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Prognostic Comparison between Mucinous and Non-mucinous Rectal Adenocarcinoma

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Abstract

Background: We aimed to analyze the prognostic impact of mucinous and non-mucinous rectal adenocarcinoma with stage II and III rectal carcinoma treated with radical surgery plus (neo) adjuvant chemoradiotherapy and evaluate disease-free (DFS) and overall survival (OS).

Method: We conducted this retrospective study on patients with pathologically proven stage II/III rectal carcinoma and treated in the Department of Clinical Oncology and Nuclear Medicine, Mansoura University Hospital between January 2008 and December 2013. We designed a clinical abstract sheet and reviewed all cases in terms of history, clinical assessment, investigations done on the patients, and pathological reports including all the details, and treatment modalities, namely neoadjuvant and adjuvant.

Results: The median DFS for non-mucinous adenocarcinoma (NMC) was beyond 60 months, while that for mucinous adenocarcinoma (MA) was 24 months (P=0.008). The median OS for NMC was beyond 60 months; whereas, the mean OS of MA was 25 months (P=0.002).Therefore, the difference between both groups was statistically significant regarding DFS and OS.

Pathological subtype was the only statistically significant independent predictor in the three-year DFS. However, pathological subtype and lymph-vascular invasion were statistically significant independent predictors in the three-year OS.

Conclusion: Histological subtype was an independent prognostic factor for both DFS ans OS in patients with stages II and III rectal carcinoma.

Keywords: Rectal carcinoma, Prognosis, Mucinous adenocarcinoma, Neoadjuvant chemoradiotherapy

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Introduction

Rectal carcinoma is one of the major global causes of morbidity and mortality, the fourth cause of death worldwide, and the second cause of cancer-related mortality in the United

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States.[1] Rectal cancers account for approximately 1/3 of all colorectal cancers.[2]

In Egypt, it is considered as the sixth prevalent cancer in males and females, accounting for 4.34% of all cancers. 30% of the patients are aged 40 or younger and the incidence reaches its peak at 60 years of age.[3]

The prognosis of the patient status mainly depends on the TNM staging for treatment selection;[4] however, some patients with the same TNM stage have different prognosis; thus, histological parameters should be considered.[5]

There exist controversies as to the relationship between histological subtypes in rectal carcinoma and cancer prognosis.[5]

Mucinous adenocarcinoma (MA) is diagnosed when the extracellular mucin exceeds 50% of the tumor. In our study, this was the case with 24% of the patients, higher than the incidence rates in Asia, which range from 3% to 9%,[6,7,8] and slightly higher than those reported in western countries (11-20%).[9,10] Such differences might be attributed to the changes in dietary habits and life style.[11]

The prognostic significance of several factors, including TNM stage, tumor grade, preoperative carcinoembryonic antigen (CEA) level lymphovacular invasion (LVI), and surgical margin status, have been clearly established in patients with colorectal cancer; however, the effect of mucinous histology on tumor local control and overall survival (OS) is yet to be thoroughly elucidated.[12]

In some studies, mucinous histologic type itself was an important prognostic factor affecting the progression of tumor and the outcome of patients; also, MA patients had a worse prognosis compared with non-mucinous adenocarcinoma (NMC).[6,13,14,15] However, American Joint Committee on Cancer (AJCC) and the College of American Pathologists hold that MA subtype has not been shown to be a statistically significant prognostic factor when matched for similar stages and grades.[16] The guidelines established by the National Comprehensive Cancer Network (NCCN) do not deem mucinous histology as a factor influencing the therapeutic decision-making; the current practice is to consider them similar to the non-mucinous tumors.[17]

The aim of the study was to analyze the prognostic impact of different mucin component in patients with stage II and stage III rectal carcinoma treated with radical surgery plus neo-adjuvant chemoradiotherapy. We focused on the differences concerning disease-free survival (DFS) and OS.

Patients and Methods

The present retrospective study comprised patients with locally advanced rectal carcinoma and treated in the Department of Clinical Oncology and Nuclear Medicine Department, Mansoura University Hospital between January 2008 and December 2013.

Patient eligibility criteria

(1) Patients with pathologically proven stage II / III rectal carcinoma.

(2) Patients receiving combined modality therapy in the form of radical surgery and neo-adjuvant chemoradiotherapy.

(3) Performance status ≤ 2 as determined by Eastern Cooperative Oncology Group (ECOG) performance status.

(4) Satisfactory liver functions (specified by liver enzymes and serum bilirubin).

(5) Normal renal functions determined by serum creatinine.

Exclusion Criteria

(1) Patients without histological confirmation of the primary tumor.

