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Original Article

Can positron emission tomography-computed tomography predict response in locally advanced rectal cancer patients treated with induction folinic acid and 5-florouracil?

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Abstract

OBJECTIVE: The aim of this study was to determine the pathological complete response rates in a group of locally advanced rectal cancer patients who underwent chemoradiotherapy (CRT) after treatment with induction folinic acid and 5-florouracil (FOLFOX) chemotherapy and the relationship between the complete response and positron emission tomography-computed tomography (PET-CT). **MATERIALS AND METHODS:** The files of 239 patients who were diagnosed with rectal cancer between January 2008 and January 2012 were evaluated retrospectively. Of these, there were 24 locally advanced rectal cancer patients who met the following criteria: They were administered CRT after receiving four courses induction oxaliplatin, FOLFOX and they underwent PET-CT for staging and for the evaluation of their response to FOLFOX treatment. Of these 24 patients, 20 operable patients were included in the study. **RESULTS:** The pathological complete response was obtained in seven patients (35%) who were operated on and then given induction four courses FOLFOX chemotherapy and CRT. We determined that age, gender, clinical stage at diagnosis and PET-CT before and after induction chemotherapy were not predictive of the pathological complete response to tumor fluorodeoxyglucose uptake activity. **CONCLUSION:** The rates of pathological complete response were increased in locally advanced rectal cancer patients who underwent short-term induction chemotherapy. Although the PET-CT has retained its importance in predicting pathological complete response, there is still a need for studies with a larger number of patients and long-term follow-ups.

Key Words: Folinic acid and 5-florouracil, induction chemotherapy, pathological complete response, positron emission tomography-computed tomography, rectal cancer

Introduction

Rectal cancer is a significant cause of morbidity and mortality in developed countries. Pre-operative chemoradiotherapy (CRT) followed by total mesorectal excision is the standard treatment for locally advanced rectal cancer.[1,2] Fluorouracil (FU)-based CRT has been shown to reduce local recurrence of rectal cancer when compared with radiotherapy alone. In colon cancer, treatment with the platinum derivative oxaliplatin in combination with FU is known to be effective in adjuvant therapy as well as in metastatic diseases. The STAR study, which was conducted in order to determine the efficacy of this treatment as a neoadjuvant therapy in rectal cancer patients, revealed that this combination did not improve the disease condition; rather, it increased toxicity.[3-5]

In the majority of patients, the pre-operative CRT indicates a decline in tumor stage, a reduction in the local recurrence and in 15-27% of patients, an achievement of pathological complete response.[1,2,6] Despite the decrease in local recurrence, 5-year distant metastasis was detected in 30% of all cases and survival was shown to be limited.[3,4] Patients with a pathologic complete response had better long-term results than those who did not. A meta-analysis evaluating 27 studies revealed a significant increase of disease-free survival in patients with a pathologic complete response.[7] Several studies have reported that induction chemotherapy increases the pathological complete response in locally advanced rectal cancer patients. Chau *et al*. reported that the radiological response rate was 88% with a neoadjuvant capecitabine/oxaliplatin treatment and that this percentage increased to 97% after CRT. In addition, the pathologic complete response rate was 24% and microscopic tumor foci were detected in surgical specimens from 48% of patients.[8] In recent years, numerous studies have been conducted to assess the use of positron emission tomography-computed tomography (PET-CT) to evaluate CRT in predicting the pathologic response. These studies have shown that PET-CT accurately predicts the pathological treatment response in patients with the decreased metabolic activity due to rectal cancer. The specificity, pathological and radiological definitions and differences in methodology account for 60-100% of the variation in these studies.[9-14]

Our study try to demonstrate the importance of systemic control as well as the contribution of the pathological complete response to survival in locally advanced rectal cancer patients. The aim of this study was to determine the ratio of the pathological complete response in patients who underwent CRT after folinic acid and 5-florouracil (FOLFOX)-induced chemotherapy. We also assessed the relationship between the complete response and PET-CT in cases that had achieved a complete response.

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Materials and Methods

We retrospectively screened the files of 239 patients who were diagnosed with rectal cancer between January 2008 and January 2012. There were 24 locally advanced rectal cancer patients who had undergone CRT after induction FOLFOX chemotherapy and whose response to treatment was monitored with PET-CT. Of these 24 patients, 20 operable patients were included in the study. One of the four inoperable patients could not be reached and therefore, we were unable to obtain his pathology results. Two of the other patients had a partial response after induction chemotherapy, but they chose not to have the operation. The fourth patient developed metastasis during the follow-up [Figure 1].

