IJBC 2016; 8(3): 75-79

Iranian Journal of Blood & Cancer

Journal Home Page: www.ijbc.ir

ORIGINAL ARTICLE

Mucinous and Non-Mucinous Adenocarcinoma in Colorectal Cancer Patients

Mehrdad Payandeh[1], Masoud Sadeghi[2,3*], Edris Sadeghi[2,3]

[1]Department of Hematology and Medical Oncology, Kermanshah University of Medical Sciences, Kermanshah, Iran
[2]Students Research Committee, Kermanshah University of Medical Sciences, Kermanshah, Iran
[3]Medical Biology Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran

ARTICLE INFO

Article History:
Received: 20.05.2016
Accepted: 12.07.2016

Keywords:
Colorectal cancer
Survival
Mucinous adenocarcinoma
Non-mucinous adenocarcinoma
Age

**Corresponding author:*
Masoud Sadeghi,
Medical Biology Research Center,
Kermanshah University of Medical Sciences, Kermanshah, Iran
Email: Sadeghi_mbrc@yahoo.com

ABSTRACT

Background: The oncologic behavior of mucinous adenocarcinoma (MA) of colorectal differs from non-mucinous adenocarcinoma (NMA). MA is more advanced at diagnosis and has a poorer prognosis than NMA. We aimed to evaluate prognostic factors and survival rate in patients with MA compared with NMA in Western Iran.

Methods: During 2008-2015 in a retrospective study, 83 patients with CRC referred to the Oncology Clinic in Kermanshah, Iran. Binary logistic regression analysis was used for the correlation between risk variables with the type of pathology.

Results: The mean follow-up was 32 months (range, 12-72 months) and in this interval, there were 26 deaths and 3 patients were lost to follow-up and therefore, were omitted them from survival analysis. There was no significant correlation between NMA and MA with sex, degree of differentiation of tumor, tumor site, tumor size, KRAS mutation and lymph node metastasis, but a significant correlation was observed with age ($P<0.05$). Binary logistic regression analysis showed there was a significant correlation between age ($P=0.01$, odds ratio 11.93 and 95% CI 1.61-88.46) and type of pathology. The survival rate and mean survival were 54.3% and 23 months for NMA group, versus 80.6% and 25.4 months for MA group, respectively.

Conclusion: The prevalence of NMA in CRC was more than MA. In this study, the MA patients had lower age and more risk of recurrence compared to NMA patients and unlike other studies, 5-year survival rate was significantly higher in NMA patients than that in MA patients.

Please cite this article as: Payandeh M, Sadeghi M, Sadeghi E. Mucinous and Non-Mucinous Adenocarcinoma in Colorectal Cancer Patients. IJBC 2016; 8(3): 75-79.

Introduction

Colorectal cancer (CRC) is the third most common neoplastic disease worldwide and is the second leading cause of cancer death in men and women in the United States.[1] In the World Health Organization (WHO) classification, mucinous adenocarcinoma (MA) is defined as an adenocarcinoma in which >50% of the lesion is composed of pools of extracellular mucin. Tumor with <50% of the lesion composed of mucin is categorized as having mucinous component.[2] MA is a histological subtype of CRC and comprises approximately 1-6% of all colorectal epithelial cancers.[3] The oncological behavior of MA differs from non-mucinous adenocarcinoma (NMA).[4] MA is more advanced at diagnosis and has a poorer prognosis than NMA.[3,5] MA is associated with proximal location of tumor, advanced stage at diagnosis, microsatellite instability, and BRAF and KRAS mutations compared with NMA,[2] however, these differences are

not definitely confirmed, yet.[6] KRAS mutations are useful markers for predicting responses to anti-epidermal growth factor receptor (EGFR) monoclonal antibodies in metastatic colorectal cancers (mCRC) and CRC patients with a KRAS mutation do not respond to treatment with cetuximab or panitumumab.[7] Clinical data have proven that mutant RAS genes are negative predictive biomarkers and that patients with a KRAS/NRAS mutation do not benefit from an anti-EGFR antibody-based therapy.[8] We aimed to evaluate prognostic factors and survival rate in patients with MA compared with NMA in Western Iran.

Materials and Methods

Patients

During 2008-2015, in a retrospective study, 83 patients with CRC referred to the Oncology Clinic in Kermanshah city, Iran. The patients were divided into two groups based on the type of pathology (51 patients in NMA group versus 32 patients in MA group). Age, sex, degree of tumor differentiation, tumor size, tumor site, lymph node metastasis, KRAS and survival rate were studied in all patients. Overall survival (OS) was defined as the length of the time from diagnosis or the start of the treatment to death due to any cause or the date of the last follow-up.

Binary logistic regression analysis was used for the correlation between risk variables with the type of pathology. The correlation between the variables was analyzed in IBM SPSS version 19 by T-test for the means and Chi-square test for other variables. The survival graph was plotted by GraphPad Prism 5. P<0.05 was significant statistically.

