Original Article

The Relationship between the Presentation of Hematochezia and Colon Cancer

Cheng-Yi Huang[1]
Chih-Chien Chin[1,3]
Meng-Chiao Hsieh[1]
Yi-Hung Kuo[1]
Wen-Shih Huang[1,3]
Chung-Hung Yeh[1]
Jinn-Shiun Chen[2]
Reiping Tang[2]
Jeng-Yi Wang[2]
[1]*Division of Colon and Rectal Surgery, Department of Surgery, Chang Gung, Memorial Hospital, Chiayi,*
[2]*Division of Colon and Rectal Surgery, Department of Surgery, Chang Gung, Memorial Hospital, Linko,*
[3]*Graduate Institute of Clinical Medical Science, College of Medicine, Chang Gung University, Taoyuan, Taiwan*

Key Words
Colon cancer;
Hematochezia;
Anemia

Objective. Hematochezia is one of the most common symptoms of colon cancer. This study investigated whether the presence of hematochezia could indicate additional clinical information on non-metastatic colon cancer.

Methods. In this retrospective study, we enrolled 3641 consecutive non-metastatic colon cancer patients. Logistic regression analysis was performed to determine the correlation between hematochezia and other characteristics and postoperative outcome of colon cancer. The Cox regression model was used to determine the correlation between hematochezia and long-term survival in colon cancer patients.

Results. Logistic regression analysis showed that hematochezia was significantly associated with tumor location (left vs. right: odds ratio [OR] = 3.19; $p < 0.001$), tumor morphology (polypoid vs. non-polypoid: OR = 1.33; $p = 0.005$), and circumferential involvement (no vs. yes: OR = 1.48; $p < 0.001$).

Compared to patients with hematochezia, those without hematochezia were more likely to have hypoalbuminemia (20.4% vs. 14.5%; $p < 0.001$), obvious anemia (27.0% vs. 23.6%; $p = 0.020$), and abnormal carcinoembryonic antigen levels (37.1% vs. 33.6%; $p = 0.028$). Postoperative morbidity and mortality were not significantly correlated with hematochezia. The 5-year overall survival rates of patients with and without hematochezia were 77.9% and 73.0%, respectively ($p < 0.004$), and the 5-year relapse-free survival rates were 74.7% and 70.4%, respectively ($p = 0.015$). However, multivariate analysis showed that hematochezia was not a significant prognostic factor of overall survival and relapse-free survival.

Conclusion. Hematochezia in colon cancer patients is not only an alert symptom, but is also correlated with tumor location, tumor morphology, and circumferential involvement. However, it is not a prognostic factor for poor long-term outcome in non-metastatic colon cancer patients.

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The incidence of colorectal cancer has recently increased to become the most common type of cancer in Taiwan. Hematochezia, abdominal discomfort, change in bowel habits, body weight loss, presence of abdominal mass and other more severe presentations such as obstruction and peritonitis, are the most common clinical presentations.[1] Colon cancer patients present the above symptoms according to tumor char-

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Correspondence to: Dr. Chih-Chien Chin, Division of Colon and Rectal Surgery, Department of Surgery, Chang Gung Memorial Hospital, No. 6, West Chia-Pu Rd., Puzeh City, Chiayi County, Taiwan. Tel: +886-5-362-1000 ext. 2729; Fax: +886-5-362-3001; E-mail: ccchin@adm.cgmh.org.tw

acteristics and severity.

Hematochezia is defined as chronic, intermittent passage of small amounts of maroon or bright red blood through the anus and is a clinical problem frequently found in adults of all ages. Scant hematochezia is a common symptom of sinister diagnoses,[2-4] including colorectal cancer. The relationship between hematochezia at presentation and characteristics of non-metastatic colon tumors is not well known, nor is the influence of hematochezia on the outcome in colon cancer patients. This study aimed to determine whether the presence of hematochezia could provide additional information on colon cancer and whether it is related to colon cancer prognosis.

Patients and Methods

In this retrospective study, we enrolled 3461 patients with non-metastatic colon cancer who underwent elective and potentially curative surgery at the Chang Gung Memorial Hospital between January 1995 and December 2004. The patients filled out preoperative questionnaires about their complete symptoms. Patients with metastasis (stage IV colon cancer of the TNM staging system), previous colon surgery, and metachronous or synchronous right and left colon cancers were excluded.