The diagnosis of each patient was confirmed through colonoscopic biopsy. The history, physical examination,

complete blood count, biochemistry and carcinoembryonic antigen levels of each patient were used for staging assessment. PET-CT was used to evaluate staging and the response to induction chemotherapy treatment.

Treatment

CRT

A total of 50.4 Gy radiotherapy in fractions of 1.8 Gy was applied to the primary tumor area of each patient 5 days a week over a 6 week period. A continuous infusion of 225 mg/m²/day 5 FU was administered intravenously during the radiotherapy.

Chemotherapy

Four cycles of FOLFOX induction, 85-100 mg/m² oxaliplatin was administered intravenously at day 1. 5-FU was administered as an intravenous bolus at 400 mg/m² and was administered as a continuous intravenous infusion at 600 mg/m² for 22 h during days 1 and 2. Folinic acid (200 mg/day) was administered intravenously during days 1 and 2. This cycle was repeated every 2 weeks.

Patients were operated on 4-6 weeks after they had completed CRT. They underwent PET-CT for staging and for the evaluation of their response to treatment.

The pathologic complete response was evaluated with a univariate logistic regression test. In cases, where there were more than two factors, a multivariate analysis was performed.

Results

The median age of the patients was 53 years (range: 31-79 years). Among the 20 patients included in our study, 6 (30%) were female and 14 (70%) were male. Patients who underwent clinical staging with PET-CT were clinical T4, lymph node positive (55%) and negative (45%) patients. The demographic data of the patients and their tumor stages are summarized in Table 1.

The mean standardized uptake value (SUV) max value of the tumor in before induction chemotherapy was 19.4 (range: 7-38) and after induction chemotherapy was 10.5 (range: 0-29).

A pathological complete response was achieved in 7 (35%) patients who were operated on after receiving induction FOLFOX and CRT. Other patients: three patients (15%) were stage 1; six (30%) were stage 2a while four patients (20%) were stage 3. The relationship between each patient's baseline stage and his/her pathological response after the treatment is summarized in Tables 2a and b.

Analyses were performed in order to determine the factors that predict the pathological complete response. Age, gender, the clinical stage at diagnosis, pre-operative lymph node involvement and PET-CT before and after induction chemotherapy and the rate of decrease in PET fluorodeoxyglucose (FDG) uptake activity were found to be not related to the pathological complete response [Table 3].

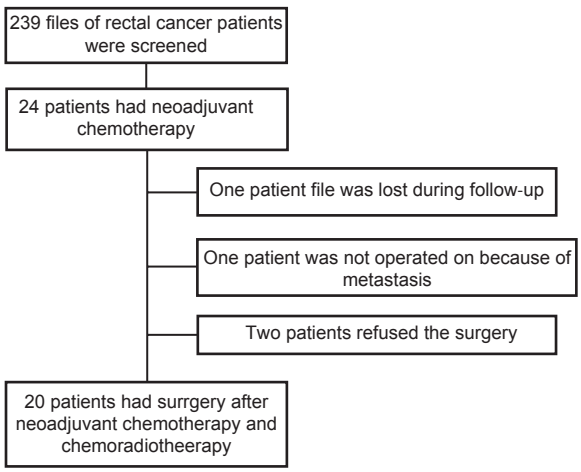

Figure 1: Consort diagram showing the fl ow of patients

Table 1: Baseline characteristics

Baseline characteristics	Number of patients (*N*=20)	%
Sex		
Male	4	70
Female	6	30
Age, years		
Median	53	
Range	31-79	
ECOG performance status		
0	8	40
1	12	60
LARC clinical staging		
CT4N0	9	45
CT4N+	11	55

ECOG=Eastern cooperative oncology group; LARC=Locally advanced rectal cancer

Table 2a: Pathological response

Clinical staging (PET-CT)	Pathological staging (*N*=20)				
	pT0	pT1	pT2	pT3	pT4
T4	7	0	3	10	0

PET-CT=Positron emission tomography-computed tomography

Table 2b: Pathological response

Clinical staging (PET-CT)	Pathological staging (*N*=20)	
	Pathological node negative	Pathological node positive
Node negative	9	0
Node positive	7	4

PET-CT=Positron emission tomography-computed tomography

Table 3: Predictive markers

Risk factor	RR (95 CI %)	*P* value
Age	1.01 (0.9-1.09)	0.61
Gender	0.90 (0.12-6.7)	0.91
PET activity (SUVmax) before treatment	0.93 (0.82-1.04)	0.23
PET activity (SUVmax) after treatment	0.98 (0.87-1.1)	0.75
Rate of decrease in PET activity	0.66 (0.1-4.2)	0.67
Pre-operative lymph node involvement	5.6 (0.74-42)	0.09

PET=Positron emission tomography; SUV=Standardized uptake value; RR=Relative risk; CI=Confidence interval

Mean follow-up time was 24 months. Four patients (20%) who had undergone the operation after induction FOLFOX chemotherapy had recurrence. These patients had distant metastases (two patients had lung metastases; one patient had liver and one patient peritonitis carcinomatosa).

