fat was serially sliced into 4-mm-thick sections and embedded in paraffin. Tumor response was evaluated according to a modification of the tumor regression grading (TRG) as described by Dworak *et al.*¹⁷ Briefly, grade 0 was no regression; grade 1, minor regression (dominant tumor mass with obvious fibrosis in 25% or less of the tumor mass); grade 2, moderate regression (dominant tumor mass with obvious fibrosis in 26% to 50% of the tumor mass); grade 3, good regression (dominant fibrosis outgrowing the tumor mass; i.e., more than 50% tumor regression); and grade 4, total regression (no viable tumor cells, only fibrotic mass). Tumors with a TRG score of 0, 1 or 2 were considered to have had a poor response, whereas the remaining tumors (scored TRG3 or TRG4) were classified as having a good response.

Statistics

For all statistical analyses, Statistica 13.0 was used. *P* values less than 0.05 or 95% were considered as statistically significant. CEA levels were tested with two cutoff points: the normal range (0-3 ng/ml) and 0-5 ng/ml, which was recently described as a predictor of tumor response. Chi-square or Fisher exact tests were performed to determine significant univariate predictors of early tumor response to preoperative CRT. Then, a logistic regression analysis was used to identify the significant multivariate predictors. All variables that were significant in the univariate analysis were entered into a multivariate model. In a backward, stepwise fashion, the significant univariate variable with the least significance was eliminated from the multivariate model. This was continued until only significant variables remained.

Results

Tumor response

Of the 98 patients, 43 (44%) had a poor pathologic response rate (TRG 0 + 1 + 2) and 55 patients (56%) achieved a good pathologic response rate (TRG 3 + 4). Patients with pretreatment CEA levels ≤3.0 ng/ml achieved better tumor responses than those with CEA level >3.0 ng/ml (70% vs 39%, *P* = 0.002). Patients with pretreatment non-fixed tumor achieved better tumor responses than those with a fixed tumor (73% vs 40%, *P* = 0.001). There were significantly higher tumor response rates in negative lymph node cases than in cases with positive lymph nodes (66% vs 44%, *P* = 0.032). Similarly, there were higher tumor response rates in cases with a tumor circumferential extent ≤50% than in those with tumor circumferential extent >50% (74% vs 40%, *P* = 0.001) (Table 1).

Correlation between pretreatment clinicopathologic characteristics and tumor response

1. Univariate predictors. Univariate analysis indicated that pretreatment CEA level ≤3.0 ng/ml (*P* = 0.002) and non-fixed tumor (*P* = 0.001) were associated significantly with a good response (TRG 3 + 4) (Table 1). Univariate analysis also indicated that pretreatment positive lymph nodes were associated significantly with a good response (*P* = 0.032). Figure 1 shows the relationship between good tumor response rates and pretreatment tumor circumferential extent. Remarkable differences in good tumor response rates were evident between the tumor circumferential extent groups of ≤50% and >50% (TRG 3 + 4-74% vs 40%, *P* <0.05). Pretreatment CEA level >5.0 ng/ml was not associated significantly with tumor response (*P* = 0.188). The other variables that were evaluated (age, gender, clinical T classification, distance from the anal verge, tumor size, grade, pretreatment

Table 1 - Correlation between pretreatment clinicopathological characteristics and tumor response

Clinicopathological characteristics	Tumor response			<i>P</i>
	No. cases	Poor (TRG 0+1+2)	Good (TRG 3+4)	
Age (yr), median 50				
<50	48	21	27	0.980
≥50	50	22	28	
Gender				
Male	57	25	32	0.997
Female	41	18	23	
Tumor size (cm), median 5				
≤5	59	24	35	0.432
>5	39	19	20	
Grade				
Well/moderately differentiated	55	21	34	0.199
Poorly differentiated	43	22	21	
Lymph node status				
Present	45	25	20 (44%)	0.032
Absent	53	18	35 (66%)	
cT category				
T3	42	16	26	0.318
T4	56	27	29	
Distance from anal verge (cm), median 6				
≤6	47	20	27	0.866
>6	51	23	28	
CEA(ng/mL)				
≤3.0	54	16	38 (70%)	0.002
>3.0	44	27	17 (39%)	
Tumor mobility				
Fixed	50	30	20 (40%)	0.001
Non-fixed	48	13	35 (73%)	
CA19-9 (U/L)				
≤35	62	26	36	0.611
>35	36	17	19	
Circumferential extent (%)				
≤50	46	12	34 (74%)	0.001
>50	52	31	21 (40%)	
CEA(ng/mL)				
≤5.0	64	25	39	0.188
>5.0	34	18	16	

