Clinical complete regression after local radiotherapy combined with chemotherapy for stage IV rectal cancer: A case report

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Abstract. Colorectal cancer is the fourth most common type of cancer worldwide with about 0.8 million new cases annually. Improving patient survival remains a challenge for clinicians. Observation waiting method provides improved quality of life compared with direct surgery. This case report suggested that colorectal cancer patients could choose active observation waiting method for treatment. A 59-year-old male patient, with rectal bleeding and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, was admitted to the hospital due to increased fecal blood volume. The electronic colonoscopy revealed multiple polyps in colon and rectum, whereas the pathological biopsy indicated poorly differentiated rectal adenocarcinoma. The clinical stage was defined as T3N2M1a according to the TNM classification of the American Joint Committee on Cancer (AJCC) staging manual (version 8). In addition, positron emission tomography/computed tomography (PET/CT) examination showed non-regional lymph node metastasis (subclavian). Subsequently, the expression of PD-L1 (-), NRAS (-), KRAS (-), HRAS (-), BRAF (-) (-, negative) and the microsatellite stability (MSS) were detected in the rectal cancer lesion using molecular pathological examination. Patients with primary rectal cancer and pelvic lymph node metastasis were treated with three-dimensional conformal radiotherapy (3D-CRT; dose, 60 Gy/30 Fr) and XELOX chemotherapy (200 mg oxaliplatin at day 1 plus 1.5 g capecitabine twice a day from day 1-14 for a total of 5 cycles). PET/CT scan revealed that the metabolism levels of the lesion returned to normal. In addition, the routine re-examination showed progressive improvement of tumor lesions. Until recently, the carcinoembryonic antigen (CEA) level of the male patient has been within normal range. The observation waiting method rather than the direct sequential surgical resection of the primary lesion in patients with advanced rectal cancer who achieved complete clinical remission (CCR) may provide a novel treatment method for rectal cancer. Thus, overall survival (OS) and quality of survival (QoS) differences between the two strategies need to be further verified by multicenter clinical trials.

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Introduction

The incidence rate of colorectal cancer ranks fourth worldwide, with about 0.8 million new cases each year, accounting for 10% of all cancer types (1). Approximately 20% of patients present with advanced metastatic disease at initial diagnosis (2). Approximately 50-60% of colorectal cancer patients may develop local or distant metastases, mostly in liver and lungs, during the course of the disease, thus seriously threatening their life (3,4). Nowadays, oncologists are committed to ensuring improved survival rates and quality of life for patients. Thus, several studies have been conducted in recent years. Previous studies conducted on patients with locally advanced rectal cancer who achieved complete clinical remission (CCR) following preoperative neoadjuvant therapy, revealed no statistical significant differences in 3-year survival and local recurrence rates between observation waiting and direct surgery (5-7). Furthermore, the quality of life of the observation waiting patients was improved. Based on these observations, many researchers hypothesize that the active observation waiting method may be considered the appropriate treatment for patients with locally advanced rectal cancer.

Currently, the effect of active observation waiting in CCR in advanced rectal cancer has not been reported. In the present case report, the patient was actively observed and waited for nearly 1 year following CCR achievement via chemoradiotherapy. No sign of tumor recurrence was observed and the patient's quality of life was not affected. These observations provide novel aspects of advanced rectal cancer management.

Case report

A 59-year-old male patient, with rectal bleeding and an Eastern Cooperative Oncology Group (ECOG) performance status

score of 0, was first admitted to the hospital in March 2018, and then followed up until May 2018. Electronic colonoscopy showed multiple polyps in the colon and rectum (Fig. 1A), whereas pathological biopsy indicated poorly differentiated rectal adenocarcinoma. The screening for rectal cancer and the evaluation of T stage were determined using positron emission tomography/computed tomography (PET/CT) and pelvic magnetic resonance imaging (MRI), respectively. The clinical stage was defined as T3N2M1a according to the TNM classification of the American Joint Committee on Cancer (AJCC) staging manual (version 8) (4). In addition, the PET/CT scan showed non-regional lymph node metastasis (subclavian). Finally, the expression of PD-L1 (-), NRAS (-), KRAS (-), HRAS (-), BRAF (-) and the microsatellite stability (MSS) were detected in rectal cancer using molecular pathological examination (Fig. 2A and B).