Discussion

In this study, we included patients who underwent an oxaliplatin-5FU-based induction chemotherapy regimen before CRT and whose treatment response was evaluated by PET-CT.

A triple modality, including superficial re-biopsy, colonoscopic examination and pelvic magnetic resonance imaging (MRI) is often used to determine the tumor response after preoperative CRT in locally advanced rectal cancer patients. The prediction of pathologic complete response rates with re-biopsy and pelvic MRI ranges from 20% to 30% and is 53.8% with colonoscopic examination.[15] PET-CT is widely used in colorectal cancer staging due to its high sensitivity.[16] The benefit of FDG PET imaging in demonstrating the response to chemotherapy and/or radiation therapy in rectal cancer was first shown in 1992.[17] During the past decade, many studies have shown that post-neoadjuvant 18 FDG uptake PET-CT can be successfully used to evaluate the response of patients with locally advanced rectal cancer to treatment. Recently, Shanmugan *et al*. investigated whether the FDG PET-CT was able to predict the pathological response in cases with locally advanced rectal cancer that were treated with neoadjuvant CRT. The pathological complete response was observed in 26% of the 70 patients that were evaluated. The median post CRT SUV was found to be 63% lower in patients that had a complete response. The authors concluded that the pathological complete response could be predicted by the SUV and the decrease in SUV%.[18] In contrast, another study by Sravana *et al*. reported that there was no correlation between a pathological complete response and PET-CT taken before and after treatment.[9] Similarly in our study, we did not detect any correlation between the pathological complete response and the PET-CT SUVmax values taken either or after the FOLFOX induction. Furthermore, the decrease in SUVmax values after the treatment also did not predict the pathological response.

Similar studies evaluating patients who underwent induction chemotherapy followed by CRT and surgery reported increased rates of the pathological complete response, increased tumor regression and an increased rate of R0 resection. However, in order to assess the contribution to overall survival, long-term follow-ups are required for these types of studies.[1,8,19-21]

The number of patients with a pathologic complete response after pre-operative CRT ranged from 15% to 27%. It has been reported that the pathological complete response has a prognostic value in the treatment of locally advanced rectal cancer.[2,6,22] However, this value was not statistically significant due to the limited number of patients in those studies. A meta-analysis that included 14 studies and 3105 patients indicated that residual tumors significantly contributed to the 5-year disease-free survival, survival with distant metastasis and the overall survival of patients with a pathological complete response.[7] The importance of a pathological complete response in locally advanced rectal cancer has led to a number of different treatment strategies. Pathological complete response rates have ranged from 20% to 44% in studies evaluating patients who underwent induction chemotherapy.[1,8,19,21] In our study, this ratio is 35%. This may be a hint for the efficacy of addition of FOLFOX to CRT. However, further studies with more patients are needed for the exact demonstration of this possibility.

Pre-operative CRT primarily improves local control, but the dominant pattern of rectal cancer recurrence is distant metastasis. It has been reported that the 5-year local relapse rate was lesser than 10% while the rate for those with distant metastases was higher than 30%.[23] Systemic neoadjuvant chemotherapy is intended to provide long-term disease control. Chau *et al*. investigated cancer recurrence in 77 patients within 23 month follow-up period. When patients were treated with a regimen that included induction with capecitabine and oxaliplatin followed by capecitabine and radiation therapy, two local recurrences and eight distant metastases (four livers, three lungs and one peritoneal metastasis) occurred. They also indicated that the 1-year disease-free survival rate was 87%.[8] This treatment strategy is based on the notion that systemic control is critical for locally advanced rectal cancer.

In conclusion, locally advanced rectal cancer is a systemic disease. The pathological complete response has been shown to contribute to disease-free survival and overall survival. The PET-CT is important in staging and in the evaluation of the response to therapy. However, there is still a need for new treatment strategies and markers that will predict the complete response.

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