The patients were classified into 3 age groups: < 50-year-old (young), 50-75-year-old (middle age), and > 75-year-old (old). Hematochezia was recorded as present (with) or absent (without). Hypoalbuminemia was defined as the condition in which the serum albumin level was < 3.5 g/l. Carcinoembryonic antigen (CEA) levels of over 5 ng/ml were considered abnormal. Hemoglobin (Hb) levels of less than 10 ng/ml were defined as obvious anemia.

Tumor stages were determined on the basis of the American Joint Committee on Cancer (AJCC) TNM staging system (6th edition).[5] Tumor morphology was classified as polypoid (including flat and polypoid tumors) and non-polypoid (including ulcerative and infiltrative tumors). Tumor location was categorized as right colon (from the cecum to transverse colon) or left colon (from the splenic flexure to sigmoid colon). Tumor circumferential involvement was classified as non-annular tumor (no) and annular tumor (yes). The tumors were classified into 2 groups based on their size: < 5 cm (in both length and width) and ≥ 5 cm (either the length or width). Tumor histologic type was classified as adenocarcinoma, signet ring cell, or mucinous tumor. Tumor histologic grade was classified into well-, moderately-, or poorly differentiated tumors.

The patients were divided into 2 groups according the presence or absence of hematochezia (blood-tinged and other kinds of bloody stool): with hematochezia or without hematochezia. Each patient underwent standard oncological resection of the colonic tumors and received routine postoperative care.

Postoperative morbidities were defined as complications occurring within 30 days of the primary surgery, and postoperative mortality was defined as death within 30 days of the primary surgery.

Overall survival (OS) was calculated after considering death from any cause, and relapse-free survival (RFS) was calculated after considering any relapses from the index cancer. Cancer relapse was confirmed histologically or radiographically.

Statistical methods

Quantitative data were compared using Pearson's chi-square and Fisher's exact tests. For multivariate analysis, logistic regression analysis was used to determine any confounding factors of hematochezia. OS and RFS were calculated using Kaplan-Meier univariate analysis. Survival curves of the different groups were plotted using the Kaplan-Meier method and were compared using log-rank test. In order to compensate for confounding factors, the Cox regression model was used for multivariate analysis. All *p* values were 2-tailed and were considered statistically significant if they were less than 0.05.

Results

The clinicopathological characteristics of patients with hematochezia are presented in Table 1.

In this study, the percentage of colon cancer patients with hematochezia but without metastatic dis-

Table 1. Clinicopathologic characteristics of non-metastatic colon cancer patients with hematochezia

Variable Category	Patient number (%) of each category in variable	Patients having hematochezia	
		Percentage in each category	*p* value
Age group			0.004
< 50	635 (17.4)	51.2	
50-75	2339 (64.2)	49.5	
> 75	667 (18.3)	43.0	
Sex			0.745
Female	1734 (47.6)	48.3	
Male	1907 (52.4)	48.9	
Tumor morphology			< 0.001
Polyploid	928 (25.5)	55.1	
Non-polyploid	2713 (74.5)	46.4	
Tumor location			< 0.001
Right	1400 (38.5)	31.4	
Left	2241 (61.5)	59.3	
Circumferential involvement			< 0.001
No	1583 (43.5)	57.0	
Yes	1453 (39.9)	39.9	
Tumor size			0.010
< 5 cm	1979 (54.4)	50.9	
≥ 5 cm	1660 (45.6)	46.1	
TNM stage			0.007
0	75 (2.1)	50.7	
I	451 (12.4)	55.9	
II	1673 (45.9)	48.4	
III	1442 (39.6)	46.5	
TNM T stage			< 0.001
T1-T2	620 (17.0)	55.6	
T3-T4	3020 (82.9)	47.2	
TNM N stage			0.104
N0	2199 (60.4)	50.0	
N1	951 (26.1)	46.6	
N2	491 (13.5)	46.2	
Histologic type			0.017
Adenocarcinoma	3320 (91.2)	49.2	
Signet ring cell	21 (0.6)	61.9	
Mucinous	300 (8.2)	41.3	
Histologic grade			0.004
Well	681 (18.8)	49.8	
Moderate	2709 (74.7)	49.4	
Poor	237 (6.5)	38.4	

