Case Report of a Clinically Complete Response in a Rectal Cancer Patient after Chemoradiotherapy with a 2-year Watch and Wait Approach

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Abstract

Background: A non-operative treatment strategy including chemoradiation (CRT) for rectal cancer, that is to say, watch and wait, is not currently recommended in Japan. However, some rectal cancer patients show a pathologically complete response after CRT. Watch and wait has been gradually applied in the U.S. and Western countries.

Case presentation: This case report describes a case report of a clinically complete response in a rectal cancer patient after CRT with a 2-year watch and wait approach. A 40-year-old woman suffered from cancer of the lower rectum without metastasis. Preoperative neoadjuvant CRT was thought to be indicated. The total dose of preoperative radiotherapy was 50.4 Gy, which was given in a fractionated manner over a long time period (1.8 Gy × 28 Fr over 6 weeks). She took tegafur-uracil (300–500mg/day) and leucovorin (75mg/day) concurrently with radiotherapy. Two months after the end of CRT, colonoscopy showed a remarkable reduction of the tumor. Although we explained to the patient the content of the surgical therapy with lymph node dissection and the possibility of stoma creation, she refused to undergo the surgery. Therefore, we planned to perform a follow-up including measurement of tumor markers, colonoscopy, and CT. She has kept a clinically complete response for two years since the end of CRT.

Conclusions: The present case showed the possibility that a watch and wait strategy might be applicable to some rectal cancer cases.

Key words: non-operative treatment strategy, watch and wait, clinical complete response, chemoradiation, rectal cancer

Introduction

The NCCN has a guideline for locally advanced rectal cancer proposing that CRT be followed by total mesorectal excision (TME)1). Pathological complete response (pCR) rates have been reported to range from 10 to 40%2). Maas et al. demonstrated that achievement of pCR is associated with an improved outcome3). These findings raised interest in the possibility of a non-operative treatment strategy for rectal cancer. Curing cancer without removing the rectum could potentially preserve quality of life and decrease long-term functional issues. This strategy has been described with a number of terms, that is to say, “watch and wait”, “watchful waiting”, “wait-and-see”, or “non-operative management (NOM)”4). Significant morbidity is associated with TME, including postoperative complications, creation of a definitive stoma, urinary and fecal incontinence, and sexual dysfunction. With watch and wait, patients

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achieving a clinical complete response (cCR) have no immediate surgery, but instead are followed closely clinically and radiographically\(^5\). Recent studies have reported rectal preservation rates of up to 78% and similar survival for patients treated operatively\(^3\). However, challenges remain in identifying which patients would benefit the most from watch and wait. In particular, watch and wait is not common in Japan, and no reports about watch and wait have been published in Japan\(^6\).

Here, we present a case of cCR in a rectal cancer patient after CRT with a 2-year watch and wait approach.

**Case Report**

A 40-year-old woman underwent a colonoscopic examination at a clinic because of bloody stools. This showed a cancer at the lower rectum, and she was referred to our hospital.

On physical examination, digital examination showed a hard tumor of about 3.0cm in diameter at the lower rectum. Laboratory tests revealed no abnormal data, for example, no anemia (hemoglobin; 13.1g/dl) and a normal serum carcinoembryonic antigen (CEA) level of 0.6 ng/ml.

On radiologic investigation, a barium enema study showed a protrusion, 3.0cm in diameter, at the lower rectum (Fig. 1a). Colonoscopy revealed an ulcerated tumor, which was easy to bleed (Fig. 1b). An abdominopelvic CT scan showed no evidence of metastasis. Pelvic MRI showed the thickening of the rectal wall without any invasion to adjacent tissues (c: white arrow). A biopsy was obtained at colonoscopy, and the pathological report was tubular adenocarcinoma (Fig. 1d). We diagnosed the rectal cancer patient’s clinical stage as cT3N0M0, cStage II according to the Japanese Classification of Colorectal Carcinoma, eighth edition.

