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Research Article

Rare Mucinous Colorectal Adenocarcinoma: Analysis of the Epidemiological Factors in Relation to Survival in Egyptian Patients

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Abstract

Colorectal carcinoma (CRC) is one of the leading causes of cancer related deaths; in Egypt it constitutes 6.5% of all cancers. Previous studies have shown conflicting results on clinicohistopathological features and survival of patients with colorectal mucinous (MA) and non-mucinous adenocarcinoma (NMA). To the best of our knowledge, this study is the first to investigate these features in Egypt. In this work, we studied tumor tissue specimens from 150 patients with colorectal MA and NMA who underwent radical surgery from Jan 2007 to Jan 2012 at Gastroenterology Centre, Mansoura University, Egypt. Their clinicohistopathological parameters and survival were analyzed using established statistical methodologies. Incidence of MA and its subtypes was much higher in Egypt than worldwide incidence. MA was significantly associated with younger age, more depth of invasion, lymph node metastasis, less microscopic abscess formation and less peri-tumoral lymphocytic response (Crohn-like response) than NMA. Both groups were not significantly different "among others" in other clinicopathological parameters including lymphovascular and perineural invasion, association with adenoma and schistosomiasis. Multivariate analyses for disease free and overall survival revealed that mucinous histology is an independent prognostic factor. Among several factors, only distant metastasis and presentation with recurrent disease were independent prognostic factors within MA patients. In conclusion, MA represents a distinct clinicopathological entity with worse survival than NMA. Distant metastasis and presentation with recurrent disease are independent prognostic factors. Further molecular investigations considering genetic features of MA will lead to drug development and better management.

Keywords: clinicopathologic; mucinous; non-mucinous; colorectal carcinoma
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Introduction

Colorectal carcinoma (CRC) is a major cause of morbidity and mortality throughout the world. It is the third most common cancer worldwide and the fourth most common cause of death [1]. It constitutes 9.5% of all cancers worldwide [2] whereas; in Egypt it contributes 6.5% of all cancers [3].

Mucinous adenocarcinoma (MA), a morphologic subtype of CRC, has more than 50% of the tumor composed of mucin, either extracellular with mucin lakes (colloid carcinoma) or intracellular where more than 50% of the tumor consists of signet ring cells (signet ring cell adenocarcinoma) [4].

Both colloid and signet ring adenocarcinomas are relatively rare, and this contributes to the difficulty of examining their clinicopathological features as well as survival outcomes [5]. In general, MA accounts for 5%-15% of CRC [6, 7] and signet ring cell tumors account for approximately 1% [8].

The importance of these distinct histological appearances lies in the observed differences between MA and NMA with regard to clinicopathological characteristics, distinct genetic profiles, and pathogenic pathways [9].

In this study, we aimed to clarify the clinicohistopathological characteristics and survival of colorectal MA and NMA in the Egyptian population.

Material and methods

Samples:

This retrospective study was carried out in surgical pathology lab at Gastroenterology Center, Mansoura, Egypt. Files of all resected CRC cases were revised during the period from 2007 to 2011 (341 cases). MA cases were selected and revised (75 cases). Another 75 cases of NMA were chosen randomly for comparison from the same period.

Clinical parameters and histopathological evaluation:

All clinicopathological data of the 150 cases were revised with re-examination of all their slides to evaluate histological criteria. This includes: age, gender, location, size, shape, multiplicity, histological type, percent of the subtype, grade, depth of invasion (T), tumor margins, lymphovascular invasion, perineural invasion, peri- and intra-tumoral lymphocytic infiltration, extent of neutrophilic infiltrate, nearby and distant mucosa, whether the tumor was on top of adenoma or not, number of LN metastases (N), distant metastasis (M), TNM staging, state of surgical cut margins, associated ulcerative colitis, associated schistosomiasis, exact site of the ova and any other finding.

Histological types and stages were classified by pathologists using the World Health Organization (WHO) criteria [4].