ease was 48.6%. With respect to sex and N stage of the TNM system, there were no significant differences in the percentage of patients presenting hematochezia. Young patients, polypoid tumors, left colon tumors, non-circumferential involvement, small tumors (tumor size, < 5 cm), early TNM stage, early T stage tumors, signet ring cell tumor, and well- to moderately differentiated tumors were more likely to be associated with hematochezia. Because these significant factors (age, tumor morphology, tumor location, circumferential involvement, tumor size, TNM stage, T stage of the TNM system, histology type, and histologic grade) that were related to hematochezia were also related to each other, forward stepwise logistic regression was performed to determine the actually significant factors. As shown in Table 2, we found that

the significant factors were left colon tumors, polypoid tumors, and non-annular tumor.

The relationships between hematochezia, preoperative laboratory data (including CEA, albumin, and Hb levels), and postoperative morbidity and mortality are shown in Table 3. Compared to patients without hematochezia, those with hematochezia were less likely to have hypoalbuminemia, obvious anemia, and abnormal CEA levels. There was no significant difference in the occurrence of postoperative morbidity (11.3% vs. 10.5%; $p = 0.457$) and mortality (0.8% vs. 1.0%; $p = 0.600$) between patients with and without hematochezia.

Survival analysis

The 5-year overall survival (OS) and relapse-free survival (RFS) rates in this study were 75.4% and 72.6%, respectively. When stratified on the basis of the presence/absence of hematochezia, the 5-year OS rates of patients without and with hematochezia were 73.0% and 77.9% ($p = 0.004$), and the 5-year RFS rates were 70.4% and 74.7% ($p = 0.015$), respectively. Compared to patients without hematochezia, those with hematochezia had significantly better OS and RFS.

To elucidate the influence of hematochezia on patient survival, we performed multivariate analysis using the Cox regression method. Predicting factors for this regression model included hematochezia, TNM stage, age, sex, CEA level, Hb level, morbidity, albumin level, tumor location, tumor morphology, tumor size, histologic type, and histologic grade (Table 4; OS and RFS).

Significant predictors for OS were TNM stage, age, sex, CEA level, albumin level, postoperative morbidity, and histologic type (signet cell tumor vs. adenocarcinoma). However, other factors, including hematochezia, Hb level, tumor location, tumor morphology, tumor size, circumference involvement, and histologic grade, had no significant influence on OS. Significant predictors of RFS were TNM stage, CEA level, tumor morphology, and histologic type (signet cell tumor vs. adenocarcinoma). Thus, hematochezia was not a prognostic factor of both OS and RFS by multivariate analysis.

Table 2. Multivariate analysis of risk factors that are significantly associated with hematochezia

Variable	*p* value	OR (95% CI)
Tumor Location (Left vs. Right)	0.000	3.215 (2.730-3.787)
Tumor Morphology (Polypoid vs. Non-polypoid)	0.006	1.328 (1.085-1.624)
Circumferential Involvement (No vs. Yes)	0.000	1.962 (1.660-2.319)

OR (95% CI), odds ratio (95% confidence interval).
(Factors in the logistic regression model of hematochezia include age, tumor morphology, tumor location, circumferential involvement, tumor size, TNM stage, T stage of the TNM system, histology type, and histologic grade.)

Table 3. Preoperative laboratory data, and postoperative morbidity and mortality associated with hematochezia

Variable Category	Number of patients (% in each variable)	Percentage of patients in each variable		
		No hematochezia	Has hematochezia	*p* value
Albumin level				
< 3.5 g/l	17.0	19.8	14.2	< 0.001
Hemoglobin level				
< 10 ng/ml	25.3	26.7	23.2	0.021
CEA level				
≥ 5 ng/ml	34.1	37.1	33.5	0.029
Morbidity				
Yes	11.0	11.3	10.5	0.457
Mortality				
Yes	0.9	0.8	1.0	0.600

Table 4. Multivariate analysis of prognostic factors associated with overall survival and relapse-free survival