(2) Patients with previous malignancy within the five years preceding the diagnosis of rectal carcinoma (except for basal cell skin cancer or carcinomas in situ).

Prior to data collection from the patients' files, the Ethics Committee of the Faculty of Medicine, Mansoura University (Ethics Code: m1702240) approved this study.

We designed a clinical abstract sheet and reviewed all cases. The following data were collected:

Table 1. Patients and tumors' characteristics in both groups

Characteristic	NMC Group (N=53) N (%)	MA Group (N=17) N (%)	*P* value
Sex			
Male	27 (50.9%)	9 (52.9%)	*P*=0.88
Female	26 (49.1%)	8 (47.1%)	
Age			
Mean±SD	51.3±6.82	43.39±9.02	*P*<0.005
ECOG			
1	48 (91%)	14 (82.3%)	*P*=0.3
2	5 (9%)	3 (17.7%)	
Tumor site			
Whole rectum	0 (0%)	2 (11.7%)	*P*<0.005
Upper 1/3	25 (47.1%)	0 (0%)	
Lower 1/3	28 (52.9%)	15 (88.2%)	
Tumor size			
<5 cm	37 (69.8%)	2 (11.7%)	*P*<0.005
> 5cm	16 (30.2%)	15 (88.2%)	
Grading			
Grade I	7 (13.2%)	0 (0%)	*P*=0.07
Grade II	34 (64.2%)	9 (52.9%)	
Grade III	12 (22.6%)	8 (47.1%)	
Staging			
II	24 (45.3%)	2 (11.7%)	*P*=0.011
III	29 (54.7%)	15 (88.2%)	
Nodal status			
N0	24 (45.3%)	2 (11.8%)	*P*=0.23
N1	25 (47.2%)	12 (70.6%)	
N2	4 (7.5%)	3 (17.6%)	
Lymph-vascular invasion			
Negative	46 (86.8%)	4 (23.6%)	*P*<0.005
Positive	7 (13.2%)	13 (76.5%)	
Perineural invasion			
Negative	45 (84.9%)	13 (76.5%)	*P*=0.4
Positive	8 (15.1%)	4 (23.6%)	
Circumferential radial margin			
Negative	51 (96.2%)	6 (35.3%)	*P*<0.005
Positive	2 (3.7%)	11 (64.7%)	
Distal margin			
Negative	45 (84.9%)	13 (76.5%)	*P*=0.4
Positive	8 (15.1%)	4 (23.6%)	

NMC: non-mucinous adenocarcinoma; MA: mucinous adenocarcinoma; ECOG: Eastern cooperative oncology group

Table 2. Treatment strategies regarding both groups

Treatment modalities		NMC Group (n=53)	MA Group (n=17)	*P*-value
Surgery	Exploration	0 (0%)	2 (11.7%)	*P*<0.005
	LAR	24 (45.2%)	0 (0%)	
	APR	29 (54.7%)	15 (88.2%)	
Chemoradiotherapy	Neo-adjuvant	18 (34%)	7 (41.1%)	*P*=0.3
	Adjuvant	35 (66%)	10 (58.9%)	

NMC: non-mucinous adenocarcinoma; MA: mucinous adenocarcinoma; LAR: low anterior resection; APR: abominoperineal resection

History and Clinical assessment of the patients

Age, sex, performance status, date of first symptoms, duration of symptoms before presentation, date and site of local recurrence, and date and site of distant metastasis.

Investigations

The following investigations were reviewed:

Pathological reports such as tumor size and location, nodal status, circumferential radical margin, lymphovascular invasion, perineural invasion, grading, histological subtypes, and resection status.

The pathologic stage, determined according to the eighth edition of AJCC staging manual (AJCC cancer staging manual, 8th ed, 2018).

Laboratory tests: complete blood count (CBC), liver function tests, and kidney function tests, serum carcinoembryonic antigen.

Radiological evaluation: colonoscopy, computed tomography (CT) and/or magnetic resonance imaging (MRI) of abdomen and pelvis, endoscopic ultrasound (EUS) if included, x-ray chest or CT chest if performed.

