Int J Colorectal Dis (2016) 31:413–419
DOI 10.1007/s00384-015-2460-y

ORIGINAL ARTICLE

Rectal cancer with complete clinical response after neoadjuvant chemoradiotherapy, surgery, or "watch and wait"

Chien-Liang Lai[1] · Mei-Ju Lai[2] · Chang-Chieh Wu[1] · Shu-Wen Jao[1] · Cheng-Wen Hsiao[1]

Accepted: 19 November 2015 / Published online: 25 November 2015

Abstract
Purpose The purpose of this study was to compare the outcomes of patients treated with chemoradiotherapy with a complete clinical response followed by either a "watch and wait" strategy or a total mesorectal excision.
Methods This was an observational retrospective study from a single institute. Patients with locally advanced rectal cancer following chemoradiotherapy with a complete clinical response from January 1, 2007 to December 31, 2014 were included.
Results The study population consisted of 18 patients who opted for a "watch and wait" policy and 26 patients who underwent radical surgery after achieving a complete clinical response. Patients had no documented treatment complications under the watch and wait policy, while 13 patients who underwent radical surgery experienced significant morbidity. There were two local recurrences in the watch and wait group; both were treated with salvage resection and had no associated mortality. In the radical surgery group, 1 patient showed an incomplete pathologic response (ypT0N1), and the remaining 25 patients showed complete pathologic responses; 1 had a distant recurrence, which was managed non-operatively, and 2 patients died of unrelated causes. The 5-year overall survival rate and median disease-free survival time were 100 % and 69.78 months in the watch and wait group and 92.30 % and 89.04 months in the radical surgery group.
Conclusions A watch and wait policy avoids the morbidity associated with radical surgery and preserves oncologic outcomes in our retrospective study from a single institute. It could be considered a therapeutic option in patients with locally advanced rectal cancer following chemoradiotherapy with a complete clinical response.

Keywords Chemoradiotherapy · Rectal cancer · Complete clinical response · Watch and wait

Introduction

Up to 70 % of patients with non-metastatic rectal cancer present with locoregionally advanced disease [1]. Locally advanced rectal cancer (LARC) is generally defined as stage II and III rectal cancer. Neoadjuvant chemoradiotherapy (CRT) followed by a total mesorectal excision (TME) remains the globally accepted method for the management of rectal LARC [2].

With TME, the incidence of morbidity ranges from 6 to 35 %, which includes anastomotic leaks, blood loss, and sexual dysfunction resulting from the procedure. In addition, the mortality rate reaches up to 2 % [3]. The length of hospital admissions ranges from 8 to 15 days [4–6]. There are also compelling data regarding the effect of resections on patients' quality of life; deterioration in bowel function is common following anterior resection, and patients with low-lying cancers may require a permanent stoma, which would be associated with psychological morbidity [7].

Neoadjuvant CRT has become the standard treatment for patients with LARC, allowing for a reduction in local

✉ Cheng-Wen Hsiao
dtdrummer@gmail.com

[1] Division of Colon and Rectal Surgery, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, No. 325, Cheng-Kung Rd, Sec 2, Neihu 114, Taipei, Taiwan, Republic of China

[2] Division of Clinical Pathology, Department of Pathology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, Republic of China

recurrence and an increase in sphincter preservation [8, 9]. Neoadjuvant CRT followed by surgery 6–8 weeks later may result in a complete pathologic response (cPR) in up to 15–30 % of cases [10], and it is also associated with a better oncologic outcome.

New trends have suggested the possibility of neglecting planned surgical resections after neoadjuvant treatment in cases of extensive tumor response. In addition, more studies have addressed the use of a non-operative "watch and wait" policy in patients with a complete clinical response (cCR) [8, 9]. There is growing evidence showing that regimented clinical assessment after CRT can identify patients with cCR, allowing for the avoidance of immediate radical surgery while preserving good oncologic outcomes.

To evaluate the benefit of a watch and wait policy in patients with cCR treated with pre-operative CRT, we compared the oncologic results of a group of patients with cCR followed with a watch and wait policy versus those followed with radical surgery at our institute.