Results

The mean duration of follow-up was 32 months (range, 12-72 months) and in this interval, there were 26 deaths and 3 patients lost their follow-up and therefore were omitted from survival analysis. All patients had stage III or IV and there was no significant difference between stage in the two groups. The mean age (range) for NMA was 60 years (28-80 year) versus 54 years (31-78 years) for MA (Table 1). There was no significant correlation between NMA and MA with sex, degree of tumor differentiation, tumor site, tumor size, KRAS mutation and lymph node metastasis, but was a significant correlation with age (P<0.05). Therefore, the mean age of MA group was lower than NMA group.

Binary logistic regression analysis between the variables and pathologic subtype of CRC has been shown in Table 2. There was a significant correlation between age (P=0.01, odds ratio (OR) 11.93 and 95% CI 1.61-88.46) and type of pathology.

The 5-year OS in CRC has been shown in Figure 1 based on the type of pathology (MA group *vs*. NMA group). The survival rate and mean survival were 54.3% and 23 months for NMA group, versus 80.6% and 25.4 months for MA group, respectively. There was a significant correlation between survival in two groups (P<0.05). Therefore, survival in MA group was better than NMA group.

Discussion

CRC is the fourth most common cancer in men and the third most common in women.[9] Out of 255 CRC

Table 1: The correlation between type of pathology and prognostic factors in colorectal cancer (n=83)

Variables	Non-mucinous adenocarcinoma N=51	Mucinous adenocarcinoma N=32	P value
Age, years			
Mean	60	54	0.039
Range	28-80	31-78	
≥60	26 (51%)	10 (31.3%)	
Sex			
Male	30 (58.8%)	21 (65.6%)	0.061
Female	21 (41.2%)	11 (34.4%)	0.351
Differentiation			
Poorly differentiated	2 (6.9%)	1 (5.9%)	0.136
Moderately differentiated	7 (24.1%)	9 (52.9%)	
Well differentiated	20 (69%)	7 (41.2%)	
Unknown	22	15	
Tumor site			
Rectum	41 (80.4%)	21 (65.6%)	0.107
Colon	10 (19.6%)	11 (34.4%)	
Tumor size, cm			
Mean	5.6	5.5	0.968
Range	1.5-12	1.5-10	
KRAS			
Wild-type	27 (52.9%)	19 (59.4%)	0.365
Mutation	24 (47.1%)	13 (40.6%)	
Lymph node metastasis			
Yes	27 (52.9%)	19 (59.4%)	0.517
No	24 (47.1%)	13 (40.6%)	

Table 2: Binary logistic regression analysis between the variables with type of pathology

Variables	P value	OR	95% CI
Age, ≥60 *vs* <60	0.01	11.93	1.61-88.46
Sex, male *vs* female	0.44	0.49	0.08-2.96
Grade, well *vs* moderate or poorly	0.78	0.82	0.21-3.19
Tumor site, rectum *vs* colon	0.10	7.65	0.66-87.98
KRAS, wild-type *vs* mutation	0.23	3.01	0.48-18.97
Lymph node metastasis, yes *vs* no	0.80	0.79	0.12-5.09

A binary logistic regression model was selected using Akaike Information Criteria (AIC) in stepwise selection. Odds ratios are adjusted for all of the factors listed in the table. OR: odds ratio.

