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Clinical Investigation

Local Recurrence After Complete Clinical Response and Watch and Wait in Rectal Cancer After Neoadjuvant Chemoradiation: Impact of Salvage Therapy on Local Disease Control

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Summary

Nonsurgical management of distal rectal cancer with after long-course chemoradiation therapy has been considered an alternative treatment strategy for patients with complete clinical response. A major limitation of this alternative would be the impossibility of salvage in the event of local recurrence. The present study suggests that salvage therapy is feasible in the majority of patients and is associated with good long-term local control of disease.

Purpose: To review the risk of local recurrence and impact of salvage therapy after Watch and Wait for rectal cancer with complete clinical response (cCR) after chemoradiation therapy (CRT).

Methods and Materials: Patients with cT2-4N0-2M0 distal rectal cancer treated with CRT (50.4-54 Gy + 5-fluorouracil-based chemotherapy) and cCR at 8 weeks were included. Patients with cCR were enrolled in a strict follow-up program with no immediate surgery (Watch and Wait). Local recurrence-free survival was compared while taking into account Watch and Wait strategy alone and Watch and Wait plus salvage.

Results: 90 of 183 patients experienced cCR at initial assessment after CRT (49%). When early tumor regrowths (up to and including the initial 12 months of follow-up) and late recurrences were considered together, 28 patients (31%) experienced local recurrence (median follow-up time, 60 months). Of those, 26 patients underwent salvage therapy, and 2 patients were not amenable to salvage. In 4 patients, local re-recurrence developed after Watch and Wait plus salvage. The overall salvage rate for local recurrence was 93%. Local recurrence-free survival at 5 years was 69% (all local recurrences) and 94% (after salvage procedures). Thirteen patients (14%) experienced systemic recurrence. The 5-year cancer-specific overall survival and disease-free survival for all patients (including all recurrences) were 91% and 68%, respectively.

Conclusions: Local recurrence may develop in 31% of patients with initial cCR when early regrowths ($\leq$12 months) and late recurrences are grouped together. More than half of these recurrences develop within 12 months of follow-up. Salvage therapy is possible in $\geq$90% of recurrences, leading to 94% local disease control, with 78% organ preservation.

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Introduction

Up to 42% of patients with distal rectal cancer may experience a complete pathologic response after neoadjuvant chemoradiation (CRT) and total mesorectal excision (TME) (1). These patients seem to have improved oncologic outcomes (2). However, these results after TME are at the cost of significant postoperative morbidity, including long-term urinary, sexual, and fecal continence dysfunction and the frequent need for temporary or definitive stomas. In this setting, alternative treatment strategies have been suggested to avoid major postoperative complications and still maintain optimal oncologic results (3). These strategies include full-thickness local excision (FTLE) or no immediate surgery (also known as the Watch and Wait strategy).

Full-thickness local excision may provide the advantage of allowing pathologic assessment of the primary tumor (4, 5). However, even though the risk of sexual, urinary, and fecal incontinence is minimal, postoperative morbidity, including wound dehiscence, is significantly higher after CRT (6, 7). Another alternative treatment strategy with no immediate resection and observation has been suggested for patients with complete clinical response (cCR) (8). This alternative has the advantages of an organ-sparing strategy, with even lower morbidity or functional consequences (9). However, it requires identification of patients with cCR who are likely to have a complete pathologic response (10). Still, these patients with cCR have the potential risk for harboring microscopic residual disease within both the rectal wall and the mesorectal nodes and therefore remain at risk for the development of local recurrence (11).

In this setting, a proportion of patients undergoing observation and no immediate surgery after a cCR (or Watch and Wait strategy) may experience local recurrence and ultimately require a salvage procedure. Ideally, the use of any organ-sparing treatment strategy without radical surgery would allow salvage resection for the majority of local recurrences with no oncologic compromise. The aim of the study was to review local recurrence, salvage rates, and oncologic outcomes among patients with cCR treated without immediate surgery and the impact of salvage on local disease control. In previous studies, cCR was considered for patients with at least 12 months of follow-up who showed no evidence of tumor regrowth. In the present study, all recurrences (including early regrowths within the initial 12 months of follow-up) were considered to enable understanding of the role and impact of salvage resection on local disease control after no immediate surgery after an initial cCR.