Treatment

Neoadjuvant chemoradiotherapy

We administered NACRT at a dose of 45 Gy

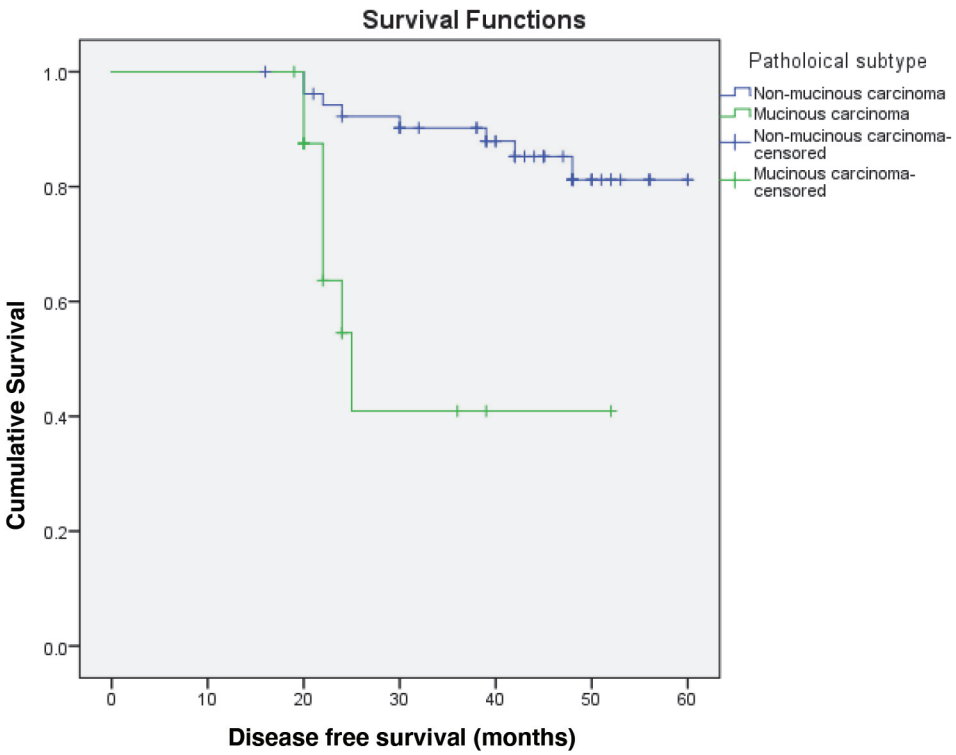

Figure 1. This figure shows the disease-free survival curves between both groups

Table 3. Pathological response of neo-adjuvant treatment in both studied groups

	NMC Group (n=18)	MA Group (n=7)	*P*-value
TGR1	2 (11.1%)	0 (0%)	0.532
TGR2	10 (55.5%)	1 (14.3%)	
TGR3	3 (16.7%)	2 (28.6%)	
TGR4	2 (11.1%)	3 (42.8%)	
TGR5	1 (5.6%)	1 (14.3%)	

NMC: non-mucinous adenocarcinoma; MA: mucinous adenocarcinoma

in 25 fractions delivering 1.8 Gy per fraction by 2D or 3D conformal radiotherapy (3DCRT).

The chemotherapy schedule was based on 5-flourouracil (5-FU) or combination

The patients underwent abdominoperineal resection (APR) or low anterior resection (LAR), 4-6 weeks after radiotherapy, depending on distance from anal verge and response to NACRT.

Adjuvant chemoradiotherapy

We administered adjuvant CRTH following surgery as six cycles of FOLFOX or Cape OX regimen and radiotherapy to the tumor site with a dose of 45 Gy in 25 fractions delivering 1.8 Gy per fraction by 2D or 3DCRT.

Concurrent chemotherapy with radiotherapy

Some patients received 5-FU 400mg/m^2 IV bolus and Leucovorin 20 mg/m^2 IV bolus, from day one to four, of weeks one and five of radiotherapy.

Other patients received Capecitabine 825 mg/m^2, twice daily, from day one to five, on a weekly basis for the five weeks of radiotherapy.

We applied radiotherapy at a total dose of 45 Gy / 5 weeks/ 25 fractions. We treated 32 patients with conventional 2D technique. The other 38 patients were treated via 3D conformal radiotherapy, using high energy linear accelerator.

Primary and secondary end points

The primary endpoint in this study was to analyze the prognostic impact of different mucin components on patients with stage II and stage III rectal carcinoma treated with radical surgery plus neoadjuvant chemoradiotherapy. The secondary end points were to evaluate DFS and OS.

Statistical analysis

We entered and analyzed the data using SPSS software (version 21).

We initially tested the quantitative data for normality using Kolmogorov-Smirnov and Shapiro-Wilk tests. Data were expressed as mean±standard deviation (SD), if normally distributed or median and interquartile range (IQR), if not.

We compared the quantitative data between the two groups using Independent-Samples t-test, if normally distributed or the non-parametric alternative Mann-Whitney U test, if not.

The standard logistic regression analysis calculated the odds ratio (OR) with its 95% confidence interval (95% CI).

We employed multivariable logistic regression to create a prediction model for the likelihood of a diagnosis to detect the significant "independent" predictors with their OR (95% CI).