Materials and methods

Study inclusion and design

The study group consisted of a consecutive series of patients treated at Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, Republic of China, from 2007 to 2014 for primary rectal cancer (up to 10 cm from the anal verge). All the patients had biopsy-verified rectal adenocarcinoma. This study was approved by the Institutional Review Board of the Tri-Service General Hospital (TSGHIRB No.: 2-103-05-076). Informed consent was obtained from all the patients.

Pre-treatment oncological staging comprised abdominal imaging (computed tomography [CT] or magnetic resonance imaging [MRI]), and tumor marker analysis (carcinoembryonic antigen [CEA] and cancer antigen [CA] 19–9 levels). As a general rule, the highest stage for each parameter evaluated (T, N, circumferential margin, involvement of adjacent organ, M) was considered to be the definitive pre-treatment stage [11, 12].

Patients selected for neoadjuvant CRT were required to meet all the following criteria: (a) a biopsy-proven rectal adenocarcinoma, (b) a tumor location up to 10 cm from the anal verge. (c) a primary clinical stage of II–III, and (d) an Eastern Cooperative Oncology Group performance status of 0–2 [2].

5-Fluorouracil (5-FU), as a single drug or in combination with other drugs (leucovorin, carboplatin, or oxaliplatin), was administered by bolus or continuous venous infusion. During this study, a single standard regimen was used; initially, 5-FU was administered as a bolus (350 mg/m^2/day) with a low-dose leucovorin bolus (10 mg/m^2/day) for 5 days on days 1–5 and 29–33 in combination with radiotherapy (45 Gy in 25 fractions or 54 Gy in 30 fractions) [13].

Patients were assessed for their tumor response 8–12 weeks after the completion of chemoradiotherapy with the same clinical and radiologic tools used in the baseline assessment of the tumor extent. All patients who were considered clinical complete responders according to rigorous criteria of clinical, endoscopic, and radiologic findings were treated without immediate radical surgery. The three criteria for cCR were (a) the absence of a residual ulceration, mass, or mucosal irregularity upon clinical/endoscopic assessment; (b) whitening of the mucosa and the presence of neovasculature (telangiectasia); and (c) radiologic imaging, such as CT, transrectal ultrasonography (TRUS), or MRI, without evidence of extrarectal residual disease, which were necessary for patients to be considered to have cCR [14]. For example, lymph nodes <5 mm in their transverse diameter, or absence of irregular borders were considered negative for metastases, on standard T2-weighted MRI study or on CT scans. In addition, there was no evidence of hypoechoic, inhomogeneous lesion with irregular borders; thickening or destruction of the bowel wall under TRUS was also considered negative for extrarectal disease. The presence of clinical or endoscopic features of an incomplete response to CRT and the radiologic evidence of residual disease within the mesorectum were diagnostic of an incomplete clinical response, and therefore, radical surgery was recommended.

Experienced pathologists handled the pathologic evaluation of resected rectum specimen. The evaluation including (a) recording the length and the diameter of the rectum; (b) looking for and documenting the presence and appearance of any visible or palpable lesion and its location relative to the margins and to any landmarks; (c) dissecting the mesentery and thin section of the mesenteric fat, and examining and palpating each section for lymph nodes; and (d) submitting for histology the entire tumor site, each identified lesion, and lymph node. The percentage of pathological response ranged from no evidence of treatment effect (0 %) to complete regression with no viable tumor cells identified (100 %) and ypT0, corresponding to a percentage of pathological response of 100 %.

We identified 829 patients with biopsy-proven rectal adenocarcinoma. Next, medical records were queried for primary clinical stage, complete CRT therapy, and surgery status; 562 patients were excluded because of stage I and IV disease (n= 200, and 137, respectively), failed in finishing the CRT (n= 103), and surgery without CRT (n=122). Thus, 267 patients remained.