Methods and Materials

Between 1991 and 2011, consecutive patients from a single institution (Angelita & Joaquim Gama Institute) were assessed before neoadjuvant CRT by a single surgeon and underwent full physical examination, digital rectal examination, and rigid proctoscopy. Carcinoembryonic antigen (CEA) levels were obtained for all patients (8). Radiologic staging included chest and abdominopelvic computed tomographic (CT) scans, pelvic magnetic resonance imaging (MRI), and/or endorectal ultrasonography (ERUS) when available. All patients with primary tumors located no more than 7 cm from the anal verge and with radiologic evidence of cT2-cT4 or cN+ disease were recommended to receive neoadjuvant CRT and were included in the study.

Neoadjuvant CRT consisted of 50.4 to 54 Gy delivered in 1.8-Gy fractions daily and concomitant 5-fluorouracil-based chemotherapy on the first and last 3 days of radiation therapy, as described elsewhere (8). None of the patients undergoing additional chemotherapy cycles during radiation therapy and the resting period ("extended" CRT regimen) were included in the present study (12).

Assessment of response and management

Patients were assessed for tumor response after at least 8 weeks from the completion of radiation therapy by the same clinical and radiologic tools used in baseline assessment of tumor extent. All patients considered to be complete clinical responders according to stringent criteria of clinical, endoscopic, and radiologic findings were treated without immediate radical surgery, as described elsewhere (8). Briefly, the criteria for considering cCR were the absence of residual ulceration, mass, or mucosal irregularity at clinical/endoscopic assessment. Whitening of the mucosa and the presence of neovasculature (teleangiectasia) were accepted features of cCR. In addition, radiologic imaging (CT, ERUS, or MRI) that showed no evidence of extrarectal residual disease (particularly nodal metastases among patients with cN+ at baseline) was required for patients to be considered to have a cCR. None of the baseline cT and cN staging features were excluding criteria for inclusion in this nonoperative approach after a cCR (10). Patients gave consent to this institutional review board-approved treatment strategy and to the storage of prospective information regarding treatment outcomes. None of the patients with cCR demanded or asked for radical surgery instead of the Watch and Wait approach.

The presence of clinical or endoscopic features of incomplete response to CRT or the radiologic evidence of residual disease within the mesorectum were diagnostic of incomplete clinical response, and radical surgery was recommended. These patients with incomplete clinical response were excluded from the study.

Follow-up

Patients with cCR were not treated by adjuvant systemic therapy regardless of their baseline staging features. Follow-up included visits every 1 to 2 months to a single experienced colorectal surgeon, with clinical and digital rectal examination in addition to rigid proctoscopy. CEA levels were obtained every 2 to 3 months. After 1 year of follow-up, patients were examined every 3 months similarly and every 6 months after 3 years. A radiologic imaging modality (including CT scans, MRI, and/or ERUS) was used to rule out mesorectal disease and for systemic follow-up after 6 months and yearly thereafter.

At baseline and reassessment, CT was available for all patients. In addition to CT, ERUS was performed at baseline and reassessment in 19 patients (21%), and MRI was performed at baseline and reassessment in 10 patients (11%). Follow-up was performed with CT scans in all patients. All patients with recurrent disease underwent MRI or positron emission tomography/CT before treatment.

Patients were fully advised that disease recurrence could develop at any time during follow-up and that in this situation, radical surgery would be required.

Local recurrence was defined as the presence of adenocarcinoma within the rectal wall or within the mesorectum confirmed by pathology. Patients with local recurrence were referred for radical surgery. Pelvic recurrences were defined as the presence