The Kaplan-Meier method estimated the probability of survival past given time points.

The survival distributions of two or more groups of the between-subjects factor could be compared for equality using log-rank test

In all the employed tests, results were considered as statistically significant, if $P \leq 0.050$.

Results

During the study period (between January 2008 and December 2013), 147 patients fulfilled the inclusion criteria of newly-diagnosed locally advanced rectal cancer. Out of these cases, we excluded 77 due to deficiency in data and report; however, 70 cases with complete records were included for this analysis. 53 (75.5%) patients fulfilled the criteria for NMC and 17 (24.3%) patients met the criteria for MA.

Table 4. Local recurrence and distant metastasis in both groups

Variables		NMC Group (n=53)	MA Group (n=17)	*P* -value
Local Recurrence	No	45 (85%)	10 (53.3%)	*P*=0.023
	Yes	8 (15%)	7 (41.1%)	
Distant Metastasis	No	38 (71.7%)	9 (52.9%)	*P*=0.152
	yes	15 (28.3%)	8 (47.1%)	

NMC: non-mucinous adenocarcinoma; MA: mucinous adenocarcinoma.

Lower third rectum was the predominant in 43 patients (61.4%), among whom 28 were classified as NMC and 15 patients were MA; upper third rectum was the next site of primary tumor in 25 patients (35.7%), all considered as NMC; whole rectum was involved in only two patients who were both MA. This difference was statistically significant (*P*<0.005).

The difference in tumor size was statistically significant between the two groups (*P*<0.05); the majority of the mucinous group (88%) had larger tumors, while the non-mucinous group mainly included patients with smaller tumors (70 %) (*P*<0.005).

A great majority of the subjects in MA group were in stage III rather than stage II (88.2% versus 11.8%), while in NMC group, 54.7% were in stage III and 45.2% were in stage II. This difference was statistically significant (*P*=0.011)

Only 20 patients (28% of all patients) had positive LVI, most of whom (65%) were MA; also, the difference between both groups was statistically significant (*P*<0.005).

All our patients underwent radical surgical operation; most of the patients underwent APR (44/70, 62.8%) and LAR was done on 24 patients, all of whom satisfied the NMC criteria. We examined severe cases for intestinal obstruction, and it occurred in only two patients who fulfilled the MA criteria (2/2,100%).This difference seemed to be statistically significant (*P*<0.005), (Table 2). All our patients received chemoradiotherapy either preoperative or postoperative. 25 patients received NACRT, 18 of whom (representing 72%)

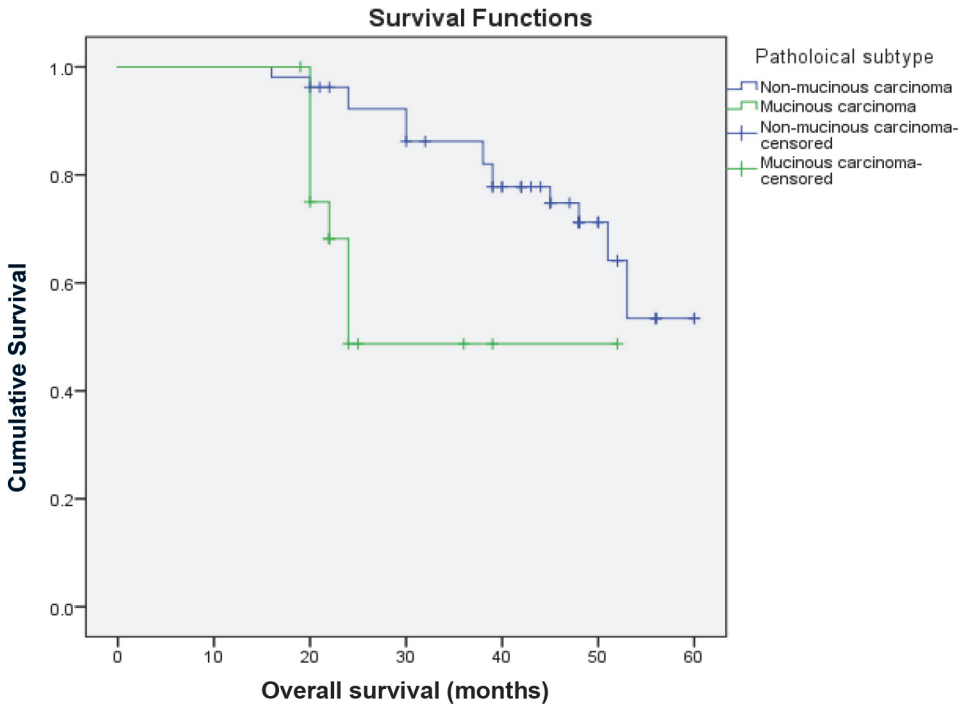

Figure 2. This figure shows the overall survival curves between both groups

Table 5. Sites of distant metastasis in both groups

Site	NMC Group (n=15)	MA Group (n=8)	*P* -value
Liver	12 (80%)	7 (87.5%)	*P*=0.3
Lung	2 (13.3%)	0 (0%)	
Both	1 (6.7%)	1 (12.5%)	