Survival and Statistical analysis

Data were analyzed, applying SPSS, version 16.0 for Windows (SPSS Inc, IBM, and Chicago, Illinois). $\chi 2$ (Chi-square) test was used to test significant differences between MA and NMA groups. Survival data were analyzed using Kaplan-Meier test. A comparison of survival curves was carried out using the log-rank test. For multivariate analysis, Cox proportional hazard models were performed. A 2-tailed $P \leq 0.05$ was considered significant in all tests.

Results

Demographics

In total, 75 cases of MA out of 341 cases of CRC (22%) were received at surgical pathology lab at Gastroenterology Center, Mansoura, Egypt, during the period from 2007 to 2011. They included 56 cases of colloid adenocarcinoma (16.7% of all cases) and 19 cases of signet ring adenocarcinoma (5.6% of all cases).

Age range at presentation for NMA was 27 to 78 years (mean, 54.9 years) and 20 to 80 years (mean, 50.5 years) for MA. Patients with MA were statistically younger than those with NMA (P=0.017) (table 1).

The participants were 93 men and 57 women, with no significantly detected difference in gender between both groups (P=0.614) (table 1).

Tumor characteristics

In this study, 150 CRC cases were analyzed. Seventy five NMA included 47 cases of ordinary adenocarcinoma and 28 cases of adenocarcinoma with mucinous component <50% of the tumor. The other 75 cases of MA cases included 56 cases of colloid adenocarcinoma and 19 cases of signet ring cell carcinoma.

The clinicopathological and histological features of 75 cases of MA and 75 cases of NMA are listed in Tables 1&2.

Regarding clinicopathological features, MA and NMA groups were not significantly different in tumor size, location, gross picture, multiplicity, surgical cut margins and pathological TNM staging (Table 1).

Ninety-two percent of MA cases showed invasion of the tumor beyond the muscularis mucosa, which was significantly higher than NMA (P=0.008). Less than 50% of NMA cases and more than 60% of MA cases showed LN metastasis at the time of presentation; MA was significantly associated with more frequency of LN metastasis (P=0.008) (Table 1).

Regarding histological features, MA and NMA were not significantly different in the frequency of lymphovascular invasion, perineural invasion, associated adenoma, associated schistosomiasis, configuration of tumor margins and intra-tumoral lymphocytic infiltration (Table 2).

However, about 70% of NMAs showed massive debris and leucocytes infiltration (mainly neutrophils) at the surface and invasive tumor margin "Microscopic abscess formation", which was significantly higher than MA (P<0.001) (Table 2).

Additionally, about 80% of mucinous CRC cases showed negative peri-tumoral lymphocytic response "Crohn-like response", which was significantly lower than NMA (P=0.017) (Table 2)

Survival

To clarify the prognostic impact of mucinous histology on CRC, univariate and multivariate analyses were carried out. The 3 years disease free survival (DFS) for patients with MA was 49.3% compared to 62.2% in NMA patients. The median DFS was significantly lower for patients with MA compared to patients with NMA, median 17 months (95% CI 13.8-20.2) versus 58 months (95% CI 47-69) respectively; (p < 0.001) (Figure 1A). Multivariate analysis demonstrated that MA histology is independent negative predictor of DFS (HR: 2.2, 95% CI 1.2 - 4.04, P= 0.01).

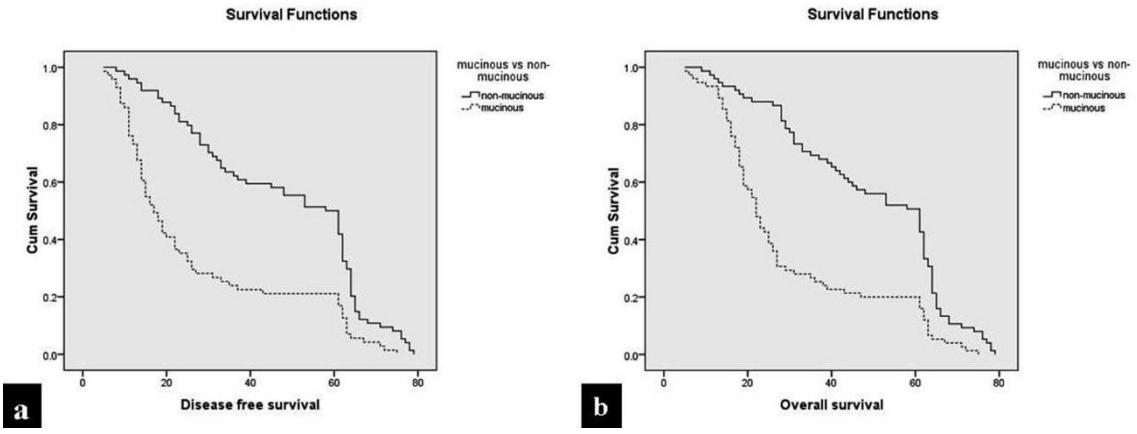

Figure 1 (a): DFS (months, log-rank test) in patients with colorectal carcinoma related to mucinous versus non-mucinous histology (P < 0.001). (b): OS (months, log-rank test) in patients with colorectal carcinoma related to mucinous versus non-mucinous histology (P < 0.001).

Table 1 Clinicopathological features of 150 cases of mucinous and non-mucinous CRC

	Non-Mucinous No. (%)	Mucinous No. (%)	Chi-square ($\chi 2$)	P value
Age (y)				
- < 40	10 (13.3%)	22 (29.3%)	5.720	**0.017***
- ≥ 40	65 (86.7%)	53 (70.7%)		
Gender				
- Male	48 (64.0%)	45 (60.0%)	0.255	0.614
- female	27 (36.0%)	30 (40.0%)		
Tumor size				
- < 6	46 (61.3%)	36 (48.0%)	2.690	0.101
- ≥ 6	29 (38.7%)	39 (52.0%)		
Location				
- Right	18 (24.0%)	23 (30.7%)		
- Left	6 (8.0%)	6 (8.0%)	0.887	0.829
- Recto-sigmoid	45 (60.0%)	41 (54.7%)		
- Transverse	6 (8.0%)	5 (6.7%)		
Gross picture				
- Fungating	34 (45.3%)	27 (36.0%)		
- Ulcerating	19 (25.3%)	27 (36.0%)	2.218	0.330
- Annular	22 (29.3%)	21 (28.0%)		
Multiplicity				
- Negative	65 (86.7%)	69 (92.0%)	1.119	0.290
- Positive	10 (13.3%)	6 (8.0%)		
Surgical cut margins				
- Free	72 (96.0%)	70 (93.3%)	0.28	0.467
- Infiltrated	3 (4.0%)	5 (6.7%)		
Depth of invasion				
- T1/T2	18 (24.0%)	6 (8.0%)	7.143	**0.008***
- T3/T4	57 (76.0%)	69 (92.0%)		
LN				
- N0	38 (50.7%)	27 (36.0%)		
- N1	25 (33.3%)	19 (25.3%)	9.729	**0.008***
- N2	12 (16.0%)	29 (38.7%)		
Metastasis				
- M1	1 (1.3%)	4 (5.3%)	1.862	0.172
- Mx	74 (98.7%)	71 (94.7%)		
TNM stage				
- I /II	37 (49.3%)	27 (36.0%)	2.725	0.099
- III /IV	38 (50.7%)	48 (64.0%)		

* $P \leq 0.05$ is significant.

