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Nonoperative management of rectal cancer after chemoradiation opposed to resection after complete clinical response. A comparative study

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Abstract

Introduction: Surgery is the standard treatment of rectal cancer after neoadjuvant therapy. Some authors advocate a nonoperative management (NOM) after complete clinical response (cCR) following chemoradiotherapy (CRT). We compare our results with NOM to standard resection in a retrospective analysis.

Methods: Rectal adenocarcinomas submitted to NOM after CRT between September 2002 and December 2013 were compared to surgical patients that had pathological complete response (pCR) during the same period. Endpoints were Overall Survival (OS), Disease Free Survival (DFS), Local Relapse (LR) and Distant Relapse (DR).

Results: Forty-two NOM patients compared to 69 pCR patients operated after a median interval of 35 weeks after CRT. NOM tumors were distal (83.3% vs 59.4%, $p = 0.011$), less obstructive (26.2% vs 54.4%, $p = 0.005$) and had a lower digital rectal score ($p = 0.024$). Twelve (28.0%) recurrences in NOM group and eight (11.5%) in the surgical group occurred after a follow-up of 47.7 and 46.7 months respectively. Isolated LR occurred in five (11%) NOM patients and one (1.4%) in the surgical group. Four (80%) LR were surgically salvaged in NOM group. No difference in OS was found (71.6% vs 89.9%, $p = 0.316$) but there was a higher DFS favoring surgical group (60.9% vs 82.8%, $p = 0.011$). Distal tumors had worse OS compared to proximal tumors in surgical group (5-year OS of 85.5% vs 96.2%, $p = 0.038$).

Conclusion: The NOM achieved OS comparable to surgical treatment and spared patients from surgical morbidity but it resulted in more recurrences. This approach cannot be advocated routinely and controlled trials are warranted.

Keywords: Rectal cancer; Neoadjuvant therapy; Complete clinical response; Rectal resection; Nonoperative treatment

Introduction

Colorectal cancer is the third most common malignant neoplasia worldwide (1.4 million new cases/year[1]) and the third leading cause of cancer-related death in both men and women in the US.[2] The standard of care for rectal mid-distal locally advanced adenocarcinoma is neoadjuvant chemoradiotherapy (CRT) followed by radical surgery.[3] 14–40% of patients who receive neoadjuvant CRT will achieve a pathological complete response (pCR)[4] and will have a favorable prognosis after total mesorectal excision (TME), with low rates of local relapse (LR) and high 5-year survival rates.[5] However, the nonoperative management strategy (NOM) proposed by Habr-Gama et al.[6] selects those rectal cancer patients showing complete clinical response (cCR) after CRT in order to avoid surgery and its related morbidity.

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Although some patients with rectal cancer have been considered cured without surgery, the results have often been suboptimal. Brierley et al. treated patients who refused surgery or had unresectable or medically inoperable disease with pelvic radiation alone and achieved a 5-year survival of 27%.[7] In contrast, pre-operative CRT followed by radical surgery results in 75% 5-year survival.[8] However, the "watch and wait" strategy developed by Habr-Gama[9] reported 5-year overall survival (OS) and disease free survival (DFS) rates of 100% and 92% respectively and LR rates of 3% among 71 NOM patients. After her seminal manuscript published in 2004,[6] four prospective series have reported encouraging results on CRT followed by observation alone.[10]

In spite of these reports, physicians are reluctant to treat patients without surgery mainly because of the lack of a standardized technique for identifying patients with cCR and the absence of consistent data (randomized trials) to support this approach.

Over the past decade, selected rectal cancer patients who have been identified as cCR were managed with the "watch and wait" strategy after neoadjuvant CRT at our institution. In this retrospective analysis of a prospectively maintained database we report the results of these NOM patients in comparison to those who underwent standard rectal resection after complete clinical response in the same period at our institution.

Methods

This study has received approval from our institution's ethics committee. All rectal adenocarcinoma patients submitted to neoadjuvant treatment were included in a retrospective database from September of 2002 to December of 2013. During this period the standard of care at our institution for locally advanced rectal adenocarcinoma within 10 cm from the anal verge was pre-operative CRT followed by surgical resection. The neoadjuvant treatment plan included external bean radiation (RT) to the pelvis (dose ranging from 45.0 Gy to 50.4 Gy) combined with a fluoropirymidine-based chemotherapy (CT).

A bolus of 5-fluorouracil and leucovorin (320 mg/m^2/ 20 mg/m^2) during the first and last week of radiotherapy (D1–D5) was the most frequent regimen. In a minority of cases, capecitabine was orally administered instead of 5-fluorouracil and leucovorin from monday through friday during all five weeks of radiotherapy in a dose of 825 mg/m^2 as part of the research protocol GI004.[11]

Patients in both groups were assessed for age, gender, tumor localization (within 5 cm of anal verge or higher) and pre-treatment CEA levels. Tumor fixation (TF) was graded by digital examination in four levels as follows: grade 1, mobile lesion; grade 2, mobility decreased; grade 3, semi fixed; grade 4, totally fixed tumors. The presence of chemotherapy (CT) adjunct to RT was also assessed, as was the presence of adjuvant (post-operative) CT after resection or during NOM "wait-and-see" management. The time interval from CRT to surgery was recorded, as the type of operation. The severity of luminal obstruction (> or <50%) was described by endoscopy before treatment, as was the endoscopic aspect of the tumor site after treatment, which was classified as residual tumor/ulceration versus a flat scar.

NOM group

The NOM group consists of all rectal cancer patients who appeared to have a complete clinical response after neoadjuvant treatment based on digital examination, endoscopy and magnetic resonance (MRI), and who were not submitted to surgery for various reasons. Among these are patients who refused surgery to avoid a permanent stoma and those who had the support of the attending surgeon to postpone surgery until clear evidence of residual disease be suspected. These patients were followed by a strict surveillance regimen, which consisted of a physical examination, serial carcinoembryonic antigen levels (CEA) measurements and endoscopy in three-month intervals during the first two years and in six-month intervals from the third to fifth year of follow-up.

NOM patients who had evidence of LR were selected to surgical salvage when resectability was presumed. At any point, patients with evidence of LR or DR were evaluated for surgical resection in both groups. When the case was deemed inoperable, palliative CT was offered.

Operative group

All operated patients who demonstrated a pCR in the specimen after neoadjuvant CRT were selected from our database to form the control group. These patients were submitted to surgery 6–8 weeks after completion of neoadjuvant treatment. The operation consisted of either a low anterior rectal resection (LAR) or abdominoperineal resection (APR), but total mesorectal excision (TME) and proximal vascular ligation were performed in all cases to ensure radicality. Free distal margins were confirmed by frozen sections before performing the anastomosis when sphincter preservation was possible. Follow-up after resection lasted for 5 years at our institution. Routinely, patients underwent a physical examination and CEA measurement. Imaging and endoscopy exams were performed annually.

Statistical analysis

The study endpoints were overall survival (OS), disease-free survival (DFS), relapse-free survival (RFS), local relapse (LR), distant relapse (DR), and specific mortality rate (SMR). For OS and DFS, we considered the starting time the last day of the neoadjuvant treatment in the NOM group and the date of resection in the operative group. For estimating OS, we used the date of the last