NMC: non-mucinous adenocarcinoma; MA: mucinous adenocarcinoma

met NMC criteria, while 7 (28%) had MA criteria.

The majority of the patients received their chemoradiotherapy after surgery (45/70, 64%); NMC represented the main bulk (35/45, 77.7%), while MA represented (10/45, 22.3%)(Table 2).

In our study, 25 patients received neoadjuvant chemoradiotherapy, representing 35.7% of all the patients included in the analysis.

Following neoadjuvant CRTH, only two patients (8%) achieved a pathologically complete response (pCR or yT0, yN0); tumor regression grading number 1(TRG1).[13] We detected no residual tumor cells after precise pathological examination of the specimen, and both patients fulfilled NMC criteria.

Partial response was achieved in 21 patients (84%); of these subjects, 11 showed fibrosis with scattered tumor cells (TRG2) and few tumor cells in fibrotic mass. Five patients showed fibrosis and tumor cells (TRG3) with abundant fibrosis cells; the remaining five patients showed fibrosis and tumor cells (TRG4) with residual tumor masses. Among these subjects, 15 fulfilled NMC criteria (71.4%), while only six were MA (28.6%).

No response showed a tumor tissue without change or regression (TRG5); this occurred in only two patients (8%), one of whom met MA criteria and the other had NMC criteria.[13] This difference was not statistically significant although MA seemed to have a more aggressive prognosis (Table 3).

DFS and OS

The median DFS for NMC was beyond 60 months, while that for MA was 24 months (95% CI, 20.82 -29.89 months). (*P*=0.008),(Figure 1).The median OS for NMC was beyond 60 months, while that for MC was 25 months (95% CI, 18.32 -28.34 months), (*P*=0.002), (Figure 2).

Of the three predictor variables, pathological subtype was the only statistically significant independent predictor (as shown in Table 6). Patients with NMC had 6.997 times higher odds to have a three-year DFS. Regarding the three-year OS, pathological subtype and LVI were statistically significant independent predictors (Table 7).

Discussion

MA is diagnosed when the extracellular mucin exceeds 50% of the tumor. In our study, this was the case in 24% of the patients, which is higher than the incidence rates in Asia, ranging from 3% to 9%,[7,14,15] and slightly higher than the incidence rates reported in western countries (11-20%).[16,17] This difference may be attributed to the change in dietary habits and life style.

This subtype classification showed its importance in the difference between MA and NMC regarding the clincopathological characteristics. MA group in our study had worse clinical factors compared with NMC group, consistent with the results of Du et al., and Mekenkamp et al.[18,19]

In the current study, MA occurred in younger patients compared to NMC, which is in line with Song et al., Hosseini et al., and Hovert etal.,[14,20,1] Another study, however, reported no age difference between the two groups.[21]

In some studies, MA was more frequently present in men than in women.[22,15] In contrast, several trials reported female predominance.[18,8] Our study showed no gender preference between MA and NMC, which is similar to other reports.[19,21,20]

Many studies observed that MA has a larger tumor size than NMC;[20,1] this is in accordance with our results (*P*<0.005) and in contrast to studies, which did not detect such a relationship.[23]

According to the tumor location, the lower

Table 6. The variables in the equation

Variables	B	S.E.	Wald	*P*	OR	95% CI for OR	
						Lower	Upper
Pathological subtype (mucinous vs. non-mucinous)	1.945	0.801	5.896	0.015	6.997	1.455	33.643
Staging	0.567	0.678	0.700	0.403	1.764	0.467	6.664
Lymph-vascular invasion	1.341	0.739	3.295	0.69	3.823	0.899	16.267
Constant	-2.053						

OR: overall survival; CI: confidence interval; SE: standard error; B: understandardized beta; Wald: Wald test

third of the rectum was involved in all MA cases as compared to the 53% in NMC (P<0.005); this affects the type of surgery, local control, OS, and the life quality of the patients.[24]

Moreover, MA often presents with advanced stages.[25,20] This characteristic is in agreement with the results of our study, where MA presented with a higher percentage of stage III patients in comparison to NMC (88% vs. 54.7%).