Table 2 Histological features of 150 cases of mucinous and non-mucinous CR

	Non Mucinous	Mucinous	Chi-square	P value
	No. (%)	No. (%)	(χ2)	
Lymphovascular emboli				
-Negative	30 (40.0%)	23 (30.7%)	1.430	0.232
-Positive	45 (60.0%)	52 (69.3%)		
Perineural invasion				
-Negative	54 (72.0%)	48 (64.0%)	1.103	0.294
-Positive	21 (28.0%)	27 (36.0%)		
Associated adenoma				
-Negative	39 (52.0%)	41 (54.7%)	0.107	0.743
-Positive	36 (48.0%)	34 (45.3%)		
Associated schistosomiasis				
-Negative	65 (86.7%)	62 (82.7%)	0.462	0.497
-Positive	10 (13.3%)	13 (17.3%)		
Tumor margins				
-Budding	68 (90.7%)	69 (92.0%)	0.084	0.772
-Pushing	7 (9.3%)	6 (8.0%)		
Microscopic abscess formation				
-Negative	24 (32%)	49 (65.3%)	16.679	**<0.001***
-Positive	51 (68%)	26 (34.7%)		
Peri-tumoral lymphocytic response (Crohn-like response)				
-Negative	48 (64.0%)	61 (81.3%)	5.672	**0.017***
-Positive	27 (36.0%)	14 (18.7%)		
Intra-tumoral lymphocytic response				
-Negative	70 (93.3%)	73 (97.3%)	1.349	0.246
-Positive	5 (6.7%)	2 (2.7%)		

* $P \leq 0.05$ is significant.

Patients with MA had significantly lower 5 years overall survival (OS) (20%) than those with NMA (50.7%), the median OS for patients with MA and NMA was 22 months (95% CI 19.5 - 24.5) and 61 months (95% CI 50–72), respectively; (P = <0.001) (Figure 1B). Furthermore, MA was noted to be independent prognostic factor for OS in multivariate analysis (HR: 2.38, 95% CI 1.3 - 4.4, P = 0.006).

Within the group of MA, a univariate analysis was done to test parameters with impact on DFS and/or OS using Kaplan–Meier analysis. It revealed that T4 disease, positive LN, lymphovascular emboli, perineural invasion, recurrent disease as well as distant metastasis were significant negative prognostic variables. For the remaining clinicopathological and histological factors, there were no significant prognostic values (data not

shown). However, by applying multivariate Cox regression analysis to test the prognostic yield of these parameters, no significant independent negative predictors for DFS (Table 3), both distant metastasis and recurrent disease proved to be independent significant prognostic factors regarding OS (Table 4).

Table 3 Multivariate analysis of prognostic factors by the Cox's proportional hazards regression models of patients with mucinous adenocarcinoma with respect to disease-free survival

	Risk ratio	CI	P-value
T4 disease	2.2	0.63 - 7.69	0.22
Positive LN	1.33	0.86 - 2.06	0.19
Lymphovascular emboli	1.39	0.6 - 3.23	0.44
Perineural invasion	1.22	0.7 - 2.13	0.48
Presentation by recurrent disease	1.33	0.32 - 5.51	0.69

Table 4 Multivariate analysis of prognostic factors by the Cox's proportional hazards regression models of patients with mucinous adenocarcinoma with respect to overall survival

	Risk ratio	CI	P-value
T4 disease	1.12	0.41 - 3.08	0.83
Positive LN	1.32	0.86 - 2	0.20
Lymphovascular emboli	1.45	0.63 - 3.32	0.38
Perineural invasion	1.28	0.75 - 2.2	0.37
Presentation by recurrent disease	4.08	1.27 - 13.09	**0.018***
Distant metastasis	0.02	0.005 - 0.111	**< 0.001***

* $P \leq 0.05$ is significant.

Discussion

MA is a commonly studied histological subtype of CRC. However, the prognostic value of mucinous histology remains controversial. To the best of our knowledge, this is the first study of clinicohistopathological features and survival of MA and NMA in Egypt.

In our study, the incidence of MA in general in Egypt was nearly double that of worldwide incidence. Especially, incidence of signet ring carcinoma in Egypt was 5 times higher than worldwide incidence. These findings suggest that genetic factors may be play an important role in the development of this subtype in our country, and further studies are needed to explore these genetic factors.

The importance of this distinct subtype lies in the observed differences between MA and NMA with regard to clinicopathological characteristics, distinct genetic profiles, and pathogenic pathways [9].

Consistent with our study, previous reports showed that MA group had worse clinical factors when compared to NMA group, including younger age at presentation [6, 7, 9-11].This finding shows that the younger the age at presentation, the more malignant the behavior of the tumor and the shorter the expected survival [12]. Surprizingly, Yamaguchi *et al.* [13] reported no difference in age between both groups although they investegated about 4300 cases of CRC!