Variable	Overall survival analysis		Relapse-free survival analysis	
	p value	HR (95% CI)	*p* value	HR (95% CI)
TNM	0.000		0.000	
Stage II vs. I	0.370	1.161 (0.838-1.609)	0.033	1.809 (1.050-3.115)
Stage III vs. I	0.000	2.057 (1.492-2.835)	0.000	4.157 (2.437-7.092)
Age Group (y/o)	0.000		0.375	
50-75 vs. < 50	0.001	1.504 (1.187-1.906)	0.178	1.188 (0.925-1.527)
> 75 vs. < 50	0.000	3.246 (2.502-4.213)	0.589	1.094 (0.789-1.518)
Sex (male vs. female)	0.037	1.175 (1.010-1.367)	0.541	1.060 (0.879-1.278)
Hematochezia (with vs. without)	0.309	0.923 (0.790-1.078)	0.138	0.864 (0.713-1.048)
CEA (≥ 5 vs. < 5 ng/ml)	0.000	1.573 (1.351-1.832)	0.000	1.905 (1.577-2.300)
Hemoglobin (< 10 vs. ≥ 10 ng/ml)	0.297	1.100 (0.920-1.315)	0.798	1.030 (0.822-1.290)
Morbidity (with vs. without)	0.000	1.564 (1.281-1.910)	0.939	1.012 (0.753-1.358)
Albumin (< 3.5 vs. ≥ 3.5g/l)	0.000	1.822 (1.517-2.188)	0.103	1.236 (0.958-1.594)
Tumor location (left vs. right)	0.608	1.047 (0.879-1.247)	0.767	0.968 (0.781-1.200)
Tumor morphology (non-polypoid vs. polyploid)	0.252	1.122 (0.921-1.367)	0.001	1.601 (1.213-2.113)
Tumor size (≥ 5 cm vs. < 5 cm)	0.086	0.866 (0.736-1.020)	0.179	0.871 (0.713-1.065)
Histologic type	0.011		0.002	
Signet ring cell vs. adenocarcinoma	0.006	2.701 (1.325-5.506)	0.001	3.857 (1.800-8.264)
Mucinous vs. adenocarcinoma	0.187	1.198 (0.916-1.566)	0.468	1.131 (0.811-1.579)
Histologic grade	0.129		0.712	
Moderately vs. well	0.153	1.164 (0.945-1.433)	0.441	1.110 (0.851-1.450)
Poorly vs. well	0.054	1.442 (0.993-2.094)	0.541	1.163 (0.716-1.890)

HR (95% CI), Hazard ratio (95% confidence interval).

Discussion

Colorectal cancer is a common disease worldwide, and its incidence in Taiwan has increased in the recent years. Advanced colorectal adenocarcinoma can be prevented by detecting and removing adenomatous polyps, and the detection of early-stage cancers reduces disease mortality.[6-8]

The time at which colon cancer is diagnosed depends on the available advanced medical facilities, patients' awareness of the disease, and economic conditions. Most colorectal cancers are diagnosed after presentation of the symptoms but they can also be detected in an asymptomatic patient undergoing comprehensive physical check up or in patients who present with anemia.

The symptoms and signs of colon cancer include abdominal pain, change in bowel habits, rectal bleeding or hematochezia, and occult blood in the stool.[9] The above symptoms frequently indicate a more advanced tumor stage unlike that in asymptomatic patients.[9] Abdominal pain and change in bowel habits are the most commonly presented symptoms of colon cancer, and hematochezia is present in as many as 25% patients with colon cancer.[2,10] There are many causes of hematochezia: colorectal neoplasm is an important one, especially in elders, and should not be neglected. In our study, hematochezia was present in 48.6% colon cancer patients.

Few studies have shown a relationship between hematochezia and colon cancer. Kent et al. reported that rectal bleeding was significantly associated with left-sided cancers;[11] Bloem et al. reported similar results in their study.[12] Recognizing of the passage of blood in the stool by the patient is uncommon in cases of right colon adenocarcinomas, because the blood tends to be mixed with the fluid stool. This study also showed that the hematochezia in colon cancer was more common in cases of left side cancers than in cases of right side cancers.

In this study, we also found, by the multivariate logistic regression analysis, that hematochezia in colon cancer was significantly associated with the location, tumor morphology, and circumferential in-

volvement of tumors.

There is very limited discussion in the existing literature about the relationship between hematochezia and tumor morphology or circumferential involvement of colon cancer. In this study, we found that the presentation of hematochezia in colon cancer is significantly associated with the polypoid tumor and circumferential involvement.