The male rectal cancer patient was treated with three-dimensional conformal radiotherapy (3D-CRT; dose, 60 Gy/30 Fr) and XELOX chemotherapy (200 mg oxaliplatin at day 1 plus 1.5 g capecitabine twice a day from day 1-14 for a total of 5 cycles) (Fig. 3). At the end of the first cycle, blood was not observed in the stool, and the electronic colonoscopy showed that the primary lesion was significantly shrunk and pathological type transformed into inflammation (Figs. 1B and 2C). Following XELOX chemotherapy, the carcinoembryonic antigen (CEA) levels were decreased from 282.7 to 10.3 ng/ml. One month later, CEA increased to 49.79 ng/ml (Fig. 4) and PET/CT scan revealed that the distant lymph nodes and the lymph nodes in the non-irradiated target sites were still active. Subsequentially, the residual lymph node underwent 3D-CRT (45 Gy/15 Fr) and the CEA level was further decreased to 25.58 ng/ml after 1 month. After 3 months the CEA levels were again increased to 154 ng/ml. The third PET/CT scan showed that the retroperitoneal lesion was reduced in size; however, recurrence of the pelvic lymph node was observed (Fig. 3). Therefore, the patient underwent systemic chemotherapy with FOLFIRI plus cetuximab for a total of 6 cycles. The individualized scheme gradually reduced the CEA level to 1.86 ng/ml and PET/CT re-examination indicated that the metabolism levels of the lesion returned to normal while the lesion was significantly reduced in size. Interestingly, his serum CEA level remained within normal range.

The study was approved by the Ethics Committee of the 986 Hospital of People's Liberation Army Air Force (file no. LZ 323-2018-07) and patient consent was obtained and provided.

Discussion

Currently, the median survival time of advanced rectal cancer has increased from 10 to 30 months (8). In order to ensure an increased survival time, patients and medical workers focus on improving the patient's quality of life. Thus, observation and waiting method is a challenging task for clinicians. This method may be considered a potential treatment for rectal cancer patients with unresectable concurrent metastasis, achieving CCR following preoperative neoadjuvant therapy, and especially for patients with initial diffuse lymph node metastasis.

The benefits of surgical excision of the primary lesion in advanced non-resectable rectal cancer are controversial. Faron *et al* reported that excision of primary lesions increased overall survival (OS) and progression-free survival (PFS) (9). However, a study by Cirocchi *et al* revealed that primary lesion resection did not affect OS, and lesion-related complications were not reduced in a comprehensive analysis based on large sample size (10). In addition to OS and PFS, the risk of surgery-related complications should not be ignored. Thus, previous studies have investigated the effect of primary lesion surgical resection on patients with advanced rectal cancer. The results showed that the postoperative complications, colostomy and 1-month mortality rates (for patients >65 years) were 30-50, 24 and 10%, respectively (11,12). Therefore, the surgical treatment in patients with non-resectable rectal cancer with initial simultaneous metastasis should be cautiously performed.

The rapid development of radiotherapy technology, novel cytotoxic drugs and targeted therapies have gradually weakened the therapeutic effect of surgery on advanced rectal cancer. A study has shown that FOLFIRI treatment with or without bevacizumab reduced primary lesion-related complications in patients with advanced unresectable rectal concurrent metastases without obvious obstruction or bleeding. Thus, surgical resection of the primary lesions was not recommended (13). In addition, 10-20% of patients achieved pathological complete response (pCR) following concurrent chemotherapy-radiotherapy, whereas the local recurrence, 5-year survival and disease-free survival rates were 4.6, 96 and 72%, respectively (14,15). Based on previous studies (14) and this first present case report, we hypothesize that patients exhibiting good response to systematic treatment may be treated by observing and waiting method, especially those >65 years of age. To the best of our knowledge, this is the first case study to report colorectal cancer, using the observation waiting method prior to non-surgical treatment.