MA was more frequent in men than in women in some reports [14, 15], whereas our data are in line with more previous studies [9, 12, 13], that similarly identified no significant diffrence in gender between both groups.

Several studies had also observed larger tumor size in MA than NMA [6, 9, 12, 13, 16-18]. Consistent with Chiang *et al*., we didn't find this relation.

Regarding location of the tumor, several studies had

observed that MA occured more frequently within the right hemicolon [6, 13, 17, 20-23]. However, consistent with Mekenkamp *et al.* [9], MA in our study occured also more frequently within the right hemicolon and rectosigmoid, but this was not statistically significant.

To the best of our knowledge, this is the first study to investigate gross appearance of the tumor (either fungating, ulcerating or annular), multiplicity and state of surgical cut margins either infiltrated or not, within MA and NMA groups. Both groups showed no statistically significant difference in these parameters.

In this study, our data confirmed that of most studies about deeper invasion of MA than NMA [6, 7, 9-11, 13]. However, some studies didn't detect a difference between both groups [17].

Similarly, we reported higher frequncy of LN metastasis with MA as previous studies [6, 7, 10-13, 20, 22]. On the other hand, other studies didn't [9, 17].

Because of previous conflicting results regarding depth of invasion and LN metastasis, the influence of mucinous histology on TNM staging of CRC is still in dispute. Many studies reported higher stage at time of diagnosis for MA than NMA [13, 16, 19, and 20]. However, other studies showed that MA was not significantly different from NMA in staging [16, 24, and 25]. In our study, although MA showed significantly more depth of invasion and more LN metastases than NMA, TNM staging was not significantly different between both groups.

These wide variations in clinicopathological features reported by many studies on MA and NMA can be attributed to large variations of the number of cases of each study, difference in races, genetic alterations, and wide heterogeneity of sampling criteria of the cases in addition to limitations inherent to retrospective analyses.

Histological criteria of MA and NMA were not extensively examined as their clinicopathological counterparts. This may be attributed to the nature of most previous studies that were dependent only on registries of their centers and focusing on survival data only. In this study, MA and NMA groups were not significantly different in lymphovascular and perineural invasion as reported by Langner *et al*. [17]. In our study, the two groups were not significantly different in association with adenomas.

Although our locality is endemic for schistosomiasis, no significant association with either group was detected in present study. Contrasting to this result, a previous study by Madbouly *et al*. [26] had shown that schistosoma mansoni-associated CRCs have distinctive pathological features including high percentage of multicentric tumors and mucinous type. In this study, CRC associated with bilharzial lesions was 15.3 % with a frequency slightly lower than the frequency reported by EL-Bolkainy *et al*. [27].

For MA, few studies examined the histological features at the tumor invasive front and their prognostic significance. Kakar *et al*. [28] classified MA into those with pushing and infiltrative advancing fronts, and showed that infiltrative growth was not related significantly to a poorer prognosis. On the other hand, Yamaguchi *et al*. [13] identified infiltrative growth pattern as an independent prognostic factor in MA. Langner *et al*. [17] demonstrated a significant association between mucinous histology and expansive (pushing) tumor border, in relation to infiltrative (budding) margin in NMA. However, we didn't find these relations. About 90% of MA and NMA groups in our study showed infiltrative rather than bushing margins.

Microscopic abscess formation was defined as the presence of debris and leucocytes (mainly neutrophils) at the invasive tumor margin, and was considered to be associated with more favourable outcome in rectal cancers [29]. Yamaguchi *et al*. [13] reported that MA was significantly associated with negative microscopic abscess formation. Our data confirmed these findings; about 65% of MA cases in our study were associated with negative microscopic abscess formation, which was significantly different from NMA that was associated with more microscopic abscess formation. In addition, we detected this abcess formation at the surface of the tumor as well as its advancing edge. However there is accumulating evidence for an important role of inflammation in tumor progression, it seems that MA does not depend on these roles for invasion; rather it invades by dissecting tissue planes with prevention of immunological recognition of tumor cells by interfering with inflammatory responses [19, 30]. Our data are also in line with Yamaguchi *et al*. [13] who similarly identified significantly lower peri-tumoral lymphocytic (Crohn-like) infiltrate in MA than NMA. More than 80% of MA cases in this study were associated with negative Crohn-like response. This finding further emphasises

that MAs are less immunogenic than NMAs, and supports the concept of prevention of immunological recognition of tumor cells either by interfering with inflammatory responses or by wrapping the tumor cells by mucin. In contrast, there was no significant difference between MA and NMA groups regarding intra-tumoral lymphocytic infiltrate.

The prognostic value of MA is still highly controversial. Our data confirmed those of most studies reported that MA was associated with poor prognosis [6, 15, 16, 21, 23], while others found no correlation between this histological subtype and clinical outcome [31- 34].

Moreover, the reasons beyond this poor prognosis of MA are still also in dispute. Some studies revealed that advanced stage at presentation was the main factor [13, 16, 19, and 20]. Consistent with Kang *et al*. [8] and Yamaguchi *et al*. [13], we didn't found staging to be an independent prognostic factor. Conversely, in agreement with Kang *et al*. [8], we confirmed that distant metastasis is an independent prognostic factor. Moreover, presentation with recurrent disease is another independent prognostic factor in our study. However, T4 tumors, positive LN metastases, lymphovascular emboli and perineural invasion were associated with poor survival in univariate but not multivariate analyses in the present study.

In conclusion, MA represents a distinct clinicopathological entity with worse survival than NMA. Distant metastasis and presentation with recurrent disease are independent prognostic factors. Further molecular studies considering genetic features of MA will lead to tailored drug development and better management.

References

1. F.A. Haggar and R.P. Boushey, Colorectal Cancer Epidemiology:Incidence, Mortality, Survival, and Risk Factors. Clin. ***Colon Rectal. Surg***. 2009, 22:191-197
2. D.M. Parkin, F. Bray, J. Ferlay J, P. Pisani, Global cancer statistics, 2002. ***CA. Cancer J. Clin.*** 2005, 55:74-108
3. T.N. El-Bolkainy, M.A.Sakr, A.A. Nouh, N.H. El-Din, A comparative study of rectal and colonic carcinoma:demographic, pathologic and TNM staging analysis journal of the Egyptian. ***Natl. Cancer Inst.*** 2006, 18:258-263
4. S.R.Hamilton, F.T. Bosman, P. Boffetta P, *et al*. Tumors of the colon and rectum. In:F.T. Bosman, F. Carneiro F, R.H. Hruban RH, *et al*. (eds.). WHO Classification of tumors of the digestive system, ***IARC Press***. 2010:132-182
5. J. Hyngstrom, C.Y. Hu, Y. Xing, Y.N. You, B.W. Feig, J.M. Skibber, M.A. Rodriguez-Bigas, J.N. Cormier, G.J. Chang, Clinicopathology and outcomes for mucinous and signet ring colorectal adenocarcinoma:Analysis from the national cancer data base. ***Ann. Surg. Oncol.*** 2012, 19:2814-2821
6. T. Nozoe, H. Anai, S.Nasu, K. Sugimachi, Clinicopathologic characteristics of mucinous carcinoma of the colon and rectum. ***J. Surg. Oncol.*** 2000, 75:103-107
7. W.Du, J.T. Mah, J. Lee, R. Sankila, R. Sankaranarayanan, K.S. Chia, Incidence and survival of mucinous Adenocarcinoma of the colorectum:a population-based study from an Asian country. ***Dis. Colon Rectum.*** 2004, 47:78-85
8. H. Kang, J.B. O'Connell, M.A. Maggard, J. Sack, C.Y. Ko, A 10-year outcomes evaluation of mucinous and signet-ringcell carcinoma of the colon and rectum. ***Dis. Colon Rectum*** 2005, 48:1161-1168
9. J.M. Mekenkamp, K.J. Heesterbeek, M. Koopman, J. Tol, S. Teerenstra, S. Venderbosch, C.J. Punt, I.D. Nagtegaal, Mucinous adenocarcinomas:Poor prognosis in metastatic colorectal cancer. ***Eur J Cancer.*** 2012, 48:501-509
10. S. Maksimovic, Survival rates of patients with mucinous adenocarcinoma of the colorectum. ***Med. Arch.*** 2007, 61:26-29
11. M. Numata, M. Shiozawa, T. Watanabe, H. Tamagawa, N. Yamamoto, S. Morinaga, K. Watanabe, T. Godai, T. Oshima, S. Fujii, C. Kunisaki, Y. Rino, M. Masuda, M. Akaike. The clinicopathological features of colorectal mucinous adenocarcin ma and a therapeutic strategy for the disease. ***World J. Surg. Oncol.*** 2012, 15:110-109
12. S. Wu, W. Sui-jing, H. Yu-long, S.R. Cai, C.H. Zhang, X.H.Zhang, W.H. Zhan, 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.*** 2009, 122:1486-1491
13. T. Yamaguchi, H. Taniguchi, S. Fujita, S. Sekine, S. Yamamoto S, T. Akasu, R. Kushima, T. Tani, Y. Moriya, T. Shimoda, Clinicopathological characteristics and

