Original Article

Long-term Outcomes in Rectal Cancer Patients with Clinical Complete Response after Concurrent Chemoradiotherapy: A Local Hospital Experience

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Key Words
Rectal cancer;
Watch-and-wait;
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Neoadjuvant

Purpose. Multimodality treatment for rectal cancer is associated with improved long-term functional outcomes and quality of life. Of the available systemic and locoregional treatments, total neoadjuvant therapy is promising. Our aim here is to share our experience with organ-preservation strategies, evaluate the oncologic outcomes of our patients, and recommend an alternative treatment strategy for patients who refuse surgery.
Methods. We included patients diagnosed with malignant neoplasm of the rectum who underwent neoadjuvant chemoradiotherapy between 1 November 2004 and 31 October 2019. We used digital rectal examination (DRE), carcinoembryonic antigen (CEA) levels, scope with biopsy, computed tomography (CT), and chest X-ray for identification and restaging. Clinical complete response (cCR) was defined as the absence of any residual viable cancer or scars after two months of surveillance. The primary endpoint was any local regrowth of rectal cancer at the tumor site or in regional lymph nodes. Secondary endpoints were incidence of distant metastasis, overall survival, and disease-specific survival or toxicity.
Results. The median age was 68.3 years and median follow-up time was 5 years. No patient had local regrowth. Distant metastases in the lungs were diagnosed in one patient in the third year after diagnosis, in the brain was diagnosed in one patient in the second year after diagnosis. Two patients died due to upper gastrointestinal bleeding and septic shock. The five-year overall survival and disease-free survival rates were 69% and 84%, respectively.
Conclusion. Despite some patients receiving unsystematic chemoradiotherapy regimens, their oncologic outcomes were promising. We conclude that "watch-and-wait" is an effective treatment for low rectal cancer patients who refuse surgery, but highlight the importance of surveillance.
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Multimodality treatment for rectal cancer is associated with improved long-term functional outcomes and quality of life including bowel, bladder, and sexual dysfunction and pain, and potential need for permanent colostomy.

For stage 0-III rectal cancer, surgery remains the primary choice of treatment. However, surgical resection is associated with higher morbidity and mortality,

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which increases with old age, frailty, and comorbidities. Over time, focus has gradually moved to organ-preservation strategies. In 2004, Habr-Gama and collaborators first reported positive outcomes for selective surgery using a nonoperative strategy in stage 0 rectal cancer patients, who achieved a clinical complete response (cCR) following chemoradiation therapy.[1]

The standard treatment for locally advanced rectal cancer is neoadjuvant chemoradiotherapy followed by major resection surgery, based on the principles of total mesorectal excision. In 2018, van der Valk and colleagues analyzed the International Watch & Wait Database (IWWD), a large-scale international multicenter registry, and revealed excellent survival of clinical complete responders following neoadjuvant treatment for rectal cancer.[2]

Regarding available systemic and locoregional treatments, recent studies suggest that total neoadjuvant therapy is a promising strategy.[3,4] The aim of this study is to share our experience with organ-preservation strategies. We aim to explore the oncologic outcome in this group and suggest alternative treatments for patients who refuse surgery.

Methods

We retrospectively included 47 patients diagnosed with malignant neoplasm of the rectum (ICD-9 code: 154.1; ICD-10 code: C20) in the first and second diagnosis, who underwent neoadjuvant chemoradiotherapy between 1 November 2004 and 31 October 2019 (Fig. 1). Patients provided written informed consent for this restaging study.

For the initial staging evaluation, all patients underwent sigmoidoscopy/colonoscopy with biopsy, contrast-enhanced computed tomography of the abdomen and pelvis, and a chest X-ray.

Data collected included clinical characteristics (e.g., age, stage), tumor characteristics at the time of diagnosis, the reason for organ-preserving treatment, treatment characteristics (e.g., RT dosage, concomitant chemotherapy), toxicity of chemoradiotherapy, imag-

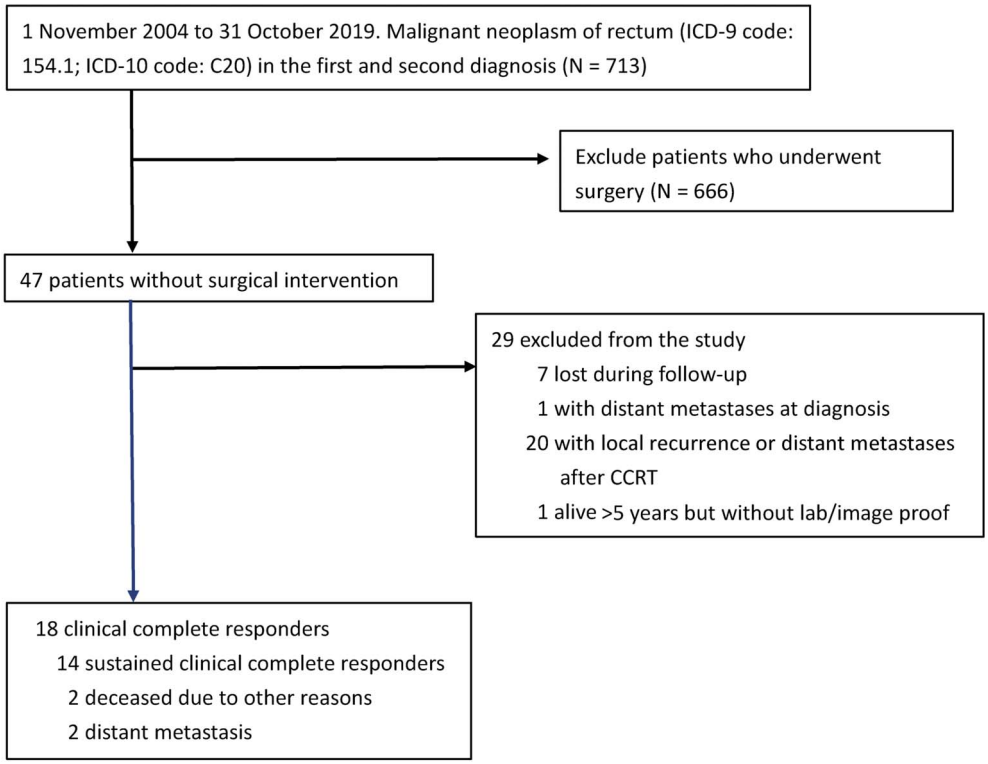

Fig. 1. Patients included in this study.

ing results at diagnosis, results of reassessment after neoadjuvant therapy and follow-up, details of treatment for disease recurrence, and survival status.

A cCR was defined as the absence of any residual viable cancer or scars after two months of surveillance by monthly digital rectal examinations (DREs) and sigmoidoscopy/colonoscopy with biopsy. After two months, we monitored patients by performing regular digital rectal examinations and assessing carcinoembryonic antigen levels every three months, computed tomography every six months, andy early sigmoidoscopy/colonoscopy with biopsy. Follow-up times were calculated from the date of rectal cancer diagnosis.

The primary endpoint was any local regrowth of rectal cancer at the local tumor site or regional lymph nodes detected with DRE, endoscopy, or imaging. Secondary endpoints were the incidence of distant metastasis, overall survival, and disease-specific survival or toxicity.

Results

We included 47 patients who were in the database of our hospital from 1 November 2004 to 31 October 2019. The baseline characteristics of the clinical complete responders are summarized in Table 1. The median age was 68.3 years, there were more males than females (83% vs. 17%), and the median follow-up time was 5.0 years (2.8-7.2).

Imaging modalities used for staging at baseline and reassessment are listed in Table 2. All patients underwent endoscopy, computed tomography (CT) imaging, and carcinoembryonic antigen (CEA) level measurements at baseline. We performed endoscopies in 17 of the 18 cases (94%) to evaluate their cCR following neoadjuvant therapy. Biopsies were performed in all patients who underwent an endoscopy for reassessment. Restaging CT was also performed in all patients. A combination of DRE, endoscopy, and CT was performed in 17 of the 18 patients (94%).

Chemoradiotherapy was most commonly used (17 of 18 patients, 94%), most frequently with scheduled 50.4 Gray (Gy) (N = 9). In most patients, we used uracil-tegafur (UFUR) (9 of 18 patients, 50%) or 5-fluorouracil (5-FU) plus leucovorin (LV) (7 of 18 patients, 39%). With respect to side effects, 14 of 18 patients (78%) reported gastrointestinal symptoms, 12 (67%) reported skin problems, and 3 (17%) reported genitourinary symptoms. Despite the side effects, the patients who received concurrent chemoradiotherapy all completed their course.

Table 1. Baseline characteristics of clinical complete responders (N = 18)

Age, mean	68.3	
	Number	%
Sex		
Male	15	83
Female	3	17
Year of W&W decision		
Before 2010	4	22
2010-2014	11	61
2015-2019	3	17
Median follow-up time, years (95% CI)	5.0 (2.8-7.2)	
Stage		
I	4	22
II	3	17
III	11	61
CEA level (ng/mL)		
< 5	13	72
> 5	5	28
Comorbidities number*		
0	6	33
1	6	33
2	3	17
3	3	17

* Comorbidities are classified into seven categories: 1, hypertension; 2, diabetes mellitus; 3, heart condition (coronary artery disease, congestive heart failure, ventricular septal defect); 4, cerebrovascular accident; 5, hyperlipidemia; 6, lung condition (chronic obstruction pulmonary disease, tuberculosis); and 7,l iver condition (hepatitis B & C).
CEA, carcinoembryonic antigen; CI, confidence interval; W&W, watch-and-wait.

Table 2. Diagnostic procedures at baseline and at reassessment after therapy

	Baseline (N =18)	Reassessment
Endoscopy	18	17 (94%)
CT abdomen + pelvis	18	18
CEA	18	18

CEA, carcinoembryonic antigen; CT, computed tomography.

No patient showed local regrowth, giving a two-year rate of 0%. Distant metastases were diagnosed in 2 of 18 patients (11%). The initial stages of these two metastatic patients were II (T4bN0) & III (T2N1). The metastases were located in the lung and brain and diagnosed in the third and second year respectively after initial diagnosis. One patient died in the third year after diagnosis due to upper gastrointestinal bleeding. Of the 18 patients, 14 (78%) patients are still alive and disease-free. The five-year overall survival (OS) and disease-free survival (DFS) rates were 69% and 84%, respectively (Figs. 2 & 3).

Discussion

The main purpose of this study was to evaluate our watch-and-wait strategy and the oncologic outcomes of these patients. Assessing cCR is best performed by combining DRE, endoscopy, and high-re-

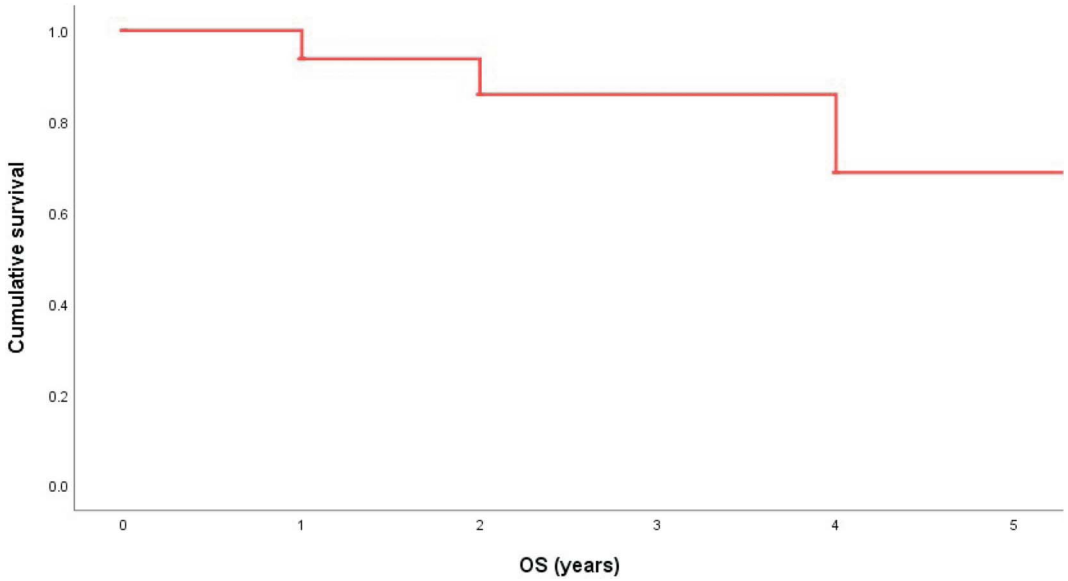

Fig. 2. Overall survival (OS) rate for all patients.

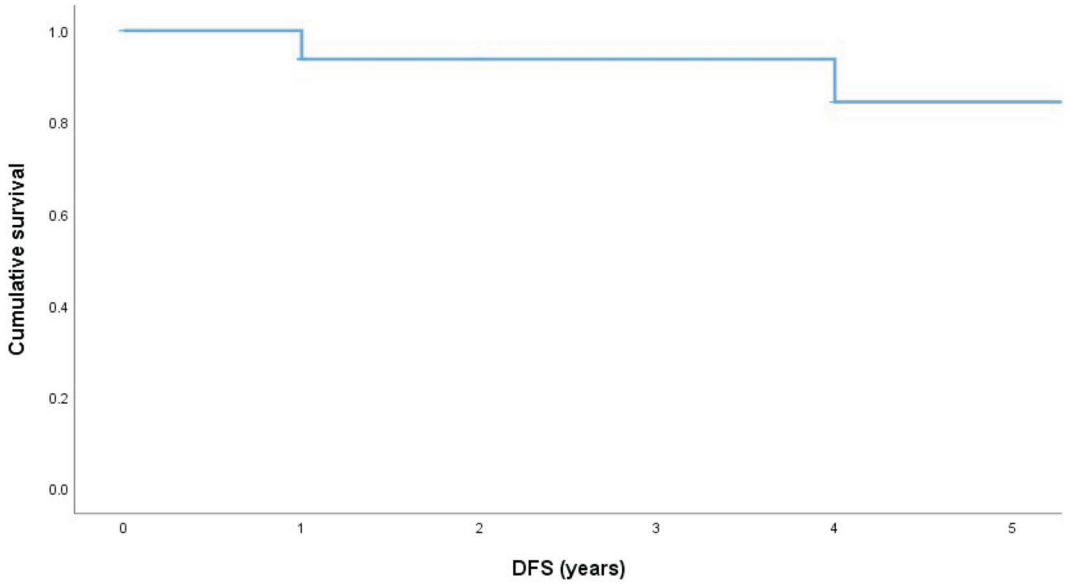

Fig. 3. Disease-free survival (DFS) rate for all patients.

solution imaging.[2,3,5] Currently, magnetic resonance imaging (MRI) is the imaging modality of choice for evaluating rectal cancer, since it allows a correct assessment of disease extent, lymph-node involvement, mesorectal fascia, and whether sphincteric exclusion is involved.[6,7] A typical cCR is seen as a flat white scar using endoscopy, with signs of fibrosis on DRE and MRI.[5] Although no guideline has yet been established, current consensus is intensive surveillance with DRE, endoscopy, and MRI in the first two years, and decreasing intensity in subsequent years.

We used computed tomography for identification and restaging. The efficacy of CT for assessing post-chemoradiotherapy rectal cancer response is limited, with an over-staging rate of 23%.[7,8] Nevertheless, the new-generation multidetector computed tomography (MDCT) scanner shows high sensitivity and accuracy in assessments, with some studies reporting similar results between CT and MRI during staging.[9,10] Considering the easy accessibility and satisfactory accuracy of this modality, CT remains our primary choice for identification and restaging.

