

Mucinous adenocarcinoma of the rectum: a poor candidate for neo-adjuvant chemoradiation?

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Background: Mucinous adenocarcinoma (MA) is a distinct pathological entity associated with poor outcome. Due to different biological behavior, the response to neoadjuvant chemo-radiation (NACRT) may be inferior compared to non-mucinous tumours. In this study we compare the pathological response of mucinous tumours after NACRT.

Methods: A total of 183 patients who underwent NACRT for rectal cancer were classified as mucinous and non-MAs. The dose of radiation was 45 Gy (at 1.8 Gy per fraction) delivered over five weeks with weekly 5-fluorouracil (5-FU) (325 mg/m^2) and leucovorin (20 mg/m^2). After surgery, the pathological specimens were evaluated and staged. The data are reported as descriptive statistics and chi-square test used to determine difference in proportions.

Results: The two varieties were comparable on the basis of the computed tomography (CT) scan in terms of tumour size and lymph node metastasis. However in terms of pathological response, it was seen that there was a higher incidence of pT4 tumours (73.5% vs. 10.7%), margin positivity (11.7% vs. 2.3%) and advanced nodal disease pN2 (29.4% vs. 9.3%) in mucinous and non-mucinous tumours respectively.

Conclusions: MA of the rectum show a poor response to NACRT as seen in terms of larger residual tumours, higher incidence of margin positivity, and greater residual nodal disease. Also they showed higher incidence of peritoneal and distant dissemination during NACRT. The role of NACRT in mucinous carcinoma of the rectum is of questionable benefit and needs to be examined in prospective trials.

Keywords: Rectal cancer; adenocarcinoma; mucinous; neoadjuvant therapy; neoadjuvant chemo-radiation (NACRT)

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Introduction

Mucinous adenocarcinoma (MA) is diagnosed when more than 50% of the tumor comprises a mucinous pattern upon histological examination (1). MA of the rectum accounts for 5-10% of all adenocarcinomas of the rectum. They have long been recognized to have a poorer survival compared to non-mucinous tumours of the rectum (1). It is believed that mucinous tumours are associated with advanced stage at presentation and the advanced stage rather than the histology is responsible for the worse outcome. The American Joint Committee (2) and the College of American Pathologists (3) consider that MA subtype has not been shown to be statistically significant prognostic factor

when matched for similar stage and grade. The guidelines established by the National Comprehensive Cancer Network (NCCN) do not ascribe mucinous histology as a factor that should influence the therapeutic decision making and the current practice is to consider them similar to the non-mucinous tumours and histology does not affect treatment decision making. Consorti *et al.* (4) have shown that between the two groups, survival was better for nonmucinous than for mucinous tumours. Uni-variate and multi-variate analyses have shown that MA histology is an independent prognostic factor. Mucinous tumours have been shown to have different oncogenic and molecular pathways (5) which may make them respond differently compared to non-mucinous tumours. Tumours with MA are associated with

mucus under pressure, which allows the tumour cells to gain access to the peritoneal cavity and have a particular higher chance of occurrence of peritoneal metastasis. Signet ring carcinoma is an epithelial tumour where the predominant component (>50% of the tumour) is made up of isolated malignant cells containing intracytoplasmic mucin (1). These tumours have even worse prognosis in the category of mucin secreting tumours. In this study we assess the difference in the pathological response patterns between the mucinous and non-MA of the rectum after a standard course of neoadjuvant chemo-radiation (NACRT).