prognostic factors of advanced colorectal mucinous adenocarcinoma. ***Histopathology.*** 2012, 61:162-169

14. R. Adell, E. Marcote, M.A. Segarra, V. Pellicer, R. Gamón, A.M. Bayón, M. Canales, A. Torner, Is mucinous colorectal adenocarcinoma a distinct entity? ***Gastroenterol. Hepatol.*** 2002, 25:534-540
15. V. N. Papadopoulos, A. Michalopoulos, S. Netta, G. Basdanis, D. Paramythiotis, A. Zatagias, P. Berovalis, N. Harlaftis, Prognostic significance of mucinous component in colorectal carcinoma. ***Tech. Coloproctol.*** 2004, 8:123-125
16. Y. Kanemitsu, T. Kato, T. Hirai, K. Yasui, T. Morimoto, Y. Shimizu, Y. Kodera, Y. Yamamura, Survival after curative resection for mucinous adenocarcinoma of the colorectum. ***Dis. Colon Rectum.*** 2003, 46:160-167
17. C. Langner, L. Harbaum, M.J. Pollheimer MJ, P. Kornprat, R.A. Lindtner, A. Schlemmer, M. Vieth, P. Rehak, Mucinous differentiation in colorectal cancer-indicator of poor prognosis? ***Histopathology.*** 2012, 60:1060-1072
18. S.Y. Park, H.S. Lee, G. Choe, J.H. Chung, W.H. Kim, Clinicopathological characteristics, microsatellite instability, and expression of mucin core proteins and p53 in colorectal mucinous adenocarcinomas in relation to location. ***Virchows Arch.*** 2006, 449:40-47
19. J.M. Chiang, C.Y. Yeh, C.R. Changchien, J.S. Chen, R. Tang, J.R. Chen, Mucinous adenocarcinoma showing different clinicopathological and molecular characteristics in relation to different colorectal cancer subgroups. ***Int J. Colorectal. Dis.*** 2010, 25:941-947
20. M. Melis, J. Hernandez, E.M. Siegel, J.M. McLoughlin, Q.P. Ly, R.M. Nair, J.M. Lewis, E.H. Jensen, M.D. Alvarado, D. Coppola, S. Eschrich, G.C. Bloom, T.J. Yeatman, D. Shibata, Gene expression profiling of colorectal mucinous adenocarcinomas. ***Dis. Colon Rectum.*** 2010, 53:936-943
21. C.S. Wu, S.Y. Tung, P.C. Chen, Y.C. Kuo, Clinicopathological study of colorectal mucinous carcinoma in Taiwan:a multivariate analysis. ***J. Gastroenterol. Hepatol.*** 1996, 11:77-81
22. S. Yamamoto, H. Mochizuki, K. Hase, T. Yamamoto, Y. Ohkusa, S. Yokoyama, Y. Ushitani, S. Tamakuma, Assessment of clinicopathologic features of colorectal mucinous adenocarcinoma. ***Am. J. Surg.*** 1993, 166:257-261
23. F. Consorti, A. Lorenzotti, G. Midiri, M. Di Paola, Prognostic significance of mucinous carcinoma of colon and rectum: a prospective case–control study. ***J. Surg. Oncol.*** 2000, 73:70-74