Of these, 223 patients were also excluded because of an incomplete clinical response. Only 44 patients with LARC undergoing complete CRT with cCR at our institute were included in the study (Fig. 1). In all cases, the decision to employ a watch and wait policy or to perform radical surgery was made after thorough discussions between the surgeon and the

Method and Material

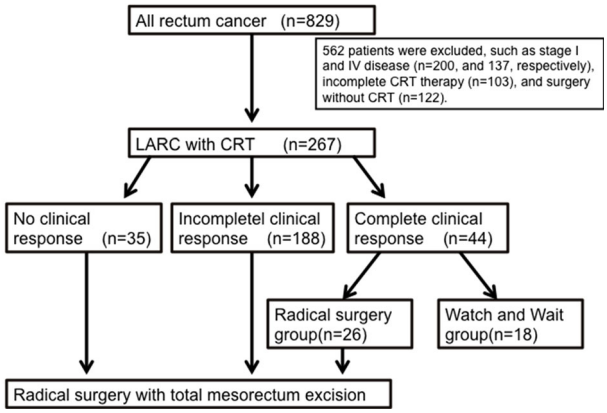

Fig. 1 Flowchart of patient selection

patient. Patients in the watch and wait group were informed that disease recurrence might occur at any moment during the follow-up period. If positive nodes were identified, radical surgery would be advised. Local recurrence was defined as the presence of adenocarcinoma within the rectal wall, with negative nodes, and no distal metastases on imaging. Patients with local recurrence were referred for transanal wide excision.

All patients with cCR were evaluated with outpatient visits every 3 months by a single experienced colorectal surgeon who performed a clinical examination in addition to a rigid proctoscopy or colonoscopy (Fig. 2). Biopsy was utilized selectively on any residual nodularity or scarring on exam. CEA levels were measured at the time of restaging (after finishing CRT at 8–12 weeks) and every 3 months thereafter. At the third year of follow-up, patients were examined every 6 months. The CEA cutoff value is ≤5 ng/dl at our institute, which has been demonstrated to have significant prognostic value in some studies [15]. A radiologic imaging modality (including chest radiography, CT scans, and MRI) was used to exclude mesorectal disease and systemic status after 6 months and annually thereafter. CT scans were routinely obtained for all patients.

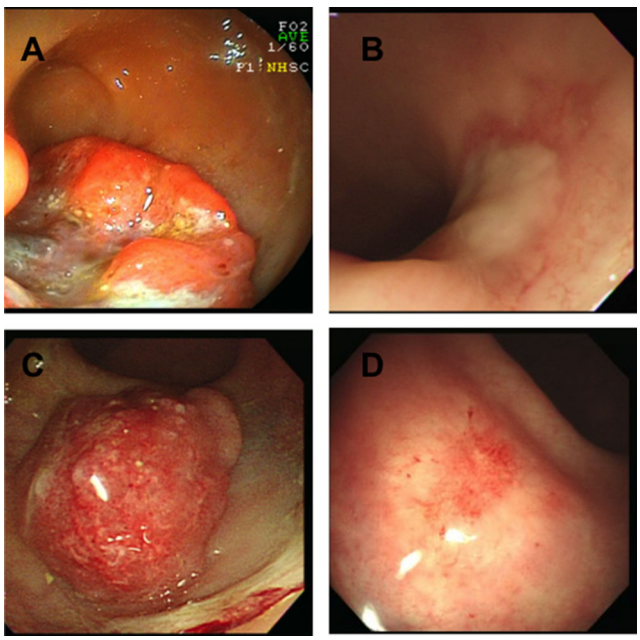

Fig. 2 Colonoscopic findings in the patient with complete clinical response. **a**, **b** The lesions pre- and post-chemoradiotherapy from one patient respectively. **c**, **d** The lesions pre- and post-chemoradiotherapy from another patient respectively. **a**, **c** One huge reddish polypoid mass occupying the lumen of the colon. **b**, **d** A whitening lesion without ulceration or mucosal irregularity and presence of neovasculature

Statistical analysis

For each patient, CEA levels were evaluated at diagnosis, after CRT, and every 3 months during follow-up. The mean CEA levels are presented in Table 1. Univariate associations between categorical variables were assessed using Fisher's exact test. The 5-year overall survival and disease-free survival rates were calculated with the Kaplan–Meier method (Fig. 3). The statistical analyses were performed using SPSS software (ver. 15.0, SPSS Inc., Chicago, IL, USA).

Results

A total of 44 patients with LARC underwent CRT with a cCR during the study period. We identified 18 patients who were treated with active surveillance, classified as the watch and wait group, and 26 patients who underwent TME, known as the radical surgery group. Of these 26 patients, 17 underwent lower anterior resection (LAR), 6 underwent LAR with diverting loop stoma, and 3 received abdominoperineal resection (APR). The watch and wait group tended to be slightly older than the radical surgery group (67.58 vs. 63.78 years, respectively, $p=0.792$). The majority of patients included in this study were men (men, 61.36 %, 27/44; and women, 38.64 %, 17/44), and of the male patients, 55.55 % (15/27) were included in the watch and wait group, whereas only 17.64 % (3/17) of the female patients were in the watch and wait group ($p=0.26$). The distance of the tumor from the dentate line was 3.55 and 4.61 cm in the watch and wait and radical surgery groups, respectively. The demographic and clinical characteristics of the study group are reported in Table 1.

The mean follow-up time was 49.92 and 42.28 months, for the watch and wait and radical surgery groups, respectively. There were no major complications documented related to the watch and wait group, while 13 patients developed post-operative complications in the radical surgery group. Three patients had complications related to their diverting stoma; one developed hypovolemic shock requiring fluid resuscitation, while two parastomal hernias

Table 1 Demographic and clinical characteristics of the study group

	Radical surgery group *N* (%)/mean (SD)	"Watch and wait" group *N* (%)/mean (SD)	*p* value
Gender			
Men	12 (46.15)	15 (83.33)	0.26
Women	14 (53.85)	3 (16.67)	
Pretreatment stage			
2	8 (30.8)	11 (61.1)	0.52
3A	2 (7.7)	4 (22.2)	
3B	15 (57.7)	2 (11.1)	
3C	1 (3.8)	1 (5.6)	
Age	63.78 (14.05)	67.58 (15.20)	0.79
Mean follow-up (months)	42.28 (17.92)	49.92 (21.93)	0.08
Distance from dentate line (cm)	4.81	3.35	0.15
Recurrence			0.27
Local	0	2	
Distant	1	0	
CEA level			
Pre-CRT CEA	3.75 (4.63)	1.94 (1.08)	0.11
Post-CRT CEA	1.97 (0.92)	2.31 (1.34)	0.31
CEA 0.5y	1.51 (0.55)	1.97 (1.57)	0.18
CEA 1y	1.87 (0.86)	1.98 (1.18)	0.75
CEA 1.5y	1.78 (0.74)	2.08 (0.93)	0.35
CEA 2y	2.27 (0.82)	2.17 (0.81)	0.80
CEA 2.5y	2.19 (0.89)	2.03 (0.44)	0.69
CEA 3y	2.58 (1.29)	2.06 (0.35)	0.46

Values are expressed as *N* (%) of patients, unless otherwise specified

cTNM clinical tumor stage, *yp* pathological tumor staging after neoadjuvant therapy, *CRT* chemoradiation therapy, *SD* standard deviation, *pre-CRT CEA* CEA level at pre-CRT status, *post-CRT CEA* CEA level at complete CRT within 8 weeks, *CEA 0.5y* CEA level after complete CRT 6 months, *CEA 1y* CEA level after complete CRT 1 year, *CEA 1.5y* CEA level after complete CRT 1.5 years, *CEA 2y* CEA level after complete CRT 2 years *CEA2.5y* CEA level after complete CRT 2.5 years, *CEA3y* CEA level after complete CRT 3 years

required elective repair. Five patients developed surgical site infections, and one had an intra-abdominal abscess requiring percutaneous drainage. One patient had an anastomotic stricture solved with a diverting stoma, and three patients were documented with poor functional outcomes related to LAR syndrome.

During the follow-up for the watch and wait group, the disease-free survival time at the median follow-up was

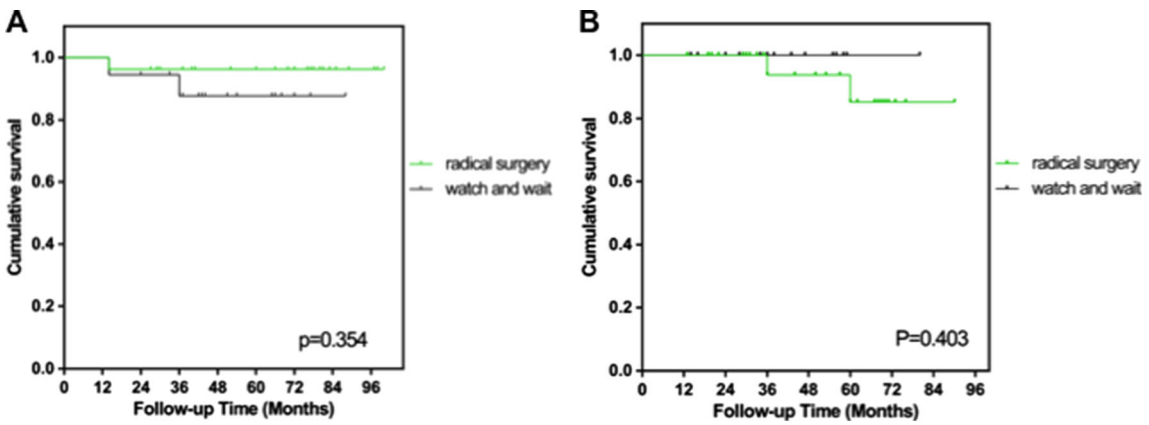

Fig. 3 **a** Disease-free survival and **b** overall survival for patients with a clinical complete response following "watch and wait" policy and patients following "radical surgery"

69.78 months, and the 5-year overall survival rate was 100 % (Fig. 3). No distant metastasis was observed; local recurrence occurred in two patients, which was treated with transanal wide excision with no associated post-operative complications at 14 and 36 months, and the pathology reports were restricted to ypT1. For each patient, CEA levels were evaluated at diagnosis, after CRT, and every 3 months during the follow-up period (Table 1).

The disease-free survival time of the radical surgery group was 89.04 months, and the 5-year overall survival rate was 92.30 %. Twenty-five patients in this group reached cPR after radical surgery with TME; one patient, whose primary stage was cT3N2, presented with ypT0N1 after radical surgery. No local recurrence was found. One patient developed a single pulmonary metastasis that was treated with wedge resection at 14 months after radical surgery; this patient currently has no evidence of disease during follow-up. Two patients died of unrelated causes at 36 and 60 months after surgery, respectively; one had cardiovascular disease and one had an intracranial hemorrhage. There was no difference in disease-free survival (p=0.354) or 5-year survival rate (p=0.403) between the groups (Fig. 3).

Discussion

Compared with patients with cCR treated with radical surgery with TME, those treated with a watch and wait policy benefit from avoiding the immediate and long-term morbidity associated with a major operation. While patients may complain about the strict surveillance schedule, the oncologic outcome was significant at our institute.

In our study, the watch and wait group showed a much lower number of rectal tumors compared to those treated with radical surgery. We presumed that radical surgery for distal rectal cancer was APR with a permanent stoma, and many patients in the watch and wait group showed a strong desire to avoid a permanent stoma. In the radical surgery group, APR was performed on only 11.53 % (3/26) of patients, and the rest had LAR with/without a diverting stoma 88.47 % (23/26). We assumed that patients with cCR after CRT were more likely to refuse a permanent stoma, instead opting for the watch and wait policy, especially those who could not maintain bowel continuity after a curative resection such as APR. Our data also showed that radical surgery with TME carries a significant risk of post-operative complications. The results of our study should encourage further investigations to standardize the criteria of cCR, which allow practitioners the ability to more reliably identify patients who are candidates for the watch and wait policy. If diagnostic and treatment strategies can be standardized, then perhaps future patients, such as the cPR patients in our study, can avoid the morbidity associated with radical surgery while preserving optimal long-term oncologic outcomes.

The treatment of patients with cCR after CRT remains controversial. Previous clinical trials have also demonstrated that patients with cCR after CRT have both better oncological outcomes and lower rates of mesorectal lymph node metastases [12]; a watch and wait policy and organ-sparing strategies have been advocated in such patients [16–18]. The use of alternative treatment strategies without TME is desirable to avoid the significant post-operative morbidity, unnecessary enterostoma, and negative outcome. A watch and wait policy avoids post-operative complications and minimizes the risk of adverse functional outcomes in patients with cCR [16–18]. However, a watch and wait policy after CRT requires that cCR be accurately identified using patients' clinical and radiologic features.

The clinical assessment of tumor response is a major concern for individualized patient management. Patients would be viewed as having a cCR if no visible or palpable irregularity nodules were found clinically. Habr-Gama et al. have detailed the clinical and endoscopic findings of patients with cCR; their findings include the whitening of the mucosa in the rectum, any telangiectasia, and a subtle loss of pliability of the rectal wall harboring the scar. cCR has also been described as the absence of positive signs of residual disease. An incomplete clinical response is considered in the presence of a deep ulceration with or without a necrotic ulceration, a palpable nodule, even with complete mucosal integrity, or any significant stenosis [14].

Current imaging techniques (TRUS, CT, and MRI) have been reported to be far less accurate while restaging rectal cancer after CRT. [8, 19] A CRT course may extensively modify cancer tissue and the surrounding structures, including overgrowth fibrosis, wall thickness, muscle disarrangement, tumor necrosis, calcification, and inflammatory infiltration [13].

Interestingly, Pomerri et al. also produced generally disappointing findings for the positive predictive value of lymph node status on TRUS, CT, and MRI, but the negative predictive value (NPV) was significant (TRUS, 95 %; CT, 93 %; MRI, 95 %) [20], indicating that it may be useful for the prediction of LN-negative status. It also provides strong evidence for the classification of negative lymph node status in our study; however, T status is much easier to evaluate via digital examination and colonoscopy with/without biopsy.

To avoid unnecessary surgery for LARC with cCR after CRT, the clinical assessment of post-CRT staging should be optimized. The diagnosis in our study was standardized, and patients were generally required to meet all the following criteria to be considered to have cCR: (a) the absence of a residual ulceration, mass, or mucosal irregularity during a digital examination and colonoscopy assessment; (b) whitening of the mucosa and the presence of neovasculature; and (c)

radiologic imaging (CT, TRUS, or MRI) that showed no evidence of extrarectal residual disease. In our study, three experienced attending colorectal surgeons assessed clinical responses to pre-treatment therapy in each patient. For this reason, these subsets of patients were strictly adhering to the criteria described above; those with incomplete tumor regression were excluded.

Our study group showed an overall initial cCR rate of 16.48 % (44/267), which was similar to the rates of 15–30 % reported in some previous studies [10, 21]. In the radical surgery group, 25 patients showed cPR in the final pathologic reports; however, one patient presented with ypT0N1, with 1 positive in the 13 retrieved lymph nodes, and a primary tumor that was classified as cT3N2M0, stage IIIC. The concordance rate was 96.15 % (25/26) for initial cCR to be cPR, which was similar to the result for NPV under TRUS, CT, and MRI [20]. We assumed that patients whose primary tumor was staged as $N \geq 2$ with a rapid response to CRT should receive two different imaging modalities to exclude the presence of micro-metastases. We supposed that this might be the key to accurately predicting cCR while using imaging modalities with the advantage of the NPV for determining lymph node status.

Follow-up included outpatient visits every 3 months by three experienced colorectal surgeons consisting of a clinical and digital rectal examination in addition to a rigid proctoscopy or colonoscopy. A radiologic imaging modality (including CT scans, MRI, and TRUS) was used to exclude mesorectal disease and to evaluate the systemic status after 6 months and annually thereafter. CEA levels were obtained every 3 months. After 2 years of follow-up, patients were examined every 6 months. Although several molecular tumor markers have been described over the past years, only CEA remains clinically significant for staging colorectal cancer [22]. The role of CEA in determining prognosis for colorectal cancer has been well documented, not only in patients with locally advanced disease but also in those with metastatic disease [15]. One study suggested that patients with a low CEA level after CRT are more likely to achieve a cCR and have a better outcome [16]. Previous studies showed that neoadjuvant CRT may provide significant local tumor control, as reflected by the significant downstaging and cancer cell necrosis resulting from increasing doses of radiation (and possibly chemotherapy). Therefore, the post-CRT CEA status could reflect the effectiveness of neoadjuvant CRT. [15] In our data, all patients presented with low CEA levels <5 ng/dl at their post-CRT follow-up (including post-CRT and 0.5, 1, 1.5, 2, 2.5, and 3 years of follow-up time, Table 1).

In the present study, the disease-free survival time of the watch and wait and radical surgery groups was 69.28 and 89.04 months, respectively, and the 5-year overall survival rates were 100 and 92.30 %, respectively. Compared to previous studies, we had similar disease-free survival and 5-year survival rates in the watch and wait and radical surgery groups. Two local recurrences were found in the watch and wait group; no local recurrence and one distant pulmonary metastasis were noted in radical surgery group. Previous studies [14, 16] had a higher rate of local recurrence than that observed in our study. This might be attributable to the differences in subjective classification of cCR between individual surgeons at each institution. If our criteria for cCR tended to be more rigorous, it could lead to lower rates of local recurrence. Radhika et al. [23] also showed significant oncological outcomes in a watch and wait group, but their data population did not completely fulfill the criteria of LARC, and patients with pre-treatment TNM stage I and IV were also enrolled into the study; in addition, they did not describe the cPR group with initial cCR. This is the first retrospective study for patients with initial cCR comparing the oncologic outcomes between watch and wait and radical surgery groups.

There were some limitations in our study. First, our approach was primarily retrospective, with a limited sample size and with patients from a single institution. Second, tumor recurrences should be considered in patients with LARC with cCR under the watch and wait policy. Habr-Gama et al. demonstrated that local recurrence may develop in 31 % of patients with an initial cCR and that more than half of these recurrences develop within 12 months of follow-up. Salvage therapy is possible in 90 % of recurrences, resulting in 94 % local disease control and 78 % organ preservation [9]. Third, during the 7 years of the study, the imaging modalities to stage rectal cancers have improved radically, while the ability to deliver radiation therapy has also evolved dramatically. Therefore, different protocols of CRT and pre-operative staging have been used over time. Fourth, a notable weakness is that patient selection into the watch and wait or radical surgery group was not randomized. The decision to treat with a watch and wait policy was mostly driven by patients' preference for the avoidance of radical surgery with TME and permanent stoma creation. Moreover, low post-CRT CEA status may be associated with increasing rates of cCR. However, all the 44 patients (100 %) with cCR in this group had low pre-CRT CEA levels, but we could not confirm that pre-CRT CEA levels were a significant predictor of cCR.

Conclusion

This study may suggest the validity of a watch and wait policy in patients with LARC with cCR after CRT. Meticulous follow-up may play an important role in cases of cCR after CRT. In addition, a low post-CRT CEA level was strongly related to cCR in this study. If local recurrence is present after CRT, transanal wide excision may be performed as salvage treatment. From our limited experience, the patients who experienced the watch and wait policy in the cCR group may have benefitted from avoiding radical surgery, and they

retained significant oncologic outcomes in terms of disease-free survival and overall survival. A watch and wait policy is a safe option for LARC after CRT with cCR. Our data also suggested that the validation of NPV with current imaging modalities might be the key to be precisely predicting cCR. Further prospective and multi-institutional studies are necessary to confirm the safety of the watch and wait policy and to create evidence-based guidelines for surgeons for the treatment of patients with cCR.

Acknowledgments We are grateful to the Cancer Registry Group of Tri-Service General Hospital from offering its data pool for the analysis.

Authors' contributions Chien-Liang Lai, MD, Chang-Chieh Wu, MD, and Shu-Wen Jao, MD, reviewed the data and prepared the initial manuscript draft, and Mei-Ju Lai, MD, participated in the initial workup of the case described herein, and reviewed the data. Mei-Ju Lai, MD, assisted Chien-Liang Lai, MD, in preparing the final version of the manuscript. Cheng-Wen Hsiao, MD, has been involved in revising it critically for important intellectual content and have given final approval of the version to be published; Chien-Liang Lai, MD, and Cheng-Wen Hsiao, MD, agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors state that there are no financial or personal relationships with other people or organizations that could inappropriately influence this work.

References

1. Gunderson LL, Jessup JM, Sargent DJ, Greene FL, Stewart A (2010) Revised tumor and node categorization for rectal cancer based on surveillance, epidemiology, and end results and rectal pooled analysis outcomes. J Clin Oncol 28(2):256–263
2. Pomerri F, Maretto I, Pucciarelli S et al (2009) Prediction of rectal lymph node metastasis by pelvic computed tomography measurement. Eur J Surg Oncol 35(2):168–173
3. Solanki AA, Chang DT, Liauw SL (2013) Future directions in combined modality therapy for rectal cancer: reevaluating the role of total mesorectal excision after chemoradiotherapy. Onco Target Ther 6:1097–1110
4. Hartley JE, Mehigan BJ, Qureshi AE, Duthie GS, Lee PW, Monson JR (2001) Total mesorectal excision: assessment of the laparoscopic approach. Dis Colon Rectum 44(3):315–321
5. Lujan J, Valero G, Hernandez Q, Sanchez A, Frutos MD, Parrilla P (2009) Randomized clinical trial comparing laparoscopic and open surgery in patients with rectal cancer. Br J Surg 96(9):982–989
6. Asoglu O, Kunduz E, Rahmi Serin K et al (2014) Standardized laparoscopic sphincter-preserving total mesorectal excision for rectal cancer: long-term oncologic outcome in 217 unselected consecutive patients. Surg Laparosc Endosc Percutan Tech 24(2):145–152
7. Kasparek MS, Hassan I, Cima RR, Larson DR, Gullerud RE, Wolff BG (2012) Long-term quality of life and sexual and urinary function after abdominoperineal resection for distal rectal cancer. Dis Colon Rectum 55(2):147–154
8. De Nardi P, Carvello M (2013) How reliable is current imaging in restaging rectal cancer after neoadjuvant therapy? World J Gastroenterol 19(36):5964–5972
9. Habr-Gama A, Gama-Rodrigues J, São Julião GP et al (2014) Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. Int J Radiat Oncol Biol Phys 88(4): 822–828
10. Dedemadi G, Wexner SD (2012) Complete response after neoadjuvant therapy in rectal cancer: to operate or not to operate? Dig Dis 30(Suppl 2):109–117
11. Mark D, Joon DL, Chao M et al (2010) The use of PET in assessing tumor response after neoadjuvant chemoradiation for rectal cancer. Radiother Oncol 97(2):205–211
12. Pucciarelli S, Capirci C, Emanuele U et al (2005) Relationship between pathologic T-stage and nodal metastasis after preoperative chemoradiotherapy for locally advanced rectal cancer. Ann Surg Oncol 12:111–116
13. Pucciarelli S, Friso ML, Toppan P et al (2000) Preoperative combined radiotherapy and chemotherapy for middle and lower rectal cancer: preliminary results. Ann Surg Oncol 7:38–44
14. Habr-Gama A, Perez RO, Nadalin W et al (2004) Operative versus non-operative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 240:711–718
15. Perez RO, São Julião GP, Habr-Gama A et al (2009) The role of carcinoembriogenic antigen in predicting response and survival to neoadjuvant chemotherapy for distal rectal cancer. Dis Colon Rectum 52:1137–1143
16. Smith JD, Ruby JA, Goodman KA et al (2012) Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy. Ann Surg 256(6):965–972
17. Park JS, Jang YJ, Choi GS et al (2014) Accuracy of preoperative MRI in predicting pathology stage in rectal cancers: node-for-node matched histopathology validation of MRI features. Dis Colon Rectum 57(1):32–38
18. Maas M, Beets-Tan RG, Lambregts DM et al (2011) Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol 29:4633–4640
19. Martellucci J, Scheiterle M, Lorenzi B et al (2012) Accuracy of transrectal ultrasound after preoperative radiochemotherapy compared to computed tomography and magnetic resonance in locally advanced rectal cancer. Int J Colorectal Dis 27(7):967–973
20. Pomerri F, Pucciarelli S, Maretto I et al (2011) Prospective assessment of imaging after preoperative chemoradiotherapy for rectal cancer. Surgery 149:56–64
21. Hiotis SP, Weber SM, Cohen AM et al (2002) Assessing the predictive value of clinical complete response to neoadjuvant therapy for rectal cancer: an analysis of 488 patients. J Am Coll Surg 194(2):131–135, discussion 135–6
22. Park YA, Lee KY, Kim NK et al (2006) Prognostic effect of perioperative change of serum carcinoembryonic antigen level: a useful tool for detection of systemic recurrence in rectal cancer. Ann Surg Oncol 13:645–650
23. Smith RK, Fry RD, Mahmoud NN, Paulson EC (2015) Surveillance after neoadjuvant therapy in advanced rectal cancer with complete clinical response can have comparable outcomes to total mesorectal excision. Int J Colorectal Dis 30(6):769–774. doi: 10.1007/s00384-015-2165-2