CA19-9) were not associated significantly with tumor response (Table 1).

2. Multivariate predictors. Multivariate logistic regression analysis showed that pretreatment CEA level ≤3.0 ng/ml (*P* = 0.003) was associated significantly with a good response (Table 2). It also indicated that non-fixed tumor and circumferential extent of tumor ≤50% independently predicted a good tumor response (*P* = 0.002 and *P* = 0.019, respectively). In multivariate analysis, pretreatment positive lymph nodes was not associated significantly with a good response (Table 2).

Discussion

Although good results are obtained with the current multimodal treatment of rectal cancer, patient-tailored treatments are expected to give greater benefit. In the

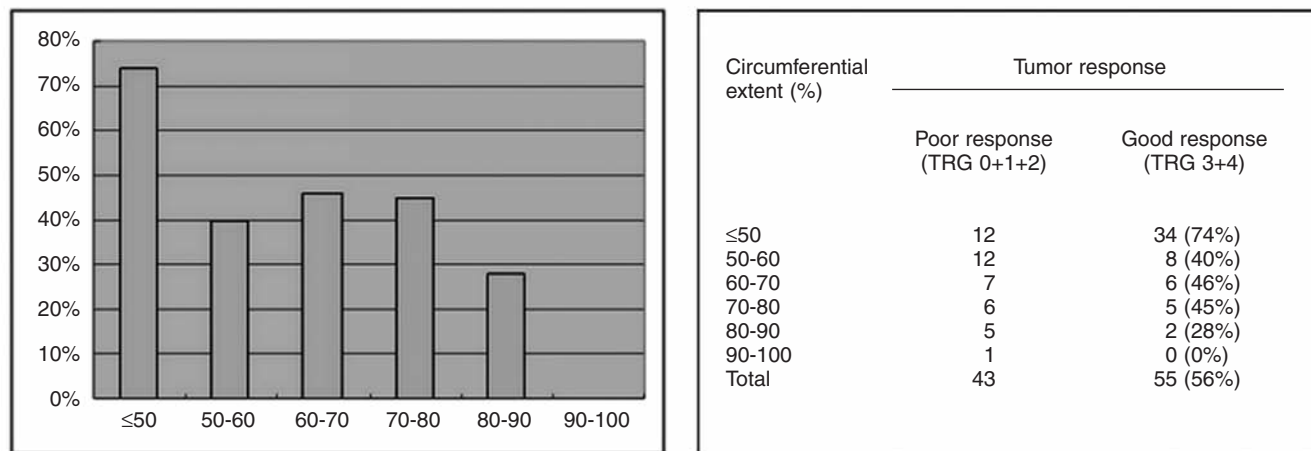


Figure 1 - Tumor regression curve of locally advanced rectal cancer patients treated with preoperative chemoradiotherapy, based on the circumferential extent between poor and good response groups. Patients with circumferential extent $\leq 50\%$ achieved better tumor responses than those with circumferential extent $>50\%$ (74% vs 40%, $P < 0.005$). TRG, tumor regression grading.