Material and methods

From 2008-2013, 183 patients who received pre-operative chemo radiotherapy followed by surgery for rectal cancer were evaluated in this study. Patients with biopsy proven rectal cancer were included in this study after a workup consisting of sigmoidoscopy/colonoscopy and a contrast enhanced computed tomography (CT) of the abdomen and pelvis. The tumour was measured on CT scan as determined by size seen in length and maximum thickness of the rectum. The number and size of lymph nodes seen on CT was also noted. The pathological evaluation of the surgical specimens was according to the TNM classification. The patients were divided based on the histology into mucinous (including signet cell variety) and non-MA. As mucin secretion can be induced during NACRT itself, only patients with pre-operative diagnosis of MA were categorized as such in this study. The patients underwent NACRT to a dose of 45 Gy in 25 fractions delivering 1.8 Gy per fraction by four field box technique or 3D conformal radiotherapy (3DCRT). Concurrent weekly 5-fluorouracil (5-FU) (350 mg/m²) and leucovorin (20 mg/m²) were administered as a radio sensitizer. The patients underwent abdomino-perineal resection or low anterior resection 4-6 weeks after surgery depending on the distance from the anal verge and depending on the response to NACRT. The descriptive data were analyzed using the Excel 2007 software package.

Results

Patient and tumour characteristics are shown in *Table 1*. It was seen that patients with MA histology presented at a younger age but showed no significant predilection to gender or smoking habit. The size of initial tumour (as seen on CT scans) and the nodal status were comparable

Table 1 Showing the age, sex and smoking patterns and tumour and nodal status as assessed on the baseline CT scan done before start of NACRT

	Mucinous (n=34)	Non-mucinous (n=128)
Age in years, mean [maximum, minimum]	34 [20, 60]	53 [18, 73]
Sex (number), male/female	22/12	93/35
Smoking status, smoker/non-smoker	6/28	23/105
Preop tumour size on CT scan (cm)		
Median	7.94×2.44	8.5×1.8
Minimum	3.5×1.9	4×1.5
Maximum	12×2.5	8×1.6
Nodal status on CT		
No LN	9 (26.4%)	20 (15.6%)
Few discrete LN	6 (17.6%)	57 (44.5%)
Multiple enlarged LN	10 (29.4%)	35 (27.3%)
Only peri-rectal fat stranding	9 (26.4%)	16 (12.6%)

CT, computed tomography; NACRT, neoadjuvant chemo-radiation; LN, lymphadenopathy.

between the two groups.

Six patients with MA of the rectum did not complete the planned treatment as they developed grade 3 enteritis during the course of radiation. Seven patients were lost to follow-up after NACRT and ten patients developed distant metastasis (including peritoneal dissemination) during the course of NACRT and were not offered surgery. These patients were subsequently excluded from the analysis (*Table 2*). The time delay from NACRT completion to surgery was similar in the two groups.

The pathological response seen in the two groups after NACRT are described in *Table 3*. The majority of the residual primary tumour in the MA arm was of pT4 stage (73.5%) whereas in the NM group 10.1% of the residual tumours was of T4 group. The incidence of margin positivity was also higher in the MA group (11.7%) compared to 2.3% positive margin in the NM group (P=0.016). Also the residual number of lymph nodes (pN2) was greater in the MA 29.4% vs. 9.3% in the NM group. The most striking difference between the two groups was seen in the occurrence complete pathological response after NACRT

Table 2 Describing events from the completion of NACRT to the definitive surgery

	Mucinous (n=34)	Non-mucinous (n=128)
Time from NACRT completion to surgery (median, days)	61	57
Developed distant metastasis during NACRT	3 (8.8%)	5 (3.9%)
Omental/peritoneal metastasis at time of surgery	2 (5.88%)	0

NACRT, neoadjuvant chemo-radiation.

Table 3 Describing the histopathological characteristics after completion of NACRT

Characteristic	Mucinous (%, n=34)	Non-mucinous (%, n=128)	P value
Stage			
pT1-T2	3 (8.8)	78 (60.9)	0.00
pT3	6 (17.6)	37 (28.9)	0.18
pT4a,4b	25 (73.5)	13 (10.1)	0.00
Margin positivity (total)	4 (11.7)	3 (2.3)	0.016
Proximal and distal	2 (5.8)	2 (1.5)	
Circumferential	2 (5.8)	1 (0.7)	
Nodal status			
N0	6 (17.6)	93 (72.6)	0.00
pN1a,N1b	18 (14.0)	23 (17.9)	0.00
pN2a, pN2b	10 (29.4)	12 (9.3)	0.002
Pathological complete remission	0	15 (11.7)	0.03

NACRT, neoadjuvant chemo-radiation.

which was seen in 15 (11.7%) of the NM groups while none of the patients in the MA group had pathological complete response to NACRT (P=0.03).

