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Original research

Is it safe to omit neoadjuvant chemo-radiation in mucinous rectal carcinoma?

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HIGHLIGHTS

- We are studying the oncologic outcome of patients having mucinous rectal carcinoma with or without Neoadjuvant chemoradiation.
- Partial tumor regression occurred in limited percentage of patients.
- A considerable percentage of patients developed tumor progression during chemoradiation and became unresectable.
- No difference between groups in the disease free survival and overall survival after total mesorectal excision.

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ABSTRACT

Background: Purpose was to compare the oncologic outcome of neoadjuvant chemoradiotherapy (nCXRT) versus postoperative chemoradiotherapy (pCXRT) for locally advanced mucinous rectal carcinoma (MRC) having curative total mesorectal excision (TME).

Methods: One hundred and two patients with MRC (T3-4 and/or N1-2) of middle and lower third rectum were included. Patients were non-randomly divided into 2 groups: Group A (N = 61) had nCXRT followed by total mesorectal excision (TME) after 8–11 weeks and Group B (N = 41) had TME followed by pCXRT. Primary end points were disease free survival (DFS) and overall survival (OS). Secondary endpoints were tumor regression grade (TRG) and morbidity.

Results: In group A, 29 patients had partial response after nCXRT, 26 patients showed no change and 6 patients had progression. TME was done in 55 patients in group A and 41 patients in group B. Six patients in group A turned to be unresectable after nCXRT due to progressive disease. Mean follow-up was 53 months. In patients received TME, Four-year DFS was higher in group A compared to group B yet not statistically significant (DFS 0.69 [95% CI 0.54–0.85] vs. 0.67 [95% CI 0.47–0.87]; P = 0.39). However, actuarial 4 years OS was comparable in both groups (0.72 [95% CI 0.59–0.91] vs. 0.70 [95% CI 0.55–0.88]; P = 0.46 in groups A and B respectively). Multivariate analysis revealed that age <40, and N2 were risk factors of recurrence.

Conclusion: Whilst accepting that the numbers are small, there was no statistical difference in outcome (DFS and OS) between patients receiving pre- or post-operative chemo-radiotherapy. In most MRC patients, tumor regression is not significant after nCXRT and there is considerable possibility of tumor progression during nCXRT treatment. So, nCXRT should be used with close follow-up in MRC for early detection of possible tumor progression. If the patient cannot tolerate nCXRT, it is possibly safe to do surgery followed by pCXRT. Prospective study is needed to study the value of nCXRT in MRC.

1. Background

Rectal carcinoma (RC) represents 30% of all colorectal cancers [1]. Mucinous carcinoma (MRC) is a specific morphological subtype of rectal cancer which is diagnosed when more than 50% of the tumor comprises a mucinous pattern upon histological

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examination [2]. It is characterized by an abundance of extracellular mucin secreted by overactive neoplastic acinar cells. The abundance of mucin within the tumor complex gives it a unique appearance both histologically and radiologically [3].

The prognostic significance of MRC is controversial. In some studies, mucinous histology was reported not to be an independent prognostic factor for survival [4,5]. However, others think that it may have bad prognostic effect on survival [6–10].Up till now, the guidelines established by the National Comprehensive Cancer Network (NCCN) do not describe mucinous histology as a clinical factor that should influence the therapeutic algorithm [11,12].

In the past two decades, management of rectal cancer has made important progress, highlighting the main role of the multimodality strategy approach, combining surgery, radiation therapy and chemotherapy. Nowadays, surgery remains the primary treatment and neoadjuvant chemoradiation, based on fluoropyrimidine 5-fluorouracil (5-FU) continuous infusion, is considered the standard in locally advanced mid and low rectal carcinoma. The aim is to reduce the incidence of local recurrence and to perform a conservative surgery.

Recent studies suggested that MRC are a distinct group of tumors which show different natural history, biological behavior, different oncogenic and molecular pathways which may make them respond differently to chemoradiation compared to non-mucinous tumors (NMRC) [13,14]. There might be a lesser value in down staging of MRC which is the principal aim of nCXRT. We conducted a retrospective analysis of MRC involving middle and lower third rectum who received or did not receive nCXRT.

2. Purpose

Aim of the current study was to compare the oncologic outcome of neoadjuvant chemoradiotherapy (nCXRT) versus postoperative chemoradiotherapy (pCXRT) for locally advanced mucinous rectal carcinoma (MRC) having curative total mesorectal excision (TME).

