Original Article

Clinicopathological Characteristics and Prognosis of Colorectal Cancer in Chinese Adolescent Patients

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Abstract

Background: Colorectal adenocarcinoma rarely occurred in adolescent. Clinical feature and prognosis of this population are not clear until now. In addition, DNA mismatch repair (MMR) status may relate to the early disease occurrence. The present study aimed to perform a retrospective analysis of adolescent patients with colorectal cancer, including clinicopathological characteristics and prognosis.
Methods: The medical records of 11,503 patients diagnosed as colorectal cancer in Cancer Hospital, Chinese Academy of Medical Sciences from January 1999 to December 2009 were retrospectively reviewed. Finally, 19 patients who were between 10 and 20 years old were selected as the study group. We summarized the clinicopathological characteristics, analyzed the association with prognosis and assessed the expression of MMR protein by immunohistochemical method.
Results: The most common primary site was the right colon in 7 patients. Ten patients had Stage III colorectal cancer, 5 patients had Stage IV disease. Signet ring cell carcinoma was the most frequent pathological type (7/19). Deficient MMR was identified in 2 patients. The 5-year survival rate and median survival time were 23.2% and 26 months. Distant metastasis was identified as an independent prognostic factor ($P = 0.02$).
Conclusions: Colorectal cancer in Chinese adolescents was very rare. The chinese adolecents with colorectal cancer were frequently diagnosed in the right colon, as Stage III/IV disease with signet ring cell carcinoma. The prognosis was relatively poor.

Key words: Adolescence; Colorectal Cancer; Prognosis

Introduction

The morbidity and mortality of colorectal cancer are rising globally, and the incidence of colorectal cancer has been increasing in China. It is the third most common cause of cancer death in both men and women.[1] Adolescent patients with colorectal cancer are a special population that cannot be overlooked. Previous studies suggested that colorectal cancer in young patients had unique clinical and pathological features and was associated with a relatively poor prognosis.[2,3] In China, several studies reported that colorectal cancer was more aggressive in biological behavior in patients who are <40 years.[4,5] However, the clinical outcome of adolescent patients was rarely reported. We hypothesized that the clinical features of colorectal cancer in adolescent might be different with adults. Therefore, we investigated the clinicopathological characteristics and prognosis of a group of patients diagnosed as colorectal cancer between 10 and 20 years old.

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Methods

General information

From January 1999 to December 2009, a total of 11,503 patients were diagnosed as colorectal cancer and received treatment at the Cancer Hospital, Chinese Academy of Medical Sciences. Of these 11,503 patients, 19 cases (0.17%) were between 10 and 20 years old and included in this study. The diagnosis of all cases was confirmed by biopsy or pathological findings. This study was approved by the review board of our hospital, and all the included patients had signed informed consent.

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Immuohistochemical analysis

Tumor slides were washed in running tap water, immersed in Tris hydroxymethyl aminomethane-ethylenediaminetetraacetic acid buffer at pH 9.0 for 20 min. We used Peroxidase Block Reagent to neutralize endogenous peroxidase for at least 5 min. Then, the slides were incubated with Protein Block Reagent for 5 min. The next step was incubation the slides overnight with optimally diluted mouse monoclonal primary antibodies as following: MSH2 (Leica Biosystems: Novocastra, UK, Lyophilized) at 1/80 dilution, MLH1 (Leica Biosystems: Novocastra, UK, Liquid) at 1/100 dilution, MSH6 (Leica Biosystems: Novocastra, UK, Liquid) at 1/100 dilution, and PMS2 (Leica Biosystems: Novocastra, UK, Liquid) at 1/100 dilution.

Next morning, the slides were incubated with Post Primary Block Reagent for 30 min and then with Novolink Polymer for 30 min. After developing peroxidase activity with diaminobenzidine working solution for 5 min, we washed the slides in water and counterstained them with hematoxylin.

Efficacy evaluation criteria

Management included radical surgery (R0, no microscopic evidence of residual disease), palliative surgery (R1, microscopic evidence of residual disease and R2, residual tumor visible to the naked eye), adjuvant chemotherapy, and palliative chemotherapy. The number of dissected lymph nodes was based on the biopsy results. The efficacy of palliative chemotherapy was assessed according to the *WHO 2000 Response Evaluation Criteria in Solid Tumors 1.0 criteria*.

Follow-up

All patients enrolled were followed up by visit, phone call, or letter once every 3 months within the first year after surgery, and then once every 6 months until October 2014.

Statistical analysis

SPSS 17.0 software was used for statistical analysis (SPSS Inc., Chicago, IL, USA). The Kaplan–Meier method was used to calculate the survival rate and for univariate survival analysis. The log-rank test was used to compare survival rates. The Cox regression was used for multivariate survival analysis. The significance level α was set at 0.05.

Results

Patient characteristics

Among the 19 patients studied, the proportion of male patients was higher than that of female (11/19 vs. 8/19). The median age at diagnosis was 16 years (range, 11–20 years). Twelve patients were between 16 and 20 years old, and 7 patients were between 11 and 15 years old. Two patients had a family history of malignant tumor [Table 1].

Clinical symptoms

The most common chief complaints were abdominal pain (11/19), melena or hematochezia (6/19), abdominal distension (3/19), and diarrhea (3/19). Four patients underwent emergency surgery due to acute intestinal obstruction. The average time from symptom onset to diagnosis was 3 months (1–12 months) [Table 1].