Table 2 - Multivariate analysis of pretreatment clinicopathologic factors correlated with tumor response following preoperative chemoradiotherapy in rectal adenocarcinoma

Variable	P	Hazard ratio	95% CI	
			Lower	Upper
Age	0.719	1.013	0.945	1.086
Gender	0.274	0.384	0.069	2.132
Tumor size	0.243	1.291	0.841	1.982
Grade	0.166	2.123	0.623	2.654
cT category	0.589	1.376	0.432	4.377
Distance from anal verge	0.313	1.579	0.650	3.834
CA19-9 (U/L)	0.994	0.994	0.260	3.807
CEA (ng/mL)	0.003	2.930	1.456	5.894
Tumor mobility	0.002	2.651	1.434	4.903
Circumferential extent	0.019	2.394	1.137	3.398
Lymph node status	0.191	0.361	0.127	1.184

present study, we analyzed the effect of preoperative CRT on the primary tumor and a potential value of these clinicopathologic factors in predicting response of the tumor to preoperative chemoradiation.

The response of the primary tumor to neoadjuvant treatment seems to be a good prognostic factor. The way to assess the response of primary tumors is TRG, as mentioned above. TRG evaluates the amount of residual neoplastic cells within fibrosis and inflammatory response following neoadjuvant therapy without regard for anatomic localization of neoplastic cells, as is the case for TN staging. Recently, Suárez *et al.*¹⁸ reported TRG to be a superior predictor of survival compared to TN-stage down-staging. Other authors have reported significantly better oncological outcomes following increased tumor regression grades¹⁹⁻²². In this exploratory analysis, complete (TRG 4) and intermediate pathologic response (TRG 2 + 3) suggested improved disease-free survival after preoperative CRT. TRG assessment should be implemented in pathologic evaluation and prospec-

tively validated in further studies²³. Another study performed by Losi *et al.*²⁴ attempted to confirm the predictive value of TRG. The small number of patients ($n = 106$) limited the results, finding statistically significant differences only when TRG 3 and 4 were grouped. However, there was a trend towards improvement in survival when TRG was stratified by pathologic stage. TRG was a significant prognostic factor in locally advanced rectal carcinoma treated with preoperative CRT. The use of a standardized system to evaluate TRG in rectal cancer can allow for comparisons between different institutions and can identify patients with a worse prognosis to be treated with adjuvant therapy.

The value of serum CEA levels in rectal cancer after the introduction of neoadjuvant CRT has been assessed in only a few studies. The first study by Park *et al.*²⁵ found an association between high serum CEA levels (>5 ng/ml) and poor response to treatment. Another study by Yoon *et al.*²⁶ also showed that the most important clinical predictor of tumor response was CEA level <5 ng/ml in univariate and multivariate analyses. However, in the largest study of predictive factors of response to CRT, which included 562 patients, pretreatment serum CEA level ≥ 2.5 ng/ml was associated with lower complete pathologic responses and down-staging rates²⁷. A study also showed that pretreatment serum CEA level ≤ 2.5 ng/ml was associated with higher complete pathologic responses and better 3-year disease-free survival²⁸. Our results are discordant with these findings; serum CEA level ≤ 3.0 ng/ml was associated with a good tumor response ($P = 0.002$), but CEA level >5.0 ng/ml was not (good tumor response, $P = 0.188$). Such findings indicate that CEA may be a useful predictor of rectal tumor response to preoperative CRT. Furthermore, to our knowledge, our study is the first to correlate low serum CEA levels (0-3.0 ng/ml), since past

studies only correlated low serum CEA levels (0-5 ng/ml and 0-2.5 ng/ml) with tumor response. This improvement disappeared when the cutoff point of 5.0 ng/ml was used, suggesting that lowering the cutoff point to 3.0 ng/ml might be more useful in current clinical practice.

Furthermore, to our knowledge, this is the first study to demonstrate that tumor mobility can serve as an important predictor of pathologic tumor response. Prior to the advent of the technique that can delineate mesorectal fascia, identification of such cases was limited to clinical assessment of fixity of the tumor and the widely held view was that a clinically fixed tumor would result in positive circumferential resection margins. Very often, it is impossible to determine by clinical examination cases with margin involvement, as they may be remote from the primary tumor. Fixation score is not objective and reproducible. MRI has the inherent advantage of being able to consistently depict the mesorectal fascia, which forms the surgical circumferential resection margins in TME surgery. When the tumor extends to within 1 mm of this fascia, infiltrates or extends beyond this fascia, this predicts subsequent margin involvement²⁹.