3. Patients and methods

This is a retrospective analysis of prospectively accrued database between January 2009 and January 2012 at 3 academic centers (Alexandria, Cairo and Mansoura University hospitals). All patients with mucinous rectal cancer who fulfilled the inclusion criteria during the time frame of the study in the 3 institutes were included in the study. The study was performed after approval of Alexandria University Ethical Committee. Informed consent was obtained from each patient to be included in the database. All procedures were done by experienced consultant surgeons.

Databases were standard across all three institutions. Patients with resectable middle and lower third rectal carcinoma with proven biopsy of mucinous rectal cancer (T3-4 and/or N1-2) were included in this study. A 50% mucinous component was required for the designation of mucinous colorectal carcinoma [15]. Neoplastic cells showed be immersed in mucin lakes for diagnosis of MRC, the finding on acellular mucin pools alone was not enough. Patients were excluded if they had signet-ring cells, distant metastasis (M_1), family history of any hereditary colorectal cancer or synchronous primary malignancies, and/or previous malignancy within 5 years prior to presentation.

All patients had colonoscopy, contrast enhanced computed tomography (CT) of the abdomen and pelvis and MRI of the pelvis (high resolution MRI, 1.5 T). The tumor size and wall thickness were measured by MRI. The number and size of lymph nodes seen on CT and MRI were also noted. Distance of the tumor from the anal verge was measured using rigid proctoscopy.

The pathologists from the three referral hospitals were asked to review tumor specimens and assess the tumor type. All pathologists were not aware of the clinical results. The pathological evaluation of the surgical specimens was according to the TNM classification. Grading was established according to the differentiation by predominant area [16].

Curative resection was defined as complete one-step removal of all gross tumors with negative surgical margins (longitudinal and circumferential) on microscopic examination (R0 resection). Chemoradiation choice was upon surgeon preference. Patients were divided into 2 groups according to the type of chemoradiation received:

Group A (nCXRT): neoadjuvant chemoradiation (nCXRT) (50.4 Gy combined with fluoropyrimidine 5-fluorouracil and leucovorin as radio-sensitizers) was administrated. MRI was done after nCXRT to assess both operability, and response to nCXRT. Total mesorectal excision (TME) was done 8–11 weeks after completion of nCXRT. According to the distance between the distal edge of the tumor and top of anal sphincter, with the respect of at least 2 cm distal resection margin, low anterior resection (with colorectal, coloanal anastomosis) or abdominoperineal resection (APR) was performed. Decision about sphincter preservation was done before neoadjuvant therapy and no change in operative strategy was adopted after nCXRT except if the tumor got advanced. All patients received adjuvant chemotherapy after surgery consisted of 5-FU and LV.

In Group B (pCXRT): patients had TME followed by adjuvant chemoradiation (50.4 Gy in 28 fractions, and the 5-FU was 450 mg/m^2 given with fractions 1–3 and 26–28). On completion of the radiation therapy, a patients was given further four cycles of bolus 5-FU at monthly intervals.

In both groups, patients had diversion ileostomy if sphincter saving TME was done. Distal loopogram was done after 12 weeks in all patients. If no anastomotic leak, closure of ileostomy was done after completion of chemotherapy. If anastomotic leak was diagnosed, closure was done after healing of the anastomotic leak.

A CT scan of the chest was done to evaluate for metastatic disease together with serum level of CEA and CA19.9. In group A: Dworak tumor regression grade was evaluated in all specimens [17].

3.1. Postoperative evaluation and follow up

Postoperative complications and mortalities were recorded. Follow up continued till April 2015 by abdominal and chest CT, every 6 months. Colonoscopy was done annually in patients with sphincter saving TME. Recurrence was determined by clinical and radiological examinations followed by histological confirmation. Locoregional recurrence was defined as the growth of the tumor within the pelvis or on the suture or staple line of the bowel anastomosis.

3.2. Statistical analysis

Primary end points were disease free survival (DFS) and overall survival (OS). Secondary endpoints were tumor regression grade (TRG) and morbidity. Overall survival (OS) was defined as the time from surgery to death or to the last date the patient was known to be alive. Disease-free survival (DFS) was defined as the time from surgery to recurrence of cancer or to the last date the patient was known to be disease free.

The Wilcoxon rank sum test was used to compare continuous variables. Fisher's exact test or Chi square test was used to compare categorical variables. All P values were based on two-sided tests with a significance level of 0.05. Univariate analysis was done to detect factors affecting recurrence in these patients. A multivariate