Hematochezia is an important presentation of colon cancer patients. A high proportion of colon cancer patients show anemia at presentation[13] primarily because of chronic blood loss. Anemia is commonly expressed in patients with proximal colon cancer.[11,12,14] Left side colon lesions usually showed fresh anal bleeding and right side colon lesions show chronic blood loss and eventually lead to anemia. However, hematochezia is not associated with anemia.[14] In this study, patients with hematochezia were found less likely to display obvious anemia (< 10 ng/ml; p = 0.021).

Hematochezia could be a symptom for early diagnosis. In previous studies, better prognosis was observed in colon cancer patients with bleeding symptoms.[15,16] Wiggers et al. reported that blood loss as an initial symptom is associated with better prognosis.[17] In the present study, the operative morbidity and mortality rates were not significantly different between colon cancer patients with and without hematochezia. Compared to patients without hematochezia, those with hematochezia had significantly better OS and RFS rates. However, multivariate analysis showed that hematochezia was not a significant predictor of both OS and RFS. Patients with hematochezia were more likely to be young patients, with early TNM stage, early T stage tumors, signet ring cell tumors, and well- to moderately differentiated tumors, all of which may be significant factors of survival. Thus, the interaction between hematochezia and the above factors may be the reason why multivariate analysis showed that hematochezia was not a significant predictor of both OS and RFS.

There are some limitations to this retrospective study. The hematochezia self-reported by patients may have been of varying intensity and color, including bright red, purple, mahogany, black, or inapparent. More distally located lesions tend to cause the passage of more reddish blood. The amount of time from the detection of hematochezia to the diagnosis of colon cancer was not well documented. Stapley et al. found no relationship between the duration of symptoms, staging, and mortality of colorectal cancer.[18] Further, Bharucha et al. reported that the median survival time for colorectal cancer patients with different lengths of symptomatic histories were not significantly different.[19] The relationship between the index of hematochezia and characteristics of cancer could not be established completely in this study. Further studies are needed to determine the role of hematochezia on various clinical and pathologic characters in colon cancer and the prognosis.

Conclusion

Hematochezia in colon cancer patients is a symptom associated with left colon tumors, polypoid tumors, and non-circumferential involvement. However, it is not a significant prognostic factor of outcome, including OS and tumor relapse.

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原　著

血便的表現與大腸癌之間的關係

黃政義[1]　靳志堅[1,3]　謝孟樵[1]　郭益宏[1]　黃文詩[1,3]
葉重宏[1]　陳進勛[2]　唐瑞平[2]　王正儀[2]

[1]嘉義長庚紀念醫院　外科部　大腸直腸肛門外科
[2]林口長庚紀念醫院　外科部　大腸直腸肛門外科
[3]長庚大學醫學院　臨床醫學研究所

目的　血便是大腸癌最常見症狀之一。本研究的目的是藉由分析血便在非轉移大腸癌患者的表現，探討是否能提供我們更多的臨床意義與訊息。

方法　在這個回溯性的研究中，我們收集了 3641 例非轉移的大腸癌病患。透過邏輯性迴歸分析探討血便與大腸癌其他因子及手術後之結果的關係。使用比例風險迴歸模式來分析血便與大腸癌患者長期存活率的關係。

結果　經由邏輯式迴歸分析發現血便與腫瘤位置 (左側比右側：風險比 3.19；$p < 0.001$)，腫瘤型態 (息肉狀比非息肉狀：風險比 1.33；$p = 0.005$)，全腸圍侵犯 (非整圈侵犯比整圈侵犯：風險比 1.48；$p < 0.001$) 等有相關聯性。對照有血便的病患來說，沒有表現血便的病患會有更高比例的低血蛋白血症 (20.4% 比 14.5%；$p < 0.001$)、明顯的貧血 (27.0% 比 23.6%；$p = 0.020$) 及異常的癌胚抗原指數 (37.1% 比 33.6%；$p = 0.028$)。血便表現並無顯著影響術後的併發症及死亡率。病患有無血便表現的 5 年存活率各為 77.9% 和 73% ($p < 0.004$)，5 年無復發存活率各為 74.7% 和 70.4% ($p = 0.015$)。但是，在多變數分析中，血便的表現並不是影響存活率和無復發存活率的預後因子。

結論　血便在大腸癌病患並不只是一個警示的症狀跟表徵，它跟腫瘤位置、腫瘤型態、全腸圍侵犯等有相關聯性；另外，它並不是非轉移大腸癌的長期預後因子。

關鍵詞　結腸癌、血便、貧血。