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Original Article

The outcome of 5-fluorouracil chemotherapy after the completion of neoadjuvant chemoradiotherapy, administered until 2 weeks before rectal cancer resection

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Abstract

Background: In most institutions, locally advanced rectal cancer is treated with neoadjuvant chemoradiotherapy followed by surgery 6–8 weeks later, allowing time for tumor response and recovery from chemoradiotherapy-related toxicities. In our hospital, we continuously administer chemotherapy after the completion of chemoradiotherapy, until 2 weeks before surgery for most patients.
Methods: This was a retrospective study. Patients received a diagnosis of adenocarcinoma of the rectum at our hospital between January 2003 and December 2008 and received neoadjuvant chemoradiotherapy and curative surgery. Chemoradiotherapy consisted of continuous infusion of 225 mg/m^2 5-fluorouracil, 5 days per week. Radiation therapy was delivered at 1.8 Gy per day, 5 days per week for 5–6 weeks (median radiation dose, 50.4 Gy). Chemotherapy was continued until 2 weeks before surgery, and surgery was performed 6–8 weeks after completion of chemoradiotherapy.
Results: The study included 119 patients (median age, 61 years; range, 24–84 years). Twenty-nine patients (24.4%) had a complete response and 65 (54.6%) had a partial response. Over a median follow-up duration of 52 months, 10 patients experienced local recurrence and 18 had distant metastasis. The 5-year overall and disease-free survival rates were 80.6% and 72.9%, respectively. Grade 3–4 toxicity only occurred in 14 patients (11.8%).
Conclusion: Continued chemotherapy with 5-fluorouracil after completing neoadjuvant chemoradiotherapy until 2 weeks before surgery for locally advanced rectal cancer results in a good pathological control rate, with low toxicity. Patients who achieved a complete pathological response had a better long-term oncological outcome than those who did not.

Keywords: chemotherapy; 5-fluorouracil; neoadjuvant chemoradiotherapy; rectal cancer

1. Introduction

Preoperative chemoradiotherapy (CRT) followed by total mesorectal excision (TME) is an important treatment strategy for locally advanced rectal cancer (defined as T3 or node-positive rectal cancer). Preoperative CRT is associated with a lower local recurrence rate and general toxicities than postoperative CRT.[1–3] Neoadjuvant CRT usually results in a reduced tumor size, increased tumor mobility, and histopathologic downstaging, with correspondingly improved long-term oncologic outcomes.[4] Approximately 15–20% of patients have a pathological complete response (pCR) at the time of surgery,[5–7] although the likelihood of a pCR may be related to

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the timing of tumor resection, the chemotherapy regimen, and the radiotherapy dose.

In most institutions, locally advanced rectal cancer is generally treated with neoadjuvant CRT followed by surgery, ~6−8 weeks later, to allow for a tumor response to CRT and recovery from CRT-related toxicity. In our hospital, we continue to administer chemotherapy after the completion of CRT until 2 weeks before surgery for locally advanced rectal cancer. Here, we report the oncological outcome, pathological complete response rate, and toxicities associated with this strategy.

2. Methods

2.1. Data source

We retrospectively reviewed the medical records of patients in whom adenocarcinoma of the rectum was diagnosed (tumor located within 12 cm from the anal verge) who received neoadjuvant CRT in our hospital between January 2003 and December 2008. Patients with tumor metastasis or unresectable tumors, those who only underwent local excision, and those who achieved a clinical complete response under observation alone were excluded. The rectal adenocarcinoma diagnosis was based on sigmoidoscopy biopsy. T staging was scored by transrectal ultrasonography or magnetic resonance imaging (MRI), and N staging was scored by pelvic computed tomography (CT). Distant metastasis was evaluated using an abdominal CT scan and chest X-ray film for all patients. Clinical data including age, sex, Eastern Cooperative Oncology Group performance status, operative method, tumor recurrence, tumor distance from the anal verge, pretreatment clinical tumor stage and size, histologic grade, radiotherapy dose, chemotherapy toxicities, preoperative clinical stage, postoperative pathological stage, site of tumor recurrence, survival status, and duration of follow-up were analyzed.