24. V. Catalano, F. Loupakis, F. Graziano, U. Torresi, R. Bisonni R, D. Mari, L. Fornaro, A.M. Baldelli, P. Giordani, D. Rossi, P. Alessandroni, L. Giustini, R.R. Silva, A. Falcone, S. D'Emidio, S.L. Fedeli. Mucinous histology predicts for poor response rate and overall survival of patients with colorectal cancer and treated with first - line oxaliplatin - and / or irinotecan-based chemotherapy. ***Br. J. Cancer.*** 2009, 100:881-887
25. M. Ghabeljoo, M.A. Jafarabadi, S.M. Mohammadi, E. Hajizadeh, A. Kazemnejad, S.R. Fatemi, Patterns of survival for anatomical sites of colorectal cancer with shift to advanced lesions in Iran. Asian Pac. ***J. Cancer Prev.*** 2011, 12:1225-12231
26. K.M. Madbouly, A.J. Senagore, A. Mukerjee, A.M. Hussien, M.A. Shehata, P. Navine, C.P. Delaney, V.W. Fazio, Colorectal cancer in a population with endemic Schistosoma mansoni:is this an at-risk population? ***Int. J. Colorectal Dis.*** 2007, 22:175-181
27. M.N. El-Bolkainy, E.W. Chu, M.N. Ghoneim, A.S. Ibrahim, Cytologic detection of bladder cancer in a rural Egyptian population infected with schistosomiasis. ***Acta. Cytol.*** 1982, 26:303-310
28. S. Kakar, S. Aksoy, L.J. Burgart, T.C. Smyrk, Mucinous carcinoma of the colon:correlation of loss of mismatch repair enzymes with clinicopathologic features and survival. ***Mod. Pathol.*** 2004, 17:696-700
29. K. Uehara, Y. Nakanishi, T. Shimoda, H. Taniguchi, T. Akasu, Y. Moriya, Clinicopathological significance of microscopic abscess formation at the invasive margin of advanced low rectal cancer. ***Br. J. Surg.*** 2007, 94:239-243
30. A.A. Foda, A.K. El-Hawary, A. Abdel-Aziz, Differential expression of matrix metalloproteinase-13 in mucinous and nonmucinous colorectal carcinomas. ***Ann. Diagn. Pathol.*** 2013, 17:347-351
31. C.A. Purdie and J. Piris, Histopathological grade, mucinous differentiation and DNA ploidy in relation to prognosis in colorectal carcinoma. ***Histopathology.*** 2000, 36:121-126
32. C. Compton, C.M. Fenoglio-Preiser, N. Pettigrew, L.P. Fielding, American Joint Committee on Cancer Prognostic Factors Consensus Conference:Colorectal Working Group. ***Cancer.*** 2000, 88:1739-1757
33. S. Leopoldo, B. Lorena, A. Cinzia, D.C. Gabriella, B. Angela Luciana, C. Renato, M. Antonio, S. Carlo, P.

Cristina, C. Stefano, T. Maurizio, R. Luigi, B. Cesare. Two subtypes of mucinous adenocarcinoma of the colorectum: clinicopathological and genetic features. ***Ann. Surg. Oncol.*** 2008, 15:1429-1439

34. L. Xie, P.J. Villeneuve, A. Shaw, Survival of patients diagnosed with either colorectal mucinous or non-mucinous adenocarcinoma:a population-based study in Canada. ***Int. J. Oncol.*** 2009, 34:1109-1115