Park *et al* have shown that the total survival time of patients with CCR was significantly increased compared with those without CCR (16). In the present case study, several factors contributed to the CCR achievement. Firstly, the ECOG score of the male patient case was 0 at the time of diagnosis. In addition, the immune function was basically normal prior treatment. Particularly, the number and proportion of CD8+ T and NK cells were within normal range, suggesting that immune function was not completely collapsed. This finding may explain the absence of liver or lung visceral metastasis, with only multiple lymph node metastasis observed. In addition, the patient did not suffer from other chronic diseases that could affect treatment response, such as inflammatory bowel disease, diabetes and the administration of immunosuppressive drugs (tacrolimus and cyclosporin) which demonstrated the patient had good compliance. Additionally, the treatment scheme was adjusted.

According to the 2019 National Comprehensive Cancer Network (NCCN) guidelines (version 2) (16), systemic translational treatment and local long- or short-term radiotherapy are recommended for advanced unresectable rectal cancer patients. In the present case study, the patient underwent local 3D-CRT radiotherapy [rectal lesions and pelvic lymph nodes; irradiation dose, DT, 60 Gy/30 Fr (17) followed by

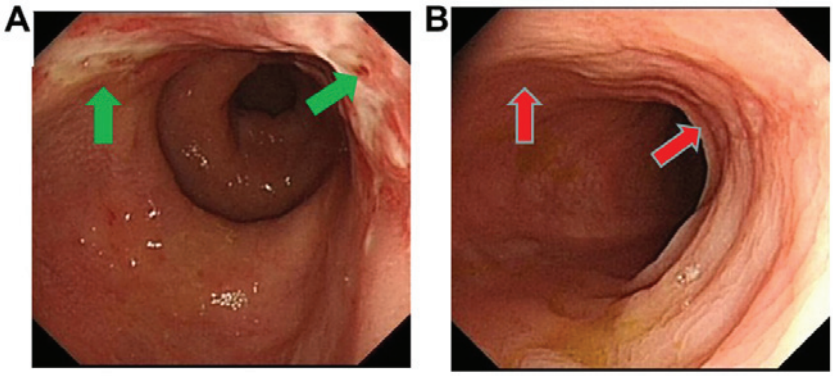


Figure 1. (A) Colonoscopy revealed the morphology and extent of the rectal lesion (cyan arrow) prior to treatment. (B) The lesion was completely disappeared and the mucosa returned to normal (red arrow) following radiotherapy and chemotherapy.

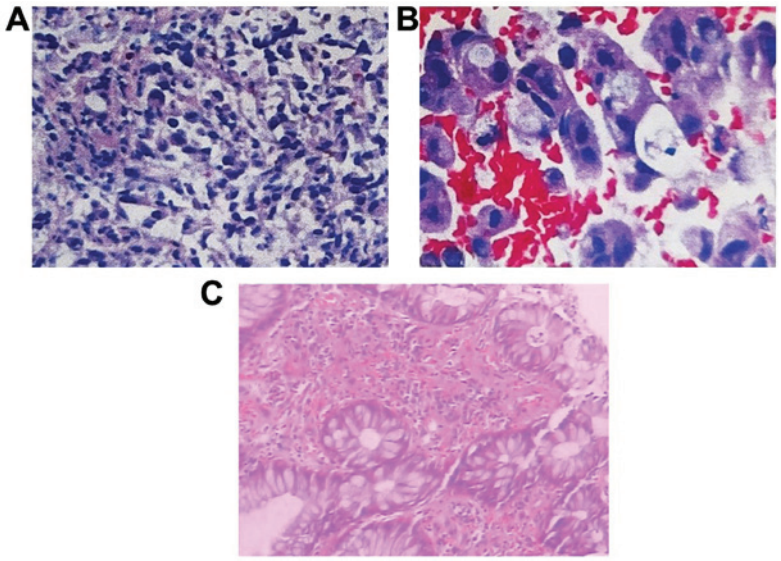


Figure 2. Pathological rectal lesion biopsy results before and after treatment. (A and B) The biopsy showed poorly differentiated rectal adenocarcinoma and PD-L1 (-), NRAS (-), KRAS (-), HRAS (-), BRAF (-) expression and MSS prior to treatment. (C) Illustrated inflammation following treatment. MSS, microsatellite stability.