Fig. 1 Pre-chemoradiation examinations. Colonoscopy showed ulcerated tumor (a: dotted circle). Barium enema showed tumor, 3.0cm in diameter, at the lower rectum (b: dotted circle). MRI showed thickening of the rectal wall without any invasion to adjacent tissues (c: white arrow). Pathological report of a biopsy was tubular adenocarcinoma (d).
From these findings, preoperative neoadjuvant CRT was thought to be indicated. Under the patient's consent, CRT was planned. The total dose of preoperative radiotherapy was 50.4 Gy, which was given in a fractionated manner over a long time period (1.8 Gy × 28Fr over 6 weeks) in the supine position. Treatment planning was done using CT scans so that the clinical target volume included the primary tumor, anus, and regional lymph nodes. The regional lymph nodes included nodes around the inferior mesenteric, internal iliac, and middle rectal vessels; the presacral nodes; and the nodes around the obturator foramen. The planning target volume was defined in several planes. Cranially, the limit was defined at the level of the superior margin of L5. Caudally, the limit was defined at the level of the inferior margin of the ischial bone. This corresponded to the level of 1 cm below the anal orifice. The lateral limit was defined as 2 cm outside the bony pelvis. Dorsally, the whole sacrum and coccyx were included. Ventrally, the external iliac artery was excluded from the planning target volume. First, she began taking tegafur-uracil (500 mg/day) and leucovorin (75 mg/day) concurrently with radiotherapy. Because a decrease of white cells (Grade 2, according to Common Toxicity Criteria for Adverse Events ver. 3.0), diarrhea (Grade 2), and fatigue (Grade 2) were observed as adverse events of CRT, the daily dose of tegafur-uracil was reduced from 500 mg to 300 in the late administration period.

Two months after the end of CRT, colonoscopy showed a remarkable reduction of the tumor from 30 mm to 6 mm (Fig. 2a). The lesion was not detected by a barium enema study (Fig. 2b). We judged the change in the tumor as a clinically partial response and the rectal cancer's post CRT clinical stage as ycTisN0M0, ycStage 0. Although we explained to the patient the content of the surgical therapy with lymph node dissection and the possibility of stoma creation, she refused to undergo the surgery. Therefore, we planned to perform a follow-up including digital examination, anoscopy, measurement of tumor markers, colonoscopy, and CT (Fig. 3). Six months after the end of CRT, examinations showed no evident lesion (Fig. 4a, b). This was judged as cCR. She has kept cCR for two years since the end of CRT (Fig. 5a, b).

Discussion

The present report showed a case of cCR in a rectal cancer patient after CRT with a 2-year watch and wait approach. We searched for papers written in Japanese by the keywords 'rectal cancer', 'chemoradiation', and 'complete response' at Web Japan Medical Abstracts Society, and 24 papers were chosen. Of the 24, only four papers described the watch and wait of rectal cancer, but all of them referred to squamous cell carcinoma. No papers written in Japanese have described the watch and wait of rectal adenocarcinoma patients. In addition, we searched for papers by the keywords 'rectal cancer', 'chemoradiation', and 'complete response' at Medline, but no papers describing the watch and wait for rectal adenocarcinoma patients have been reported from Japa-
Fig. 3 The contents and frequencies of examinations during follow-up. AS: anoscopy, DE: digital examination, TM: tumor marker, CS: colonoscopy, CT: computed tomography, MRI: magnetic resonance imaging, BE: barium enema.

Fig. 4 Six months after the end of CRT, colonoscopy showed no evident lesion (a). A biopsy showed no evidence of neoplasm.

Fig. 5 One year after the end of CRT, colonoscopy showed no evident lesion (a). Eighteen months after the end of CRT, pelvic CT showed no evidence of recurrence (b).
surgery. NCCN showed a guideline for locally advanced rectal cancer proposing that CRT be followed by TME\textsuperscript{1}. In Japan, the Japanese Society for Cancer of the Colon and Rectum described that radiotherapy is used as an adjuvant therapy\textsuperscript{6}. In both guidelines, surgery is a primary treatment for rectal cancer. However, the ratio of pCR after CRT was reported to be 10-40\%.\textsuperscript{2} Achievement of pCR is associated with an improved outcome\textsuperscript{2,7}. In our data, the pCR was 10\% in patients who underwent neoadjuvant CRT and whose chemotherapy was tegafur-uracil and leucovorin\textsuperscript{8}. The 5-year cancer-specific survival rate of the pCR cases was 100\% (not published). The role of surgery in patients with pCR is being questioned because radical rectal resection causes significant morbidity and effects on quality of life\textsuperscript{7}.

Recently, increasing numbers of reports about watch and wait and NOM have been published overseas\textsuperscript{4,5,7,9-11}. The watch and wait approach for patients with rectal cancer who achieved cCR after neoadjuvant CRT was initially described by Brazilian investigators. In an updated series published in 2013, 69 patients concluded extended CRT (54 Gy, 5-FU/leucovorin 6 cycles), 47 (68\%) patients had initial cCR, and 35 (50\%) patients never underwent surgery\textsuperscript{5}. Maas et al. prospectively selected 21 rectal cancer patients with cCR after CRT and compared them with a control group of patients with pCR after surgery\textsuperscript{3}. Only one patient (5\%) developed a local recurrence, but 20 (95\%) were alive without disease. The oncologic outcome after watch and wait was comparable with that of patients with pCR after surgery, and the functional outcome in the watch and wait group was significantly better. In Table 1, the recurrence rates in watch and wait studies are summarized\textsuperscript{3,5,11-13}.

Table 1 Recurrence rate in watch-and-wait studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Recurrence rate</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renehan</td>
<td>2016</td>
<td>34% (44/129)</td>
<td>12</td>
</tr>
<tr>
<td>Creavin</td>
<td>2016</td>
<td>9% (4/45)</td>
<td>13</td>
</tr>
<tr>
<td>Habr-Gama</td>
<td>2013</td>
<td>25% (12/47)</td>
<td>10</td>
</tr>
<tr>
<td>Smith</td>
<td>2012</td>
<td>19% (6/32)</td>
<td>11</td>
</tr>
<tr>
<td>Maas</td>
<td>2011</td>
<td>5% (1/21)</td>
<td>3</td>
</tr>
</tbody>
</table>

Which patients will benefit most from watch and wait? Bitterman et al. reported that 5 factors, that is to say, a lower CEA level at diagnosis, decreased tumor size, decreased distance from the anal verge, node-negative disease at diagnosis, and a larger interval from CRT to surgery were predictors for CR after CRT\textsuperscript{2}. Our case fulfilled 4 of the above 5 requirements. Ellis et al. assessed U.S. national trends in NOM and reported that NOM use doubled from 2.4\% in 1998 to 5\% in 2010\textsuperscript{14}. Although NOM use has spread in the U.S., they pointed out the problems of NOM. They reported that NOM use increased more frequently in black and uninsured/Medicaid patients, and the increase in NOM might actually represent increasing disparities in rectal cancer care rather than innovation.

How long is a critical time for recurrence after CRT? Smith, et al. showed that isolated local recurrence was the most common type of relapse and suggested that the critical time frame was the first 14 months after CRT\textsuperscript{11}. Habr-Gama et al. reported that local recurrences occurred more frequently during the initial 12 months of follow-up, whereas late recurrences were less common\textsuperscript{5}. They suggested that the first year after CRT was important for local recurrence. As for our case, more than two years have passed since the end of CRT.

When the oncologic outcome and the treatment-related morbidity and mortality are taken into consideration, watch and wait could be useful for the elderly and for patients with comorbidity\textsuperscript{9,15}. In clinical practice, however, younger patients have strong hopes of anus preserving therapy or watch and wait. Indeed, our case was a young, 40-year-old woman without comorbidity, and she hoped for watch and wait. Smith et al. have started a multi-institutional phase II randomized control study on NOM in locally advanced rectal cancer\textsuperscript{9}. More individually tailored treatments are expected to be established.

Conclusions
We experienced a patient with a clinically complete response for rectal cancer after chemoradiotherapy with a 2-year watch and wait approach. Watch and
wait may be applicable for some patients with rectal cancers achieving cCR. A clinical study of watch and wait may be feasible to evaluate its efficacy in Japanese rectal adenocarcinoma patients.

**Abbreviations**

**Author’s contributions**
MK treated the patient, gathered the patient’s data and wrote the manuscript. OK, OY, MY, TM, FY, AT, HA, SR, HT, OK, TT, TJ, IH, NK and FS had a hand in the daily medical treatment for the case. SY and KF were responsible for histopathological diagnosis. HY represented our surgical department and supervised the writing of the manuscript. All authors significantly contributed to this study and approved the final manuscript.

**Consent for publication**
Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of interest: None.

**References**