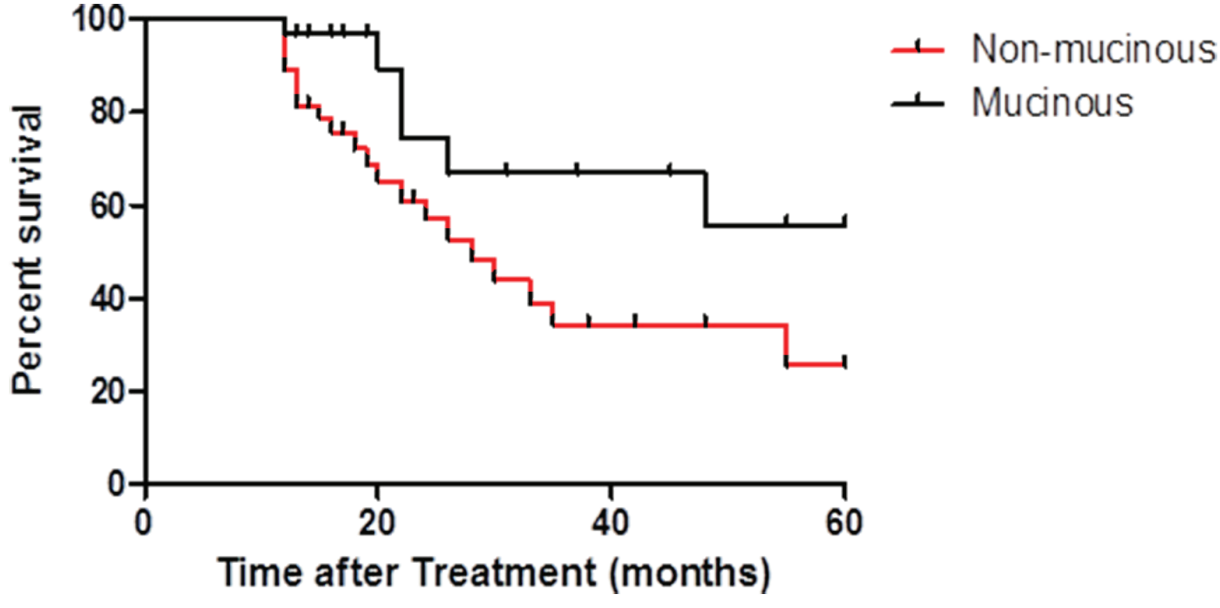

Figure 1: The 5-year overall survival in colorectal cancer based on type of pathology

patients, 49 (19%) patients had a histologically confirmed diagnosis of MA.[10] MA comprises approximately 1 to 6% of all colorectal epithelial cancers.[5] In our study, out of 83 patients, 51 patients (61.4%) were NMA patients. The results of more studies has shown that the prevalence of NMA in CRC is more than MA.

In one study on CRC patients, the distribution for age at diagnosis, stage and treatment of patients with MA was similar to that of NMA patients and patients with mucinous histology had fewer well or moderately-differentiated tumors than NMA patients (P<0.05).[11] In another study, only the tumor recurrence was significantly more common in MA, whereas the TNM stage, metastatic site and pattern of metastasis were not significantly different from each other in the two groups.[3] Maksimović S. and colleagues reported that MA patients compared to patients with NMA were found to have younger age, more lymph node metastases and higher frequency of advanced stage disease (P<0.05).[5] As compared with NMA, the tumor diameter of MA was significantly longer and their age was younger. Also, MA had more lymph node metastasis and less recurrence.[12] Tumor stage and histological grading were higher in MA patients (P<0.001); whereas rate of lymphatic invasion was higher in NMA.[13] In this study, MA patients had lower age compared to NMA patients that was a statistical significant finding, but there was no other significant correlation between sex, differentiation of tumor (grade), tumor size, tumor site, lymph node metastasis and KRAS mutations and pathologic subtype of the tumor. Although, the prognostic factors in MA and NMA patients are not the same in different studies, but the majority have reported younger age for MA tumors of colorectal and also a higher risk for recurrence in this group.

Different studies in patients with colorectal cancer has shown that prognosis of MA tumors is poorer than NMA tumors.[3] One study reported that no statistically significant difference was noted in 5-year survival between MA and NMA tumors of CRC.[12] Maksimović S reported that the statistics for 5-year survival had a significant difference in MA patients compared to patients with NMA pathology(39% vs. 60,3%)[5] and in another study, 5-year overall survival was 81.4% in MA versus 87.4% in NMA (P=0.005).[4] In patients with stage III and IV (advanced stage), MA was associated with a worse survival compared with NMA.[14] It was recently reported that mucinous histology indicates a poor response to oxaliplatin and/or irinotecan-based protocols and is associated with poor overall survival. In contrast to BRAF mutations, no significant difference has been

observed in clinicopathological parameters based on KRAS genotype in many studies.[15] This shows the impact of KRAS/BRAF mutations on the clinicopathological features and prognosis of the CRC patients, particularly in terms of the type of KRAS mutations; at codons 12 *vs.* 13.[7] KRAS mutation was not associated with a specific clinicopathological feature including age, sex, ethnicity of the patient, site of the tumor, differentiation of the tumor and mucinous status.[15] In comparison to NMA patients, MA patients had worse outcome and long-term overall survival rates. MAs may have special biological behavior which is an independent prognostic factor for patients with CRC.[13] Five-year cause-specific survival was 67% for NMA and 61% for MA (P<0.05).[11] After a median follow-up of 45 months in another study, median OS for MA patients was 14 months compared with 23.4 months for NMA group.[16] In this study, 5-year survival rate was 54.3% (median OS, 23 months) in NMA patients compared with 80.6% (median OS, 25.4 months) for MA patients (P<0.05). This result was in contrast to the results in previous studies. Therefore, genetics and probably ethnicity can affect on the metabolism of the drugs, especially anti-EGFRs that in a research,[6] has been reported that MA have distinct clinicopathological and genetic characteristics compared to NMA. Therefore, the differences in the rate of OS in the various studies are presumed to be due to genetic differences. Future studies should focus on genetics of the patients, so can exactly check the impact of these two factors on survival.