XELOX (18) systemic chemotherapy. The treatment scheme reduced the local tumor load and eliminated rectal bleeding. Following radiotherapy and chemotherapy, PET/CT examination indicated that the metabolism of the primary lesion was basically returned to normal and the pathological properties of the tumor changed from poorly differentiated adenocarcinoma to high-grade intraepithelial neoplasia. Following XELOX chemotherapy, the CEA levels were decreased from 282.7 to 10.3 ng/ml. With progress of the disease, local lymph nodes recurred and distant lymph nodes still exhibited increased metabolism levels. However, primary lesions were well controlled, reflecting the beneficial effect of radiotherapy in primary rectal cancer lesions. Following chemotherapy with FOLFIRI plus cetuximab regimen (19), the residual metastatic lymph nodes were completely relieved, and CEA and metabolism levels returned to normal. Furthermore, treatment was well tolerated by the patient, with no perforation, radiation proctitis and other complications, whereas only grade II hematology and gastrointestinal toxicity was observed. In addition, in terms of tumor characteristics, the pathologic features of the patient indicated common poorly differentiated adenocarcinoma, rather than mucinous adenocarcinoma characterized by poor prognosis or hepatoid adenocarcinoma characterized by AFP expression (18,20,21). At present, there is no consensus on the prognostic impact of RAS/RAF mutations in localized disease. Douillard *et al* (22) provided new information on different aspects of the RAS/BRAF mutations, together with a combination of BRAF mutations in serum and tumor MMR status. Neoadjuvant chemotherapy may be an option in the near future and plasma mutations may serve as a tool for relevant selection. Finally, whole-body PET/CT scan and CEA levels detection was performed during the treatment process in order for disease changes to be monitored (23). When the CEA levels were abnormally elevated, a PET/CT scan was performed in order for the tumor changes to be accurately evaluated in a timely manner. Thus, an effective local and whole-body antitumor treatment was performed, which significantly improved the antitumor effects.

In summary, there are many factors that affect the efficacy of advanced rectal cancer treatment and permanently eliminate interfering factors. Individualized and accurate treatment under the suggestion of multi-disciplinary specialist