In the current study, LVI was more frequent in MA group as compared to the NMC group (76.5% vs. 13.2%, P<0.005). This is consistent with the results of Wang et al.,[5] and in contrast to the results of Hosseini et al.,[25]

The presence of tumors containing lymph nodes is the most important prognostic factor for survival or recurrence.[26] In the present study, MA showed a high frequency of nodal involvement; however, the difference did not reach a statistically significant level (P=0.23), which might be attributed to the small number of patients involved in our study. Other researchers reported the high frequency of nodal involvement in the mucinous variety.[20,1]

The prognostic value of MA is still controversial. In our study, it showed a poor prognosis. Verhulst et al. observed similar results.[8] However, Compton et al. and Xie et al., showed no association.[11,27] Recently, Hosseini et al., concluded that mucinous histologic subtype was associated with adverse pathologic features in patients with CRC; nevertheless, it was not an independent prognostic factor for oncologic outcome.[20]

The reason behind the poor prognosis of MA is yet to be completely known. MA was proved to have a different natural history. Sugarbaker et al., believes that MA has very high component of mucin inside the cells causing the mucous to dissect between the fat planes and carry the tumor cells, which float between the mucin and allow the tumor to penetrate deeply and mostly reach the peritoneal cavity leading to worse clinical factors and poor prognosis.[28] They also suggest that these tumors are relatively radio- and chemo-resistant due to genetic and molecular factors.[5]

In our study, staging and LVI were proven to affect both DFS and OS. This is in line with College of American Pathologist (CAP), as they define the staging and LVI are prognostic factors category I.[11]

NACRT has become the standard treatment for LARC, especially that located in the lower third as it is associated with tumor down staging, significantly higher rates of PCR, fewer cases with venous invasion, PNI or LVI, increased tumor resectability, thereby increasing the chance of sphincter-sparing surgery.[29]

Hosseini et al., and Tan et al., reported that the MA of the rectum showed a poor response to NACRT. In our study, the response of NMC to NACRT was higher than MA, where pathological complete response was achieved in 11% of the patients in the NMC group vs. no patients in the MA group.[20,29] We reported poorer tumor regression grades in the mucinous variant;TRG1, 2 were achieved in 67% of the NMC patients versus 14% in the MA group; however, the difference was not statistically significant, which might be due to the retrospective nature of the study and the small number of patients in the neoadjuvant arm.[13]

Table 7. The variables in the equation

Variables	B	S.E.	Wald	*P*	OR	95% CI for OR	
						Lower	Upper
Pathological subtype (mucinous vs. non-mucinous)	2.370	0.828	8.187	0.004	10.695	2.110	54.217
Staging	0.198	0.802	0.61	0.805	1.218	0.253	5.872
Lymph-vascular invasion	1.953	0.785	6.186	0.013	7.048	1.513	32.842
Constant	-2.256						

OR: overall survival; CI: confidence interval; SE: standard error; B: understandardized beta; Wald: Wald test

Numata et al., Nitsche et al., and Hosseini et al., reported the adverse effects of MA on local recurrence, which was confirmed in our study. Therefore, whether the management of MA should be more different than the traditional treatment for the classic adenocarcinoma is still not known.[30,31,20]

As regards distant metastases, Simha et al., reported higher distant metastasis incidence in the MA group as compared with the NMC group. In our study, the incidence of distant metastasis was higher in the MA group (47%) in comparison to the NMC group (28%), but the difference was not statistically significant.[32]

Similar to Song et al., we did not find a difference in hepatic metastasis by histological type; also, Hosseini et al., suggested that mucinous tumors are locally invasive with peritoneal seeding and hematogenous metastasis is not common.[14,20]

We found that the histologic subtype was an independent prognostic factor for both OS and DFS in stage II and III rectal cancer patients as *P*= 0.002 and *P*=0.008, respectively. This is consistent with the results of Biffiet al., Hugen et al., and Wang et al.,[9,10,5] On the other hand, AJCC and the CAP believe that MA has no statistically significant effect for the same grade and stage.[11] Moreover, Hogan showed an improved survival in patients with MA of the colon. These differences might be due to the difference in the population of patients, exclusion of rectal tumors in some studies, and different number of patients included in different studies.[33]

The first limitation of this study was that it was retrospective, which may be intrinsically associated with an imbalance between patients and tumor characteristics. The second limitation was the modest number of patients in the mucinous subtype arm, which might preclude the detection of very small differences. However, it was sufficient to evaluate the prognostic value of adenocarcinoma with different extracellular mucin components.