Discussion

Though mucinous and signet cell varieties have been regarded as a distinct pathological entity, they are treated as for the non-MAs and hence underwent NACRT followed by surgery. Apart from being associated with worse prognosis and poor survival, mucinous histology is

an independent prognostic factor and MA have been seen to have a different natural history (4-6). Sugarbaker *et al.* (7) have suggested that MA have mucus under pressure causing the mucus to dissect between the fat planes and carry the tumour cells which float amidst the mucin-“the dissecting mucus theory” which allows the tumour to penetrate deeper and gain access to the peritoneal cavity leading to worse clinical factors including larger primary lesions, deeper invasion, and higher rates of nodal and distant metastasis. Hence peritoneal lavage and intraperitoneal chemotherapy have been proposed during surgery. Molecular and genetic causes may be responsible for the relative radio/chemo resistance of these tumours. The tumour size as evaluated by the CT and the nodal status seen on CT scans were comparable between mucinous and non-mucinous groups. Both the groups underwent NACRT to the same doses and the time interval from completion of NACRT to surgery was also comparable between the two groups. It was seen that patients with MA had poorer response as seen by the post-operative pathological picture of these tumours. Zhang *et al.* (5) have demonstrated that MA had more K-ras mutations (50% vs. 25%, P=0.02), but less p53 expression (72% vs. 49%, P=0.02) and less apoptotic activity (19% vs. 51%, P=0.01) compared to nonmucinous lesions. In addition, higher rates of loss of heterozygosity and abnormal expression of E-cadherin have been demonstrated in these tumours (6). This observation may be of importance as apoptosis is an important response of the tumour to radiation and has been proposed as predictor of histopathological response to NACRT (8,9). NACRT in rectal cancer is associated with improved local control and survival (10) and the response to NACRT is considered a surrogate marker for oncologic outcome (9,11,12). The presence and number of tumours containing lymph nodes are the most important prognostic factors for survival or recurrence (13). In our study, patients with MA had higher incidence of positive nodes (redundant) after NACRT suggesting poor down-staging and hence are likely to have poor prognosis. Subjecting such poorly responding tumours to NACRT which would delay surgical intervention by 8-10 weeks would also risk tumour dissemination into the peritoneal cavity (7) or development of distant metastasis. Perez *et al.* (14) studied the PET based response in patients who underwent NACRT and were able to identify a category of poor responders. It was suggested by them that it was not advisable to wait six weeks from the completion of NACRT to the time of surgery. Sengul *et al.* (15) studied the pathological response after NACRT in different histological

types of rectal cancer and demonstrated poorer tumour regression grades after NACRT in the mucinous variety. The limitations of our study is that it is a retrospective study where the preoperative tumour staging was done by CT scan rather than an MRI or transrectal ultrasound which better characterize the depth of the tumour and the lymph nodal stage. However all of the patients did not undergo an MRI preoperatively and hence a CT scan was used to characterize the pre-operative tumour status. Also other pathological features like lympho-vascular invasion, Ki-67 proliferation index, and tumour grade have not been examined in this study for the sake of uniformity as the data was not available in all of the records examined.

Conclusions

MAAs of the rectum are a distinct group of tumours which show different natural history, biological behavior and response to NACRT compared to non-mucinous tumours. There may be a lesser value in down staging of tumours which is the principal aim of NACRT. Hence it is recommended that upfront surgery be done in this group rather than the time delay caused due to NACRT which may lead to progression of disease in the form of peritoneal dissemination or development of distant metastasis. Prospective randomized studies are required to verify the true value of NACRT in MA.

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