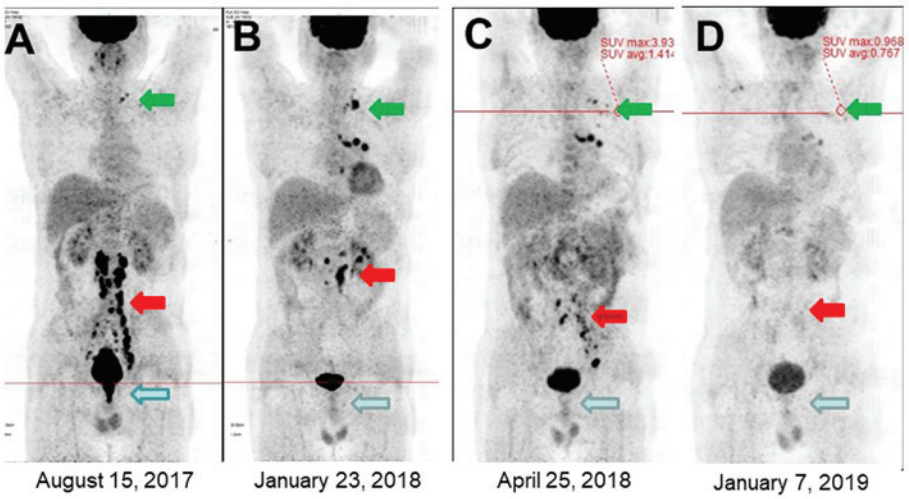
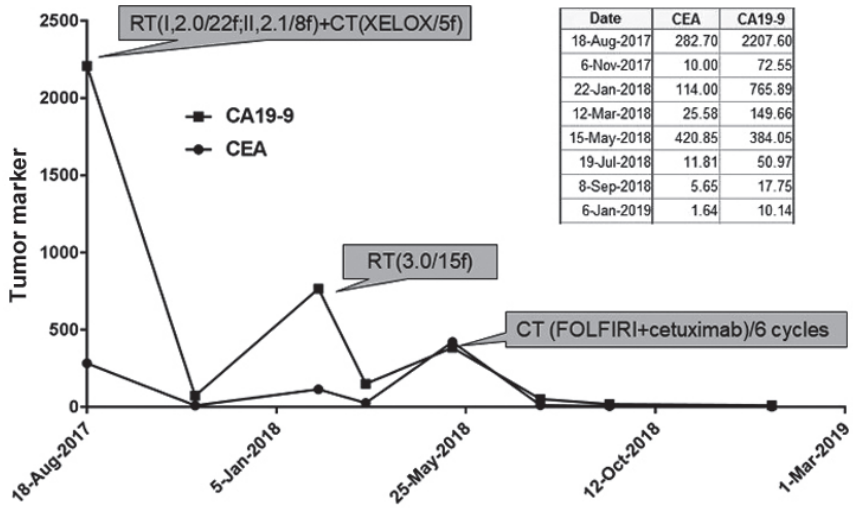


Figure 3. The course of advanced rectal cancer during treatment with the 'observe and wait' method. (A) Primary rectal tumor (green arrow), retroperitoneal metastatic (red arrow) and subclavian lymph nodes (cyan arrow) before treatment were identified using PET-CT examination. (B) The primary rectal tumor was completely shrunk and the retroperitoneal lymph node region remained partially residual. However, the number of unirradiated lesions in the subclavian lymph nodes increased following first radiotherapy. (C) The primary lesion disappeared and the subclavian lymph nodes were shrunk following radiotherapy. However, some lesions were relapsed. (D) The enlarged subclavian and retroperitoneal lymph nodes disappeared, and the primary rectal cancer lesion was completely relieved without recurrence. PET-CT, positron emission tomography/computed tomography.



Date	CEA	CA19-9
18-Aug-2017	282.70	2207.60
6-Nov-2017	10.00	72.55
22-Jan-2018	114.00	765.89
12-Mar-2018	25.58	149.66
15-May-2018	420.85	384.05
19-Jul-2018	11.81	50.97
8-Sep-2018	5.65	17.75
6-Jan-2019	1.64	10.14

Figure 4. Interventions process and changes in tumor markers in the advanced rectal cancer patient. Despite carcinoembryonic antigen (CEA) levels initially being decreased from 282.7 to 10.3 ng/ml, one month later, the CEA levels increased to 49.79 ng/ml. RT, radiotherapy; CT, chemotherapy.

is an effective strategy to improve the CCR rate. Observation and waiting method may be a new treatment approach, rather than direct sequential surgical resection of the primary lesion, for patients with advanced rectal cancer who achieved CCR after non-surgical therapy. Thus, the differences between observation and waiting method, and direct sequential surgical resection on OS and QoS need to be further verified by multicenter clinical trials.

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Availability of data and materials

Data and materials are available from correspondence author.

Authors' contributions

YD, HG, SH designed the study and contributed to the study. SH reviewed and edited the manuscript, and TQ analyzed the data and supervised the study. All authors read and agreed to the final version of the manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the 986 Hospital of People's Liberation Army Air Force (file no. LZ 323-2018-07).

Patient consent for publication

Patient consent was obtained and provided.

Competing interests

The authors declare that they have no competing interests.

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