Conclusion

In this study, the prevalence of NMA in CRC was more than MA subtype. MA patients had lower age at diagnosis and had a more risk of recurrence compared to NMA patients and unlike other studies, 5-year survival rate was significantly higher in NMA patients than that in MA patients.

Conflict of Interest: None declared.

References

1. Shahriari-Ahmadi A, Fahimi A, Payandeh M, Sadeghi M. Prevalence of oxaliplatin-induced chronic neuropathy and influencing factors in patients with colorectal cancer in Iran. Asian Pac J Cancer Prev. 2015; 16(17):7603-6. PubMed PMID: 26625769.
2. Lee DW, Han SW, Lee HJ, Rhee YY, Bae JM, Cho NY, et al. Prognostic implication of mucinous histology in colorectal cancer patients treated with adjuvant FOLFOX chemotherapy. Br J Cancer. 2013; 108(10):1978-84. doi: 10.1038/bjc.2013.232. PubMed PMID: 23652310. PubMed Central PMCID: PMC3670503.
3. Jivapaisarnpong P, Boonthongtho K. Clinicopathological characteristics of mucinous and non-mucinous adenocarcinoma in the colon and rectum in Rajavithi Hospital, Thailand. J Med Assoc Thai. 2011; 94 Suppl 2:S41-5. PubMed PMID: 21717877.
4. Park JS, Huh JW, Park YA, Cho YB, Yun SH, Kim HC, et al. Prognostic comparison between mucinous and nonmucinous adenocarcinoma in colorectal cancer. Medicine (Baltimore). 2015; 94(15):e658. doi: 10.1097/MD.0000000000000658. PubMed PMID: 25881840. PubMed Central PMCID: PMC4602499.
5. Maksimović S. [Survival rates of patients with mucinous adenocarcinoma of the colorectum]. Med Arh. 2007; 61(1):26-9. PubMed PMID: 17582971.
6. Tanaka H, Deng G, Matsuzaki K, Kakar S, Kim GE, Miura S, et al. BRAF mutation, CpG island methylator phenotype and microsatellite instability occur more frequently and concordantly in mucinous than non-mucinous colorectal cancer. Int J Cancer. 2006; 118(11):2765–71. doi: 10.1002/ijc.21701. PubMed PMID: 16381005.
7. Yokota T. Are KRAS/BRAF mutations potent prognostic and/or predictive biomarkers in colorectal cancers? Anticancer Agents Med Chem. 2012; 12(2):163-71. PubMed PMID: 22043994. PubMed Central PMCID: PMC3343383.
8. André T, Blons H, Mabro M, Chibaudel B, Bachet JB, Tournigand C, et al. Panitumumab combined with irinotecan for patients with KRAS wild-type metastatic colorectal cancer refractory to standard chemotherapy: a GERCOR efficacy, tolerance, and translational molecular study. Ann Oncol. 2013; 24 (2): 412-9. doi: 10.1093/annonc/mds465. PubMed PMID: 23041588.
9. Madani SH, Sadeghi E, Rezaee A, Sadeghi M, Khazaee S, Amirifard N, et al. Survey of HER2-neu expression in colonic adenocarcinoma in the west of Iran. Asian Pac J Cancer Prev. 2015; 16(17):7671-4. doi: 10.7314/APJCP.2015.16.17.7671. PubMed PMID: 26625779.
10. Catalano V, Loupakis F, Graziano F, Torresi U, Bisonni R, Mari D, et al. 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(6):881-7. doi: 10.1038/sj.bjc.6604955. PubMed Central PMCID: PMC2661784.
11. 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. doi: 10.3892/ijo_00000238· PubMed PMID: 19287969.
12. Song W, He YL, Cai SR, Zhang CH, Chen CQ, Peng JJ, et al. [Clinical features of colorectal mucinous adenocarcinoma]. Zhonghua Wei Chang Wai Ke Za Zhi. 2009; 12(5):487-90. PubMed PMID: 19742341.
13. 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. PubMed PMID: 23989057. PubMed Central PMCID: PMC3888475.
14. 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. PubMed PMID: 22703761. PubMed Central PMCID: PMC3407705.

15. Phua LC, Ng HW, Yeo AH, Chen E, Lo MS, Cheah PY, et al. Prevalence of KRAS, BRAF, PI3K and EGFR mutations among Asian patients with metastatic colorectal cancer. Oncol Lett. 2015; 10(4):2519-26. doi: 10.3892/ol.2015.3560. PubMed PMID: 26622882. PubMed Central PMCID: PMC4579971.
16. Negri FV, Wotherspoon A, Cunningham D, Norman AR, Chong G, Ross PJ. Mucinous histology predicts for reduced fluorouracil responsiveness and survival in advanced colorectal cancer. Ann Oncol. 2005; 16(8):1305-10. doi: 10.1093/annonc/mdi244. PubMed PMID: 15857840.