Conclusion

Histological subtype (with different mucin components) was an independent prognostic factor for both DFS and OS of patients with stages II and III rectal carcinoma. However, more well-designed multicentered prospective trials should be conducted to evaluate any need for histology-based treatment modulation in patients with locally advanced rectal carcinoma.

References

1. Horvat N, Hope TA, Pickhardt PJ, Petkovska I. Mucinous rectal cancer: concepts and imaging challenges. *Abdom Radiol (NY)*. 2019;44(11):3569-80. doi: 10.1007/s00261-019-02019-x.
2. American Cancer Society. Cancer Facts & Figures 2017. Atlanta: American Cancer Society; 2017.p.1-70. Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2017/cancer-facts-and-figures-2017.pdf.
3. Ibrahim AS, Khaled HM, Mikhail NN, Baraka H, Kamel H. Cancer incidence in Egypt: results of the national population-based cancer registry program. *J Cancer Epidemiol*. 2014;2014:437971. doi: 10.1155/2014/437971.
4. Greene FL. Current TNM staging of colorectal cancer. *Lancet Oncol.* 2007;8(7):572-3.
5. Wang M, Zhang YC, Yang XY, Wang ZQ. Prognostic significance of the mucin component in stage III rectal carcinoma patients. *Asian Pac J Cancer Prev.*

2014;15(19):8101-5.
6. Hamilton SR, Bosman FT, Boffetta P. Carcinoma of the colon and rectum. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO classification of tumours of the digestive system. 4th ed. Lyon: International Agency for Research on Cancer; 2010.p.134-146.
7. Kanemitsu Y, Kato T, Hirai T, Yasui K, Morimoto T, Shimizu Y, et al. Survival after curative resection for mucinous adenocarcinoma of the colorectum. *Dis Colon Rectum.* 2003;46(2):160-7.
8. Verhulst J, Ferdinande L, Demetter P, Ceelen W. Mucinous subtype as prognostic factor in colorectal cancer: a systematic review and meta-analysis. *J Clin Pathol.* 2012;65(5):381-8. doi: 10.1136/jclinpath-2011-200340.
9. Biffi R, Botteri E, Bertani E, Zampino MG, Cenciarelli S, Luca F, et al. Factors predicting worse prognosis in patients affected by pT3 N0 colon cancer: long-term results of a monocentric series of 137 radically resected patients in a 5-year period. *Int J Colorectal Dis.* 2013;28(2):207-15. doi: 10.1007/s00384-012-1563-y.
10. Hugen N, Verhoeven RH, Radema SA, de Hingh IH, Pruijt JF, Nagtegaal ID, et al. Prognosis and value of adjuvant chemotherapy in stage III mucinous colorectal carcinoma. *Ann Oncol.* 2013;24(11):2819-24. doi: 10.1093/annonc/mdt378.
11. Compton CC, Fielding LP, Burgart LJ, Conley B, Cooper HS, Hamilton SR, et al. Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. *Arch Pathol Lab Med.* 2000;124(7):979-94.
12. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer (Version 3.2017); 2017. Available at: http://www.nccn.org. (Accessed on: March 17, 2017).
13. Nasierowska-Guttmejer A, Szawtowski A. How to standardize the evaluation of tumor regression grading of gastrointestinal cancers after neoadjuvant therapy? *Virchows Arch*. 2018;473(2):255-6. doi: 10.1007/s00428-018-2391-4.
14. Song W, Wu SJ, He YL, Cai SR, Zhang CH, Zhang XH, et al. Clinicopathologic features and survival of patients with colorectal mucinous, signet-ring cell or non-mucinous adenocarcinoma: experience at an institution in southern China. *Chin Med J (Engl)*. 2009;122(13):1486-91.
15. Soliman BG, Karagkounis G, Church JM, Plesec T, Kalady MF. Mucinous histology signifies poor oncologic outcome in young patients with colorectal cancer. *Dis Colon Rectum*. 2018;61(5):547-53. doi: 10.1097/DCR.0000000000001060.
16. Consorti F, Lorenzotti A, Midiri G, Di Paola M. Prognostic significance of mucinous carcinoma of colon and rectum: a prospective case-control study. *J Surg Oncol.* 2000;73(2):70-4.
17. Purdie CA, Piris J. Histopathological grade, mucinous differentiation and DNA ploidy in relation to prognosis in colorectal carcinoma. *Histopathology*. 2000;36(2):121-6.
18. Du W, Mah JT, Lee J, Sankila R, Sankaranarayanan R, Chia KS. Incidence and survival of mucinous adenocarcinoma of the colorectum: a population-based study from an Asian country. *Dis Colon Rectum.* 2004;47(1):78-85.
19. Mekenkamp LJ, Hesterbeek KJ, Koopman M, Tol J, Teerenstra S, Venderbosch S, Punt CJ, et al. Mucinous adenocarcinomas: poor prognosis in metastatic colorectal cancer. *Eur J Cancer.* 2012;48(4):501-9. doi: 10.1016/j.ejca.2011.12.004.
20. Hosseini S, Bananzadeh AM, Salek R, Zare-Bandamiri M, Kermani AT, Mohammadianpanah M. Prognostic significance of mucinous histologic subtype on oncologic outcomes in patients with colorectal cancer. *Ann Coloproctol.* 2017;33(2):57-63. doi: 10.3393/ac.2017.33.2.57.
21. Yamaguchi T, Taniguchi H, Fujita S, Sekine S, Yamamoto S, Akasu T, et al. Clinicopathological characteristics and prognostic factors of advanced colorectal mucinous adenocarcinoma. *Histopathology.* 2012;61(2):162-9. doi: 10.1111/j.1365-2559.2012.04235.x.
22. Papadopoulos VN, Michalopoulos A, Netta S, Basdanis G, Paramythiotis D, Zatagias A, et al. Prognostic significance of mucinous component in colorectal carcinoma. *Tech Coloproctol*. 2004;8 Suppl 1:s123-5.
23. Chiang JM, Yeh CY, Changchien CR, Chen JS, Tang R, Chen JR. Mucinous adenocarcinoma showing different clinicopathological and molecular characteristics in relation to different colorectal cancer subgroups. *Int J Colorectal Dis.* 2010;25(8):941-7. doi: 10.1007/s00384-010-0958-x.
24. Parfitt JR, Driman DK. The total mesorectal excision specimen for rectal cancer: a review of its pathological assessment. *J Clin Pathol.* 2007;60(8):849-55.
25. Hosseini S, Zohourinia S, Zare-Bandamiri M, Mokhtari M, Pourhashemi S, Hosseinzadeh M, et al. Clinical and pathological characteristics of mucinous colorectal adenocarcinoma: A comparative study. *Ann Colorectal Res.* 2016;4(1):e34404. doi:10.17795/arc.34404.
26. Adell R, Marcote E, Segarra MA, Pellicer V, Gamón R, Bayón AM, et al. Is mucinous colorectal adenocarcinoma a distinct entity. [Article in Spanish] *Gastroenterol Hepatol*. 2002;25(9):534-40.
27. Xie L, Villeneuve PJ, Shaw A. Survival of patients diagnosed with either colorectal mucinous or non-mucinous adenocarcinoma: a population-based study in Canada. *Int J Oncol.* 2009;34(4):1109-15.
28. Sugarbaker PH, Graves T, DeBruijn EA, Cunliffe WJ, Mullins RE, Hull WE, et al. Early postoperative intraperitoneal chemotherapy as an adjuvant therapy