Table 1: Clinicopathological characteristics of 19 patients with adolescent colorectal cancer

Characteristics	Values
Age, years, median (range)	16 (11–20)
Male/female, *n*	11/8
Symptoms, *n*	
Abdominal pain	11
Abdominal distension	3
Diarrhea	3
Melena/hemafecia	6
Acute intestinal obstruction	4
Tumor stage, *n*	
II	1
IIIB	5
IIIC	5
IV	5
Unknown	3
Tumor size, *n*	
≤5 cm	4
>5 cm	7
Unknown	8
Lymph node status, *n*	
Positive	17
Negative	2
Pathological classification, *n*	
Adenocarcinoma	7
Moderately differentiated	2
Poorly differentiated	4
Differentiation unknown	1
Mucinous adenocarcinoma	5
Signet ring cell carcinoma	7
Location of primary lesion, *n*	
Transverse colon	4
Right hemicolon	7
Left hemicolon	3
Rectum	5

Pathology and staging

The clinicopathological characteristics of the 19 patients are shown in Table 1. Lesions were most commonly found in the right hemicolon (7/19), followed by rectum (5/19), transverse colon (4/19), and left hemicolon (3/19). In terms of pathology type, adenocarcinoma was found in 7 cases, mucinous adenocarcinoma in 5 cases, and signet ring cell carcinoma in 7 cases. The number of patients with Stage I, II, IIIB, IIIC, and IV disease was 0, 1, 5, 5, and 5, respectively [Table 1].

Detection of mismatch repair gene

Mismatch repair (MMR) protein expression was examined in 9 patients. Expression of MMR protein was negative in 2 patients who both had right hemicolon cancer (PMS2 expression was negative in 1 patient; both MSH2 and

MSH6 expression were negative in the other patient). The proportion of deficient MMR (dMMR) was 2/9.

Treatment

A total of 16 patients underwent either radical surgery ($n = 13$) or palliative surgery ($n = 3$). Nine patients received postoperative adjuvant chemotherapy consisting of FOLFOX (oxaliplatin, 5-fluorouracil [5-FU] plus leucovorin) (8/9) or XELOX (oxaliplatin plus Xeloda) (1/9). The median number of chemotherapy cycles was 6 (range: 1–10). In the palliative treatment setting, one patient received 4 cycles of FOLFOX regimen as the first-line chemotherapy, one received 4 cycles of FOLFIRI (irinotecan, 5-FU plus leucovorin) regimen as the second-line chemotherapy. Besides, one patient received only palliative radiation therapy.

Survival analysis

Survival data were complete in 15 of the 19 patients, 9 of whom died and 6 of whom survived. Four patients were lost to follow-up. The 3- and 5-year survival rates were 34.9% and 23.2%, respectively, with median survival time of 26 months [Figure 1]. Univariate analysis of factors including gender ($P = 0.78$), pathological classification ($P = 0.29$), lymph node metastasis status ($P = 0.77$), distant metastasis ($P = 0.02$), surgical treatment ($P = 0.46$), chemotherapy ($P = 0.10$), and location of the primary lesion ($P = 0.28$) showed only one factor (distant metastasis) was significantly associated with the 5-year survival rate. Multivariate analysis of the aforementioned factors identified distant metastasis as an independent prognostic factor ($P = 0.02$) [Table 2].

Table 2: Results of survival analysis of adolescent colorectal cancer patients depending on different factors ($n = 19$)

Characteristics	mOS (months)	χ^2	*P* (log-rank)
Gender			
Male ($n = 11$)	26	0.08	0.78
Female ($n = 8$)	36		
Pathological type			
Adenocarcinoma ($n = 7$)	36	2.42	0.29
Mucinous ($n = 5$)	46		
Signet ring ($n = 7$)	12		
Lymph node metastasis			
Negative ($n = 2$)	26	0.12	0.77
Positive ($n = 17$)	36		
Distant metastasis			
Negative ($n = 14$)	36	5.22	0.02
Positive ($n = 5$)	8		
Surgical treatment			
No ($n = 6$)	26	0.53	0.46
Yes ($n = 13$)	46		
Chemotherapy			
No ($n = 9$)	10	2.52	0.10
Yes ($n = 10$)	36		
Primary lesion site			
Rectum ($n = 5$)	10	3.75	0.28
Right-side ($n = 7$)	NR		
Left-side ($n = 3$)	16		
Transverse ($n = 4$)	NR		

NR: Not reached; mOS: Median overall survival.

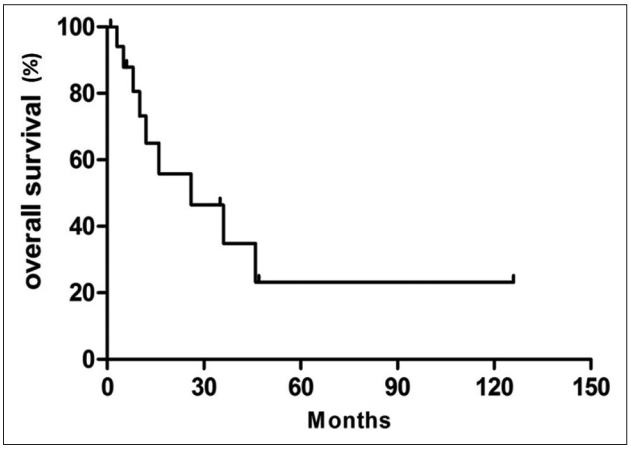

Figure 1: The survival curve of patients (10–20 years old) with colorectal cancer ($n = 19$).

Discussion

Colorectal cancer rarely occurs during the second decade of life. According to the statