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A Complete Pathological Response to Neoadjuvant Chemoradiotherapy in A Young Female with Local-Progressed Low Rectal Cancer Following 'Wait-And-Watch' Surveillance: A Case Report

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1. Abstract

Low rectal cancer is a common malignant tumor around the world, and the incidence rate is increasing over years. The abdominoperineal resection, known as the Miles procedure, combined with postoperative chemotherapy and radiotherapy are recommended for the low rectal cancer, that sacrifices the sphincter and can severely affect patient's quality of life post-surgery. There is a young-onset tendency, and the young patients are more concerned about sphincter-preserving and life-quality post-surgery. With the advances in neoadjuvant therapy, the patient's options without sacrificing sphincter are expanded. We hereby report a 31-year-old female patient with ultra-low rectal adenocarcinoma, 1.4 cm to the anus edge, was treated through Neoadjuvant chemoradiotherapy (nCRT), which combined CAPEOX chemotherapy and radiotherapy. The initial staging of the tumor was cT3N1M0, and the MRI indicated a threatened circumferential resection margin (CRM). After three cycles of treatment the tumor lesion was completely gone on MRI and colonoscopy, and a complete pathological response (cPR) was yielded then a 'Wait-and-Watch' surveillance was being pursued. We aim to advance further studies on the particular molecular and genetic mechanism for neoadjuvant therapy complete remission in young adult patients with low rectal cancer, so as to increase anal preservation rate in the population.

2. Introduction

According to Global Cancer Statistics 2021, colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related deaths in the world [1], and becomes a global burden of disease [2]. There are no specific symptoms and signs in the early stage, and most patients have already progressed into an advanced stage at the time of diagnosis. The treatment of rectal cancer is dictated by the stage of tumor, and often includes surgical and non-surgical/ comprehensive treatment. For low-grade rectal cancer, neoadjuvant chemoradiotherapy (n-CRT) combined with total mesengectomy of rectum (TME) can significantly improve the outcomes of the cancer and are recommended [3, 4]. Since the early 1990s, surgical resection has the large chance in curing the early-stage malignant cancer [5]; however, due to the complexity of pelvic anatomy, as well as the heterogeneous characteristics of the tumor, and complex lymphatic drainage, R0 is still hard to achieve in some cases [6]. In the cases treated by surgery, the rate of anus-preservation is still low, where the rates of complications and local recurrence are still high, and the long-term survival is unsatisfied and the quality of life and psychological effect on patients with sphincter-sacrificing surgery become

a tremendous concern [7]. Despite the effectiveness of treatment, people are now increasingly concerned about the life quality after surgery. Therefore, non-surgical treatments have attracted more and more attention. In this paper, we report a case of a 31-year-old female diagnosed ultra-low rectal adenocarcinoma who was effectively treated by neoadjuvant chemoradiotherapy and reached a complete recession, aiming to raise the concern of the quality of life in young patients with low rectal cancer and expand our vision of neoadjuvant therapy in this setting.

3. Case Presentation

A 31-year-old female patient with a BMI of 20.32 kg/m2 was admitted into our hospital on October 14, 2022 with the major complaint of "a change in bowel habit with intermittent blood in stool for 2 years". In the two years, the patient had an increase in the bowel movements, about 2 to 4 times per day, with irregular blood stools. Recently, the patient's symptoms were getting worsened, so she came to the hospital to seek special medical advises and treatment. The medical history was no significance. Physical examination first demonstrated that the patient was in moderate distress. Her vital signs were stable. Inspection, auscultation, percussion and palpation of abdomen found nothing significant. Rectal examination was performed in KC position. Mixed hemorrhoids were first revealed around the canal of anal by inspection. Then, the rectal wall was palpated. A 3 cm mass between 3 o'clock and 6 o'clock was felt by digit. The lesion was hard and immobilized. After the examination, the digital glove was noted with stain of blood. Laboratory tests at admission showed that blood cell counts, coagulation and liver and kidney function were within the normal limits. Image study with Abdominal and pelvic enhanced CT scan (Figure 1) demonstrated a high-density irregular image at the junction of the distal part of the rectum and the anal canal, and multiple small lymph nodes were noted on the right side of the rectum. Colonoscopy was also performed and showed a rectal mass about 1.4 CM proximal to the dentate line (Figure 2). The initial clinical staging indicated cT3N1M0 classified as stage IIIB. Pathological examination then diagnosed (Figure 3) rectal adenocarcinoma with the immunohistochemistry staining showing CK (+) and CEA (+ -). The enhanced pelvic MRI detected that the circumferential resection margin (CRM) was threatened (Figure 4). PET-CT ruled out distant metastasis. Neoadjuvant chemotherapy of CAPEOX with concurrent radiotherapy were administered. The patient's height and weight were measured as 162cm and 54kg, and the body surface was calculated to be 1.59m2. Specifically, oxaliplatin of 130mg/m2 was delivered intravenously with a total dose of 200mg IV on day 1 and day 21; capecitabine of 825mg/m2 was taken orally and twice daily with 1.0 g in the morning and 1.5g in the evening, five days a week. The doses of concurrent radiation used 95% PTV 5040 cGy with 28 fractions to the pelvis using 4 fields.

After 3 cycles of treatment, the symptom of hematochezia was improved, and another MRI and colonoscopy were prescribed to follow up. The MRI (Figure 5) showed that the thickened rectal wall and tumor were significantly shrunk compared with the previous images (Figure 4). And the Colonoscopy (Figure 6) revealed that the former visible mass was completely gone. Pathologic biopsy (Figure 7) indicated a local rectal wall surface mile inflammation, that was common after radiation therapy. To note that during the initial chemotherapy the patient developed gastrointestinal infections, mild intestinal obstruction and myelosuppression and due to the strong side-effects of capecitabine, the dosage of capecitabine was reduced to 0.5g in the morning and 1.0g in the evening afterwards. Following it, another 3 cycles were ordered: the radiation dose was adjusted to 5940 cGy for shrinking radiation field to local rectal lymphatic drainage; the chemotherapy of capecitabine combined with sindilizumab was given as an sustainable treatment. Upon the completion of those treatments, the tumor markers of glycoantigens 19-9, glycoantigens 125 and glycoantigens 15-3 were tested for evaluation and all within normal limits. The follow-up enhanced MRI (Figure 8) showed a homogeneous enhanced intestinal wall with a local rectal intestinal wall mild edema due to chemoradiotherapy. Multiple small lymph nodes in the pelvis and rectum were reduced in number and size from before. And the follow-up colonoscope found nothing significant. After 5-month follow-up, the patient's former symptoms were completely relieved, and the cancer was gone. The follow-up colonoscopy revealed a complete remission.

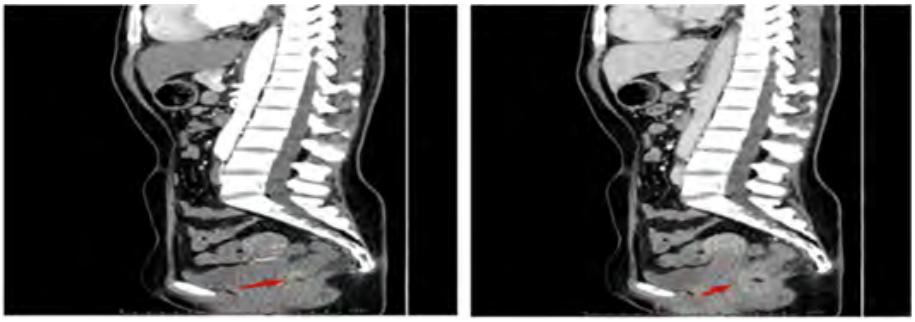

Figure 1: Contrast-enhanced CT results. The local intestinal wall becomes thickened at the junction between the lower rectum and the anal canal, with patchy enhancement and blurry fat around the intestinal wall (red arrow). The left image is arterial phase, and the right is venous phase.

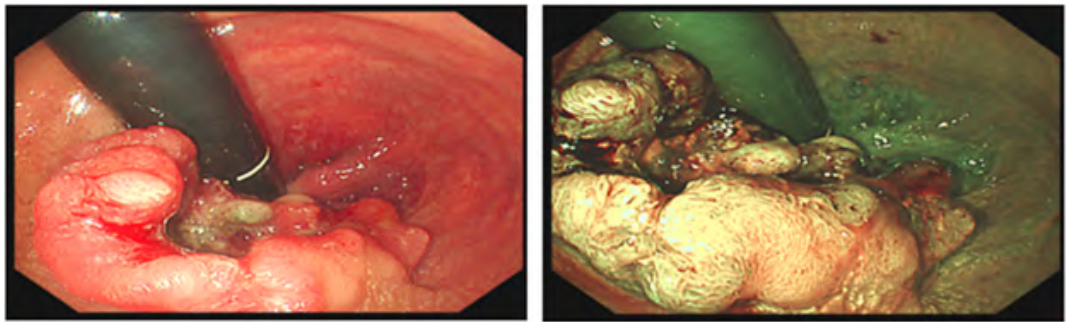

Figure 2: Colonoscope. Near the dentate line, the ulcerated mass, growing half of the intestinal wall, is demonstrated; there are some mosslike dirt at the base of the mass, which is easily bleeding upon touching, NBI staining suggests mucosal vascular disorders.

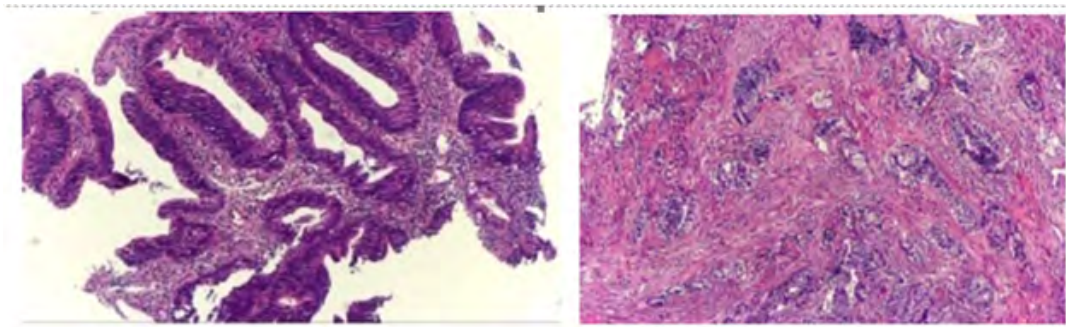

Figure 3: Pathology of rectal masses. Pathological examination shows gland forming neoplasm where the cells show hyperchromasia, large nuclei and increased nuclei-cytoplasm ratio.

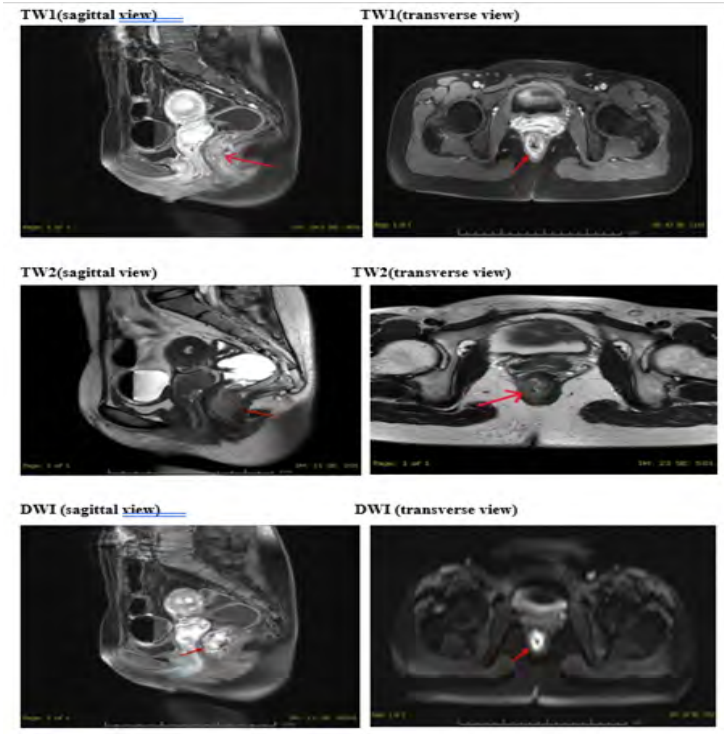

Figure 4: Enhanced magnetic resonance imaging. The lesion is hypointense on TW2 and hyperintense on TW1. The local uneven enhancement (red arrow) of the intestinal wall at the junction of the lower rectum and the anal canal is about 46×23×20mm ,and the lower margin is about 14mm from the anus' edge. It threatens the mesorectal fascia. The tumor is irregular in shape, with uneven signals (T2 and T1) and unclear boundaries; the signal of the muscle layer of the posterior wall of the anal canal is not continuous, where the boundary is slightly blurred with slightly local protrusion. Multiple small lymph nodes are detected in the rectal mesentery and bilateral iliac vascular zone, the largest about 0.6 cm. Diffusion Weighted MRI shows restricted diffusion area of the lesion.

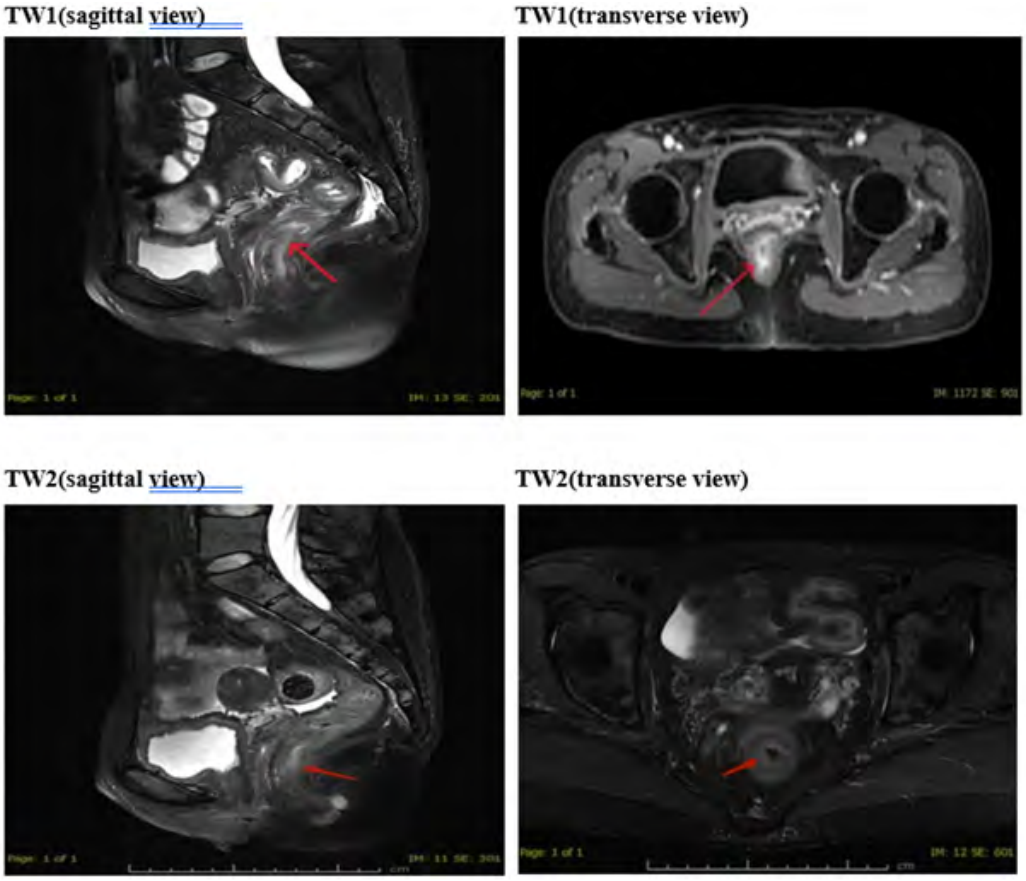

Figure 5: Enhanced magnetic resonance after the neoadjuvant chemoradiotherapy. The local intestinal wall is slightly thick, and the tumor is largely shrunk as compared with Figure 4.

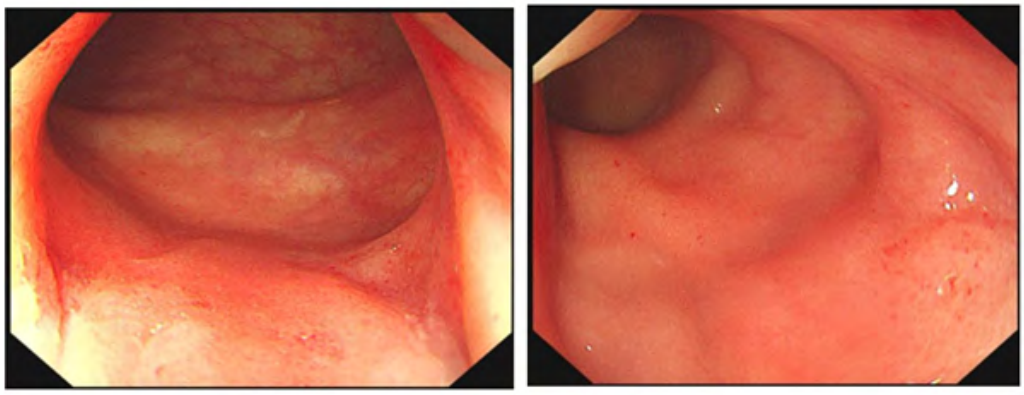

Figure 6: Colonoscope of follow-up. Grossly, the mucosa of the whole colon is smooth.

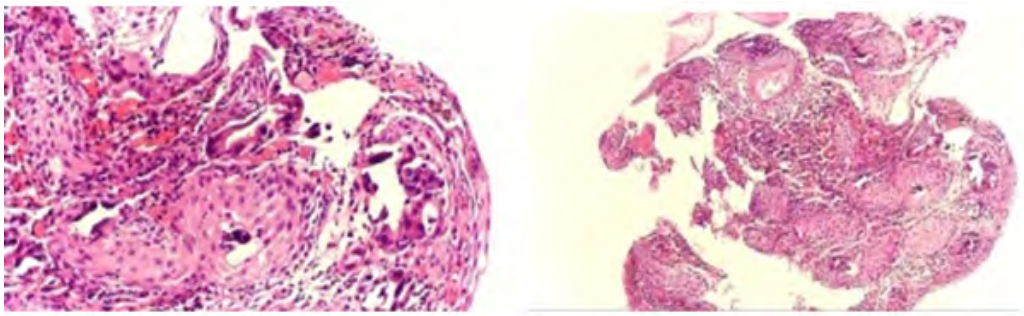

Figure 7: Pathology examination after the neoadjuvant chemoradiotherapy shows inflammatory reaction on the surface of the rectal wall.

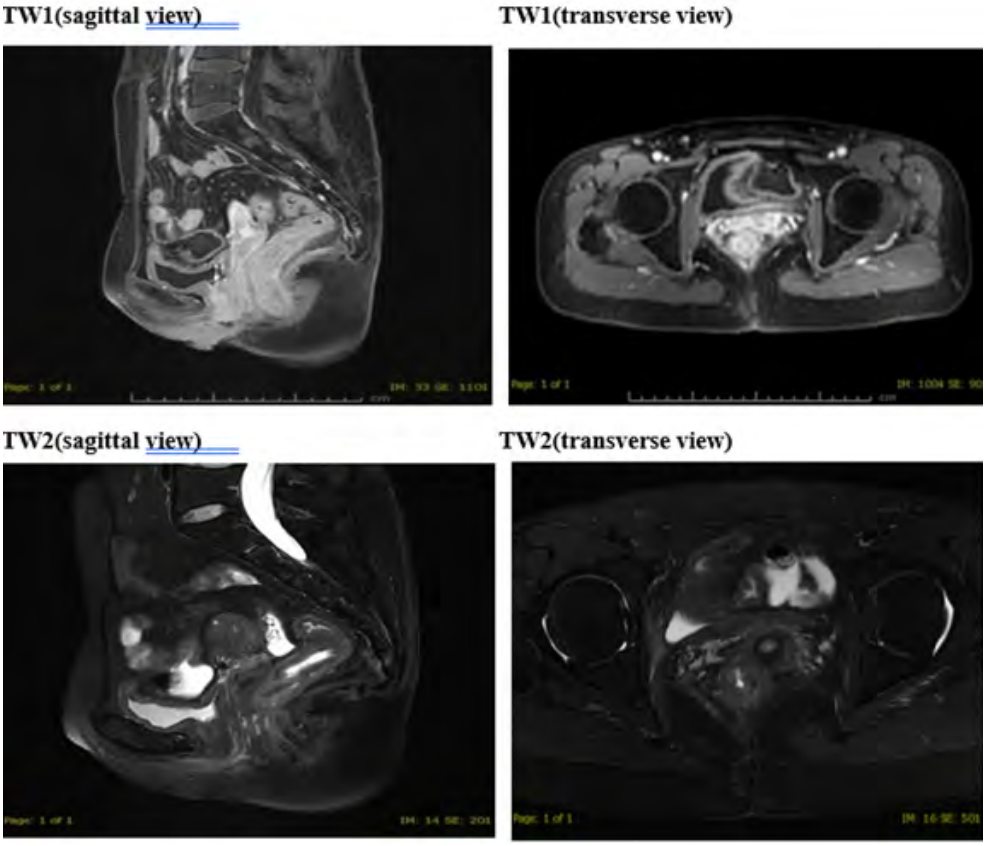

Figure 8: Enhanced MRI follow-up. The intestinal wall of the lower rectum is slightly thickened, with an upper and lower range of 31 mm, homogeneous enhancement, and the boundary with the surrounding organs is clear, which is considered to be rectal intestinal wall edema after chemoradiotherapy. No obvious diffusion-restricted nodules noticed in the rectum, sacrum and bilateral iliac bones.

4. Discussion

4.1. Neoadjuvant therapy for low-level locally advanced rectal cancer

For unresectable advanced rectal cancers, the neoadjuvant therapy may help downstage the tumor into resectable stage and provide a choice and hope for those patients. Furthermore, clinical practices have found that some patients receiving neoadjuvant therapy can achieve a clinical complete remission, that may spare them from surgery. As CRC presents a young-onset feature, the young adult patients have major concern for quality of life after the disease treatment. Thus, clinical complete remission after neoadjuvant therapy becomes another ultimate goal for them.

4.2. Neoadjuvant radiotherapy: short course vs. long course

There are two approaches of neoadjuvant radiotherapy, short vs. long courses [8, 9]. The short course is carried out with 5.0 Gy per session and a total of 25.0 Gy for 5 sessions, followed by a resectable surgery. The long course uses 1.8 to 2.0 Gy per session and a total of 45.0~50.4 Gy for 25 sessions, and the surgery is performed 6 to 8 weeks later. Long course arm had a better tumor shrinkage and downstaging effect compared with short course arm, however, both types of radiotherapy have similar R0 resection with no difference in overall survival [10]. Studies have found that there were no differences in local recurrence or survival in short course compared with long course [11, 12]. Besides, toxicity rates, distant recurrence, and relapse free survival showed no significant difference between the two arms [13]. Therefore, short-course radiotherapy has been recommended for preoperative treatment of rectal cancer in some countries.

4.3. Total Neoadjuvant Therapy Approach (TNT)

TNT comprised of neoadjuvant chemoradiotherapy (chemoRT) and neoadjuvant chemotherapy followed by surgical resection in stage II or III rectal cancer [14-17]. NCCN guidelines 2022 only recommend TNT for cT3 lesions and N any lesions with involved or threatened CRM [18]. TNT approach recommends 12 to 16 weeks of chemotherapy followed by chemoRT or short-course RT, and restaging to transabdominal resection. ChemoRT or short-course RT may be initiated prior to a 12 to 16 weeks chemotherapy and, then, restaging for surgery as an alternative approach. CAPEOX can be used for chemotherapy for this stage of tumor. With no residual lesion and sign of disease on digital rectal examination, MRI and colonoscopy, there can be a clinical/pathological complete response produced. There are about 50 to 60% rate for tumor downstaging; and the pathologic complete response rate can reach about 20% after neoadjuvant therapy [19-21]. A nonoperative approach of Watch-and-Wait may be pursued for surveillance.

Interestingly, after three cycles of CAPEOX and radiation treatment, the MRI, colonoscopy and physical examination showed a pathological complete response in our case. Study has reviewed that clinicopathological features and genetics in young adult patients with CRC may be different from older patients and requires to develop peculiar treatment strategies [22].

4.4. Neoadjuvant immunotherapy

Referring to individualized and tailored rectal cancer treatment, neoadjuvant immunotherapy has also gained attention. Study has shown that immunotherapy combined with preoperative chemoradiotherapy could enhance the efficacy of preoperative treatment to produce a favorable pCR rate [23]. A prospective, non-randomized and phase 2 clinical trial showed that neoadjuvant immunocellular therapy combined with chemotherapy was safe and increased the pCR rate in the treatment of advanced rectal cancer [24]. The study demonstrated that preoperative chemoradiotherapy plus Nivolumab brought forth a 30% of pCR rate in stable and instable microsatellite locally advanced rectal cancer cases [23]. It is anticipated that further large cohort study can bring out more promising results to benefit the young adult population with low rectal cancer and increase the anal-preservation rate.

4.5. 'Watch and Wait' surveillance in low rectal cancer

For patients reaching cPR, the radical surgery may be spared without negatively affecting the survival rate and tumor recurrence. Thus, preserving the function of anus and genitourinary system and improving the quality of life of patients become promising in those low rectal cancer patients. The approach of " Watch and Wait" (WW) has attracted more and more attention. Although many clinicians were skeptical of this approach, studies showed promising results of long term outcomes and low local recurrence [25-27]. Many still criticized that there were lack of larger sample sizes, longer follow-up and strict studies, that could make WW a routine approach [28]. In addition, studies demonstrated that imaging studies of FDG-PET, MRI and CT were inaccurate in determining a pathological complete response, making the selection of appropriate candidates difficult [29]. After all, the current recommendation is a careful surveillance after choosing WW approach to patients achieving cPR.

5. Conclusion and limitations

Neoadjuvant chemoradiotherapy can downstage the unresectable low rectal cancer and be promising in providing an alternative for anus preserving without sacrificing sphincter, so as to improve the young adult patients' life-quality. For patients achieving cPR, a careful surveillance is essential, and digital rectal examination, colonoscopy, CEA follow-up test, and imaging studies of CT and MRI are still necessary after choosing WW approach.

6. Contributors

X.M. is the first author and responsible for the manuscript writing and data collection; L.F. is the corresponding author, and has conceptualized this paper and reviewed and edited the manuscript.

7. Competing Interests

None

8. Patient Consent for Publication

Informed consent was obtained from the patient, consent form available upon request.

9. Ethics Approval and Consent to Participate

Not applicable. We submitted a case report which was a retrospective review and intended for quality improvement, thus it should not be considered research. Besides, we have our patient's signed consent to publish this report.

10. Availability of Data and Materials

Not applicable

11. Funding

None from any funding agency in the public, commercial or not-for-profit sectors.

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