In our study, the patients showed no local recurrence. The reported local recurrence rate varies from 3% to 32%.[2,3,13] A local recurrence can be achieved via salvage resection and at least 90% of local regrowth can be managed.[11-13] Distant metastases were diagnosed in 2 of the 18 patients (11%). The initial stage of one patient was II (T4bN0), with underlying conditions of hypertension and diabetes mellitus. The metastasis was diagnosed in the third year after the initial diagnosis and was located in the lungs. The initial stage of the other patient was III (T2N1), with underlying status of heart disease, stroke and chronic obstructive pulmonary disease. The metastasis was diagnosed in the second year after the initial diagnosis and was located in the brain.

The five-year OS rate of our patients was 69%, and the five-year DFS rate was 84%. Recent studies show better findings. An international, multicenter registry-based study[2] reported favorable outcomes with an OS rate of 84.7% and a disease-specific survival rate of 93.7%, with only 8% of patients developing distant metastasis at five years. For patients who were diagnosed with local regrowth, the five-year disease-specific survival was 84.0% and the five-year OS was 75.4%. Two recent meta-analyses also reported favorable long-term outcomes in patients forgoing surgery after neoadjuvant chemoradiation therapy.[13,14]

One limitation of our study was its retrospective design and small sample size. Further, the chemoradiation therapy regimen before 2010 was less systematic than it is currently. Although the chemotherapy regimen was based on 5-FU, both the combination of drugs and the duration of treatment varied from patient to patient. The radiotherapy dosage and duration also varied.

Conclusion

Despite the fact that some of the patients received a less systematic chemoradiotherapy regimen, the overall oncologic outcomes were promising. Our study shows that "watch-and-wait" is an effective alternative treatment for selected low rectal cancer patients who refuse surgery and highlights the importance of surveillance for such patients.

Conflicts of Interest

This article is not supported by any grant. All authors declare no conflicts of interest.

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原　著

同步放射及化學治療後達到臨床完全緩解的直腸癌患者之預後：區域醫院的經驗分享

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目的　直腸癌的多模式治療與改善長期器官功能及生活品質有關。在目前可用的全身性和局部性治療，研究顯示接受前導性放化療後的直腸癌病人，只有大約 1/4 的病人復發，而且幾乎都是兩年內局部復發，整體五年生存率有 85%。本研究的目的是分享我們的經驗，評估接受“觀察與等待”的患者的長期預後，並為拒絕手術的患者提供替代治療。

方法　我們納入了 2004 年 11 月 1 日至 2019 年 10 月 31 日期間接受過前導性放化療的直腸惡性腫瘤患者。我們使用了肛門指診 (DRE)、癌胚抗原 (CEA) 指數，大腸鏡、活體組織切片、斷層掃描 (CT) 和胸部 X 光片來診斷及分期。臨床完全緩解 (cCR) 定義為在監測兩個月後不存在任何殘留的腫瘤或疤痕。我們評估了在腫瘤部位或區域淋巴結中是否有局部復發、遠處轉移的發生率，整體存活率、無疾病存活期及放化療副作用。

結果　病人平均年齡為 68.3 歲，平均追蹤時間為 5 年。沒有病患出現局部復發。一名患者在診斷後第三年診斷出肺遠處轉移，另一名患者在診斷後第二年診斷出腦遠處轉移。兩名病患因上消化道出血和敗血性休克死亡。五年總生存率和無病生存率分別為 69% 和 84%。

結論　儘管部分年代較久遠的病人接受了不同劑量的放射及化學治療，但其預後還是與當前的研究不相上下。我們認為“等待及觀察”這個策略對於拒絕手術的低位直腸癌患者是一種有效的治療方法，但治療後的追蹤扮演了很重要的角色。

關鍵詞　直腸癌、觀察等待、化學與放射治療、臨床完全緩解、前輔助性。