The present study demonstrated that tumor mobility predicts for pathologic tumor response in patients with rectal cancer who receive preoperative CRT. Non-fixed tumors were associated significantly with a good response (TRG 3 + 4). A study performed by Ferrigno *et al.*³⁰ attempted to confirm the prognostic value of tumor mobility. It showed that fixation of the lesion was the main adverse prognostic factor.

Studies have also demonstrated that circumferential extent of the tumor may be used to predict response to preoperative CRT. The value of circumferential tumor extent in rectal cancer after the introduction of neoadjuvant CRT has been assessed in only one large study. The study with 562 patients showed tumor circumferential extent >60% was associated significantly with poor pathologic tumor response²⁷. Our study also demonstrated that tumor circumferential extent >50% was associated significantly with a poor pathologic tumor response. It suggested that circumferential extent of the tumor may be an independent predictor.

We also found that there is a correlation between tumor response to preoperative treatment and lymph nodal status. The correlation of TRG with lymph node status, however, has not been extensively studied. The aim of our study was to determine whether a correlation exists between TRG after neoadjuvant CRT and lymph node status before treatment. A study showed that there is a correlation between TRG after neoadjuvant CRT and lymph node status in resected specimens³¹. The study showed lymph node metastasis, suggesting that neoadjuvant CRT may have a positive impact on overall patient survival. However, our results demonstrated pre-treatment positive lymph nodes with a poor tumor re-

sponse to preoperative treatment. In our study, lymph node status turned out to be an important predictive factor, with a significantly higher response rate in N-negative than in N-positive tumors (66% *vs* 44%; $P = 0.032$). It indicated that lymph node status may predict a short-term curative effect.

Some studies on predictors of tumor response are particularly important for rectal cancer, since the response to preoperative CRT, in turn, predicts long-term outcome³²⁻³⁴. Molecular imaging technologies are dramatically improving the ways in which colorectal cancer is diagnosed and treated. Research in molecular imaging is also contributing to our understanding of the disease and directing more effective care of patients with colorectal cancer. PET scanning and PET combined with CT is used for colorectal cancer. It is used to evaluate the effectiveness of treatment for colorectal cancer by determining the patient's response to therapy. A retrospective study showed that ¹⁸fluoro-deoxy-glucose-PET is potentially useful as a method to assess tumor response after preoperative CRT for rectal cancer³⁵. Although biologic markers are likely to play increasing roles in predicting treatment response in the future³⁶⁻³⁸, the importance of clinical predictive factors, such as circumferential extent of tumor and CEA level, should not be overlooked. Indeed, studies of molecular imaging, molecular markers and gene expression profiles should incorporate and account for significant clinical predictors to obtain better prediction models. Compared with biologic markers, the clinical predictors are inexpensive and easily measurable. We first found some new significant clinical predictive factors, such as lymph node status and tumor mobility. Predictive factors can be useful in the design of clinical trials on new therapies. Patients can be stratified in terms of known predictive factors. Research of non-surgical treatments and local excision could be pursued in patients who are highly likely to respond to preoperative CRT. Moreover, predictive factors may be used to investigate newer, more aggressive preoperative regimens in specific subgroups of patients who are less likely to respond to standard preoperative CRT. Such factors may promote the development of individualized, risk-adapted treatment strategies for patients.

Conclusions

The present results suggest that CEA level, tumor mobility and circumferential tumor extent may be useful in predicting pathologic response in patients with rectal cancer who receive preoperative CRT. These predictive factors may lead to predict outcomes for patients and also may be used to guide tailored and targeted treatment for patients who receive newer therapies for rectal cancer. However, larger and more homogeneous studies of these factors for rectal cancer treated with CRT should be conducted.

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