



Association Between Surgical Margin Status and Local Recurrence in Iranian Patients Suffering from Colorectal Cancer

Narges Sistany Allahabadi ¹, Hossein Yahyazadeh ¹, Hossein Pourtavakoli ¹, Azita Abdollahinejad ¹ and Marzieh Beheshti ¹

¹Clinical Cancer Research Center, Milad General Hospital, Tehran, IR Iran

*Corresponding author: Clinical Cancer Research Center, 12th floor, Milad General Hospital, Hemmat Highway, Tehran, Iran. Email: nickpiert990@gmail.com

**Corresponding author: Clinical Cancer Research Center, Milad General Hospital, Tehran, Iran. Email: hyahyazadeh@gmail.com

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Abstract

Background: Colorectal cancer is a highly prevalent cancer around the world and Iran. There are different criteria that can affect the survival rate of this disease. Surgical margin status is one of these criteria; there are still challenges about how it can change the surveillance of the disease.

Objectives: In this study, we assessed the relativity between surgical margin status and the stage of disease in Iranian patients suffering from colorectal cancer.

Methods: This is an observational cross-sectional study. A total of 797 patients with colorectal cancer were included and a checklist of demographic, clinical, and pathological data was filled for each one. Based on the pathology result of the biopsy, the patients were divided into different histological groups. Surgical margin status was defined individually. To declare the relativity between surgical margin status and independent variables, we used Spearman's rho test.

Results: The stage of the disease and its histological type and grade were significantly correlated. There was also a significant correlation between histological grade and type of the disease.

Conclusions: Surgical margin status and stage of the disease are challenging prognostic factors in disease recurrence and survival. The patients who participated in this study had meanly higher age and stage of diagnosis than earlier studies either global or local. It can be due to a lack of a systematic program for early detection of CR cancer in Iran that emphasizes the necessity of GI screening systems.

Keywords: Neoplasm, Colorectal Tumor, Iran

1. Background

Nearly 1.4 million people were suffering and 693900 died from colorectal cancer (CRC) in 2012 around the world. It is the third common cancer among men and the second one among women, but its overall prevalence is higher in men. It is more prevalent in whites. Australia/New Zealand, Europe, and North America have the highest and Africa and South Central Asia have the lowest incidence rate around the world (1). In Iran, the third leading cause of death is cancer and gastrointestinal cancers are the second prevalent ones (7/100000) (2,3). The median survival of CRC is 30 month, but there are different prognostic factors that affect the survival rate of the patients like early detection, chemotherapy, clinical and histological factors, pathological grading, primary localization of the tumor, and number of metastatic sites (4). One of the criteria that improves the prognosis is complete resection

of tumoral surgical margins (5). Resection of 1-centimeter (cm) margin is the gold standard of liver metastatic colorectal resection (6). However, there are a number of surgical factors that can alter the results and patient's survival rate. In this study, we attempt to assess the relativity among surgical margin status and the stage of disease in Iranian patients suffering from CRC.

2. Methods

This is an observational cross-sectional uni-center study to assess the clinical and pathological characteristics of patients with colorectal cancer during 2009 to 2015 in Tehran. All the patients with pathological diagnosis of CRC based on pathologist diagnosis by non-probable judgmental sampling method were included in the study and all the patients, who received only chemotherapy or palliative care or had tumor surgery in another center, were

excluded. A checklist including 88 variable about the demographic and clinical and pathological factors was filled by the pathology specialist after performing the surgery by surgeon. Based on the pathology result of the biopsy, the patients were divided into mucinous and non-mucinous adenocarcinoma groups and histologically arranged in 4 different grade; grade I: Well-differentiated, grade II: Moderately differentiated, grade III: Poorly differentiated and grade IV: Non-differentiated. The patients were staged in 10 different stages according to TNM Classification of Malignant Tumors Staging Protocol 8th edition (T stands for primary tumor site, N describes regional lymph nodes that are involved, and M is for existence of metastasis).

Surgical margin status was defined in 11 different characteristics. All data were unanimous and coded by a random coding soft wear. No extra intervention out of National Comprehensive Cancer Network (NCCN) version 1.2018 guideline was performed for the patients and all the steps of the study were performed based on national ethical standards involving human subjects and in accordance with Helsinki Declaration of 1964 and later versions revised in 2000. All the patients who participated in the study signed the informed consent form and all data were preserved by code and anonymously. The study was conducted under supervision and approval of Milad Hospital Ethical Committee.

To analyze demographic data, we used descriptive tests like frequency and mean and to declare the relativity between surgical margin status and independent variables according to the type of our variables, we used non-parametric correlation test (Spearman's rho) by SPSS version 16. P value less than 0.05 was considered significant.

3. Results

A total of 797 people with CRC participated in this study, 165 (20.7%) of whom were histologically typed as mucinous adenocarcinoma and 632 (79.3%) were diagnosed as non-mucinous adenocarcinoma. The mean age of the patients was 59.5 ± 13.8 years old (male: 59.3 ± 14.1 , female: 64.1 ± 15.0). 61.7% were male and 38.3% were female. The highest prevalent diagnosing stage was IIIB (30.6%) (Figure 1) and most of them had distal and proximal free margin (54.6%) and were histological moderately differentiated (49.8%) (Figure 2). Details of the demographic data are mentioned in Table 1.

Frequencies of surgical margin status in different stages of the disease are displayed in Figure 3.

In all the age groups, stage IIIB was the most prevalent one except in 30 to 40-year-old patients that were mostly diagnosed with stage IIA disease. Stage IIIB had the high-

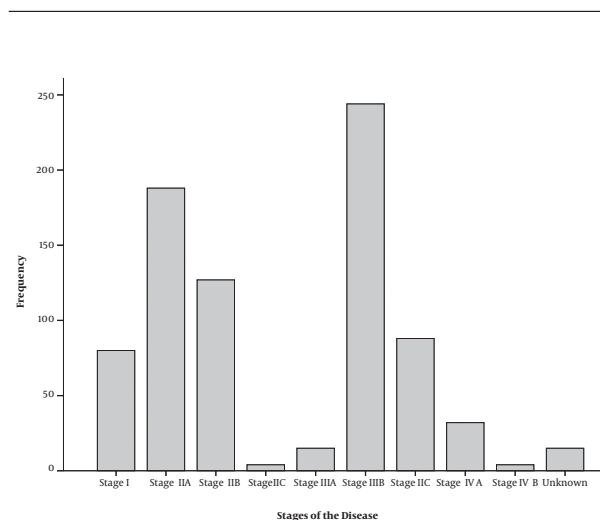


Figure 1. Frequency of different stages of CRC among participants

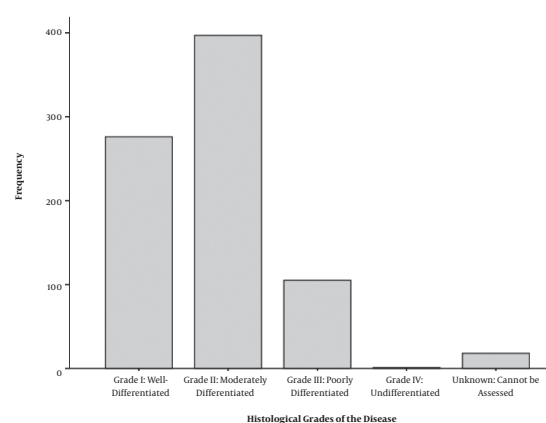


Figure 2. Frequency of different histological grade of CRC among participants

est prevalence among both female and male and also mucinous and non-mucinous patients (Table 2).

Mucinous adenocarcinoma histological type was 53.8% more in male than female (male: N = 100, 12.5%, female: N = 65, 8.2%). Number of patients with non-mucinous adenocarcinoma lesion was 4.03 times more than patients with mucinous adenocarcinoma lesion (N = 541, 80.1%, N = 134, 19.9%).

The stage of the disease and its histological type and grade were significantly correlated ($P = 0.02$, and < 0.0001 , respectively). There were also significant correlation between histological grade and type of the disease ($P = 0.04$), but no significant correlation was observed between other variables (Table 3).

Table 1. Patient's Characteristics Data Summary

	Frequency	Percentage
Surgical margin status		
All surgical margin free	143	37.7
Proximal margin free	5	1.3
Distal margin free	2	0.5
Proximal margin free, distal margin free	207	54.6
Margin cannot be assessed; unknown	20	5.3
Proximal margin free, distal margin involved	1	0.3
All surgical margin free, proximal margin free: Distal margin free	1	0.3
Staging		
Stage I	80	10.0
Stage IIA	188	23.6
Stage IIB	127	15.9
Stage IIC	4	0.5
Stage IIIA	15	1.9
Stage IIIB	244	30.6
Stage IIIC	88	11.0
Stage IV A	32	4.0
Stage IV B	4	0.5
Unknown	15	1.9
Sex		
Male	234	61.7
Female	145	38.3
Valid	379	100.0
Missing	418	
Total	797	
Histological type		
Mucinous	165	20.7
Non-mucinous	632	79.3
Total	797	100.0
Histologic grade		
Grade I: Well-differentiated	276	34.6
Grade II: Moderately differentiated	397	49.8
Grade III: Poorly differentiated	105	13.2
Grade IV: Un-differentiated	1	0.1
Unknown: Cannot be assessed	18	2.3
Total	797	100.0

4. Discussion

In this assay, we have analyzed the relativity between the status of surgical margin in patients with colorectal cancer and their disease stage.

There are some known negative prognostic factors like positive surgical margin, margins > 5 cm, multiple metastases and their site, age > 60 years old, CEA (carcinoembryonic antigen), advance TNM stage of disease, etc. (5, 7-10).

It is not still completely clear that weather palliative or un-palliative margin resection (R1 - R2) or R0 according to Union for International Cancer Control (UICC) criteria is a more important prognostic factor or the width of surgical margins in a case that there is a tight relationship between

narrow margins and extensive disease. It seems complicate to find a single surgical prognostic factor in patients with CRC (6, 9, 11-16).

In our study, the mean age of the patients and the most prevalent stage of diagnosis was higher than earlier studies either global or local studies that can be the result of lack of systematic program for gastro-intestinal (GI) and CR cancer early detection in Iran that emphasize the necessity of GI screening systems (3, 17-20).

In this study, 50 to 60 years old age group is the most populated group both in male and female that is equal to other study that was performed in 2014 in Tehran, but less than an Irish study in 2018 (18, 21).

In our survey, stage IIIB is the most populated in all

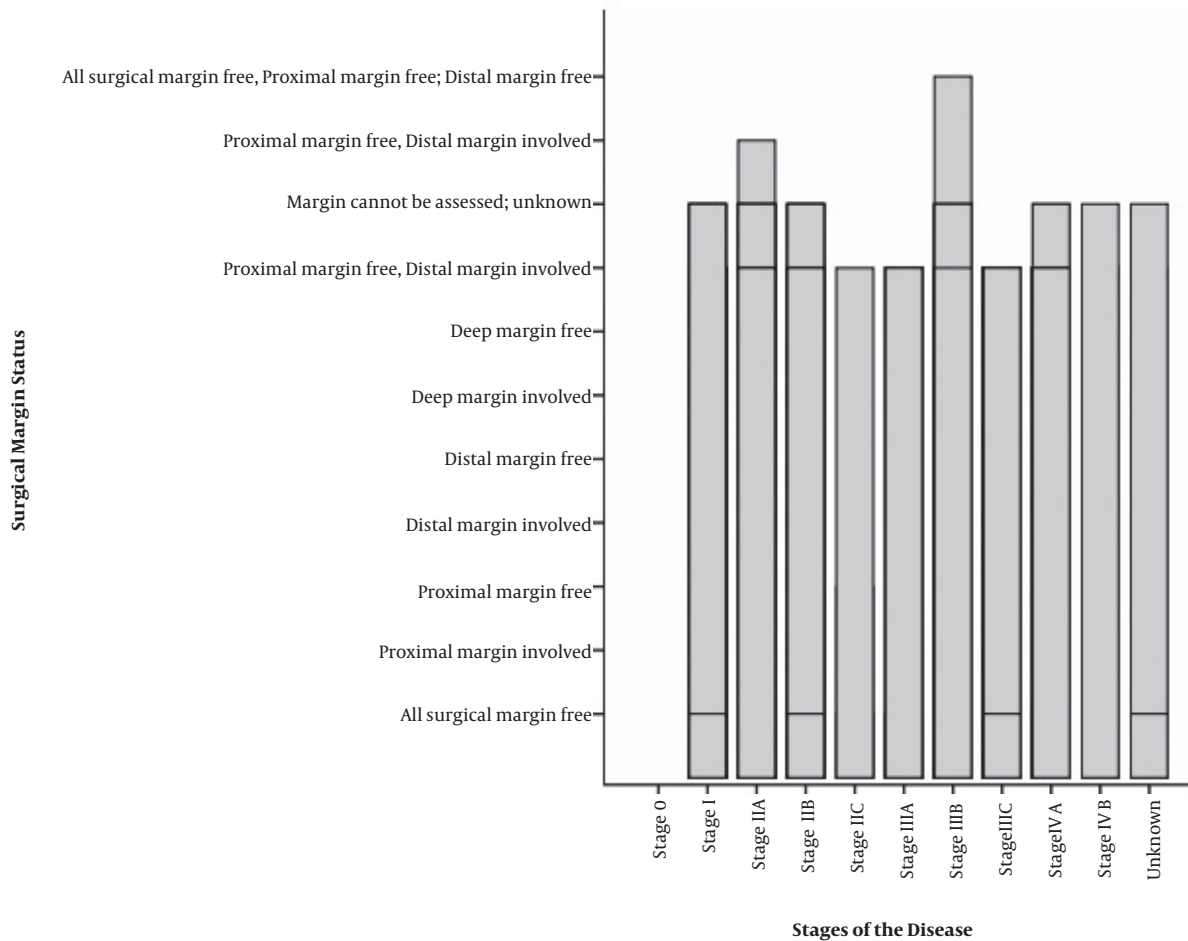


Figure 3. Frequencies of surgical margin status in different stages of CRC among participants

age groups except 30 to 40 years old group that is higher than the Irish study. And another one in 2012 in Tehran that showed stage IV is the most prevalent stage (44.5%) (3, 21).

Surgical margin status and stage of the disease are two important prognostic factors in disease recurrence and survival; there are different ideas about effectiveness of each one and some studies claim the biology of tumor and tumor factors have higher impact on survival than surgical margin status (SMS) (11, 22). Another study found that SMS is not directly effective on survival rate, but it is the reflection of more acute disease (15). In a study, free surgical margins was an independent prognostic factor (6) and in another one, recurrent rate was not related to margin's width (12). Some studies declare that free surgical margin is more important than the width of margins and it is related with extensive disease (13, 14, 23). But, they both are effective on survival pattern in potentially curable patients (5). On the other hand, some studies found no significant difference

among SMS and SMW and overall survival, but showed that free surgical margins independently from their width are related with patient's disease free survival (11, 24).

Historically, 1 cm margin resection was the gold standard of colorectal liver metastasis, but now there are discussions on the efficacy of 1 mm resection. In 2009, Vandeweyer et al. claimed that there is a significant difference in 5-year patient survival between patient with ≤ 1 mm and > 1 mm margin resection; although, their 5-year disease free survival was not significantly different (6). Another study found that 1 cm margin resection is the golden standard, but free surgical margin is another independent factor (12). There is also another one that say 1 mm surgical margin is optimum and there is no statistically difference among the survival rate of patients with free surgical margins and patients with > 1 mm margins (9).

In this study, the stage of the disease and its histological type and grade were significantly correlated.

Table 3. Correlation Between Surgical Margin Status and Disease Pathological Factors Among Patients with CRC

	Histologic Grade	Surgical Margin Status	Disease Stage	Histological Type
Histologic grade				
Correlation coefficient	1.000	0.092	0.203 ^b	-0.071 ^a
P value	-	0.064	0.000	0.046
N	797	404	797	797
Surgical margin status				
Correlation coefficient	0.092	1.000	-0.005	-0.080
P value	0.064	-	0.915	0.110
N	404	404	404	404
Disease stage				
Correlation coefficient	0.203 ^b	-0.005	1.000	-0.108 ^b
P value	0.000	0.915	-	0.002
N	797	404	797	797
Histological type				
Correlation coefficient	-0.071 ^a	-0.080	-0.108 ^b	1.000
P value	0.046	0.110	0.002	-
N	797	404	797	797

^aCorrelation is significant at the 0.05 level.

^bCorrelation is significant at the 0.01 level.

There were also significant correlation between histological grade and type of the disease, but there was no significant relativity among surgical margin status histological type and grade and stage of the disease.

4.1. Conclusions

Surgical margin status and stage of the disease are challenging prognostic factors in disease recurrence and survival.

The patients who participated in this study had meanly higher age and stage of diagnosis than earlier studies either global or local. It can be due to lack of systematic program for early detection of CR cancer in Iran that emphasizes the necessity of GI screening systems.

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Footnotes

Authors' Contribution: None declared.

Conflict of Interests: None declared.

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Table 2. Prevalence of Different Stage of Disease in Different Age Group and Sex and Histological Types of Disease

Staging	Age Group, y										Sex		Histological Type				
	10-20	20-30	3-40	40-50	50-60	60-70	70-80	80-90	90-100	110-120	Total	Male	Female	Total	Mucinous	Non-mucinous	
Stage I																	
Count	0	3	8	10	18	13	10	1	1	0	64	43	37	80	12	68	80
% of total	0.0	0.4	1.2	1.5	2.7	1.9	1.5	0.1	0.1	0.0	9.5	5.4	4.6	10.0	1.5	8.5	10.0
Stage IIA																	
Count	0	2	14	23	27	52	35	5	1	0	159	109	79	188	32	156	188
% of total	0.0	0.3	2.1	3.4	4.0	7.7	5.2	0.7	0.1	0.0	23.6	13.7	9.9	23.6	4.0	19.6	23.6
Stage IIB																	
Count	0	3	6	18	36	22	20	5	0	0	110	84	43	127	26	101	127
% of total	0.0	0.4	0.9	2.7	5.3	3.3	3.0	0.7	0.0	0.0	16.3	10.5	5.4	15.9	3.3	12.7	15.9
Stage IIC																	
Count	0	0	0	0	2	0	2	0	0	0	4	2	2	4	1	3	4
% of total	0.0	0.0	0.0	0.0	0.3	0.0	0.3	0.0	0.0	0.0	0.6	0.3	0.3	0.5	0.1	0.4	0.5
Stage IIIA																	
Count	0	1	1	3	2	3	3	0	0	0	13	11	4	15	2	13	15
% of total	0.0	0.1	0.1	0.4	0.3	0.4	0.4	0.0	0.0	0.0	1.9	1.4	0.5	1.9	0.3	1.6	1.9
Stage IIIB																	
Count	2	6	10	27	62	54	35	8	0	1	205	145	99	244	47	197	244
% of total	0.3	0.9	1.5	4.0	9.2	8.0	5.2	1.2	0.0	0.1	30.4	18.2	12.4	30.6	5.9	24.7	30.6
Stage IIIC																	
Count	1	2	11	14	20	15	10	5	0	0	78	55	33	88	31	57	88
% of total	0.1	0.3	1.6	2.1	3.0	2.2	1.5	0.7	0.0	0.0	11.6	6.9	4.1	11.0	3.9	7.2	11.0
Stage IVA																	
Count	0	0	3	4	10	3	7	1	0	0	28	17	15	32	10	22	32
% of total	0.0	0.0	0.4	0.6	1.5	0.4	1.0	0.1	0.0	0.0	4.1	2.1	1.9	4.0	1.3	2.8	4.0
Stage IVB																	
Count	0	0	2	1	0	0	0	0	0	0	3	2	2	4	1	3	4
% of total	0.0	0.0	0.3	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.3	0.3	0.5	0.1	0.4	0.5
Unknown																	
Count	0	0	1	1	2	2	5	0	0	0	11	7	8	15	3	12	15
% of total	0.0	0.0	0.1	0.1	0.3	0.3	0.7	0.0	0.0	0.0	1.6	0.9	1.0	1.9	0.4	1.5	1.9
Total																	
Count	3	17	56	101	179	164	127	25	2	1	675	475	322	797	165	632	797
% of total	0.4	2.5	8.3	15.0	26.5	24.3	18.8	3.7	0.3	0.1	100.0	59.6	40.4	100.0	20.7	79.3	100.0