to surgery for peritoneal carcinomatosis from gastrointestinal cancer: pharmacological studies. *Cancer Res.* 1990;50(18):5790-4.
29. Tan Y, Fu D, Li D, Kong X, Jiang K, Chen L, et al. Predictors and risk factors of pathologic complete response following neoadjuvant chemoradiotherapy for rectal cancer: A population-based analysis. *Front Oncol.* 2019;9:497. doi: 10.3389/fonc.2019.00497.
30. Numata M, Shiozawa M, Watanabe T, Tamagawa H, Yamamoto N, Morinaga S, et al. The clinicopathological features of colorectal mucinous adenocarcinoma and a therapeutic strategy for the disease. *World J Surg Oncol.* 2012;10:109. doi: 10.1186/1477-7819-10-109.
31. Nitsche U, Zimmermann A, Späth C, Müller T, Maak M, Schuster T, et al. Mucinous and signet-ring cell colorectal cancers differ from classical adenocarcinomas in tumor biology and prognosis. *Ann Surg*. 2013;258(5):775-82; discussion 782-3. doi: 10.1097/SLA.0b013e3182a69f7e.
32. Simha V, Kapoor R, Gupta R, Bahl A, Nada R. Mucinous adenocarcinoma of the rectum: a poor candidate for neo-adjuvant chemoradiation? *J Gastrointest Oncol.* 2014;5(4):276-9. doi: 10.3978/j.issn.2078-6891.2014.020.
33. Hogan J, Burke JP, Samaha G, Condon E, Waldron D, Faul P, et al. Overall survival is improved in mucinous adenocarcinoma of the colon. *Int J Colorectal Dis.* 2014;29(5):563-9. doi: 10.1007/s00384-013-1826-2.