The treatment program is shown in Fig. 1. All patients were treated with 5-fluorouracil (5-FU) continuous infusion at a dose of 225 mg/m^2, 5 days per week, concurrent with radiotherapy. Radiation therapy was delivered at 1.8 Gy per day, 5 days per week for 5−6 weeks, and the median radiation dose was 50.4 Gy (range, 43.2−65.5 Gy). Chemotherapy was continued until 2 weeks before surgery, and the patient underwent surgery within 6−8 weeks after finishing radiotherapy. The clinical response was evaluated by post-CRT CT, sigmoidoscopy, and digital rectal examination. After surgery, planned adjuvant treatment was a 5-FU based chemotherapy regimen.

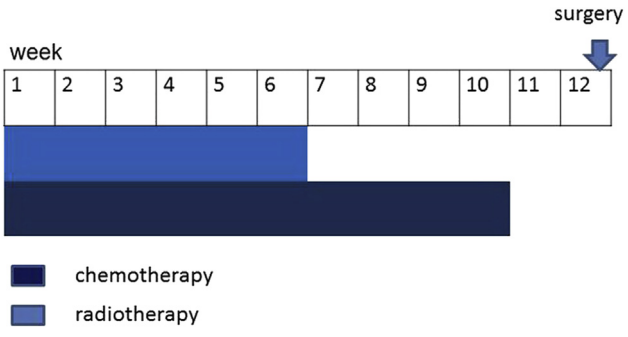

Fig. 1. Treatment schedule for patients included in this study.

2.2. Statistical analyses

We compared the general characteristics between groups with and without pCR. We analyzed differences with respect to specific clinical factors according to whether patients had a complete response using Student t test, Yates' correction and Fisher's exact test. We compared the recurrence rate between groups with and without pCR using Fisher's exact test.

Overall survival was defined as the time from the beginning of CRT to the date of the last follow-up visit or death. Disease-free survival was defined as the time from surgery to the date of death, last follow-up visit, or treatment failure (local or distant recurrence). Local recurrence was defined as tumor recurrence in the pelvis, perineum, or anastomosis site. Distant metastasis was defined as tumor recurrence outside the pelvis. The follow-up duration was defined as the time from surgery to the last follow-up visit or any type of event. We used the Kaplan−Meier survival method to compare disease-free and overall survival for patients with and without pCR, and log-rank test to identify significant differences. All analyses were performed using GraphPad Prism Version 5 (GraphPad Software, San Diego, CA, USA). A p value <0.05 was considered statistically significant.

3. Results

Between January 2003 and December 2008, 127 patients were included in our study; eight patients did not complete the full course of CRT (6 due to CRT intolerance and 2 due to disease progression during CRT). Finally, a total of 119 patients were included in the analysis. The characteristics of all 119 patients are summarized in Table 1. Seventy-four patients were men and 45 were women, with a median age of 61 years (range, 24−84 years). Thirty-six patients (30.3%) underwent transrectal ultrasonography for clinical T staging and 83 (69.7%) underwent MRI for clinical T staging. The preoperative clinical stage of the patients was stage II in 41 cases (34.5%) and stage III in 78 cases (65.5%), and the median tumor size was 2.8 cm (range, 0.8−12 cm). After neoadjuvant CRT, all patients underwent surgery, which involved lower anterior resection in 81 cases (31 cases with protective ileostomy), abdominoperineal resection in 37 cases, and Hartmann procedure in one case. Of 67 patients with a low rectal tumor (tumor located $\leq$ 5 cm from the anal verge), 30 patients (44.8%) had sphincter preservation. The final pathological stage revealed complete remission in 29 cases (24.4%), stage 0 (ypTisN0M0) disease in one case (0.8%), stage I disease in 31 (26.1%), stage II disease in 31 (26.1%), and stage III disease in 27 (22.7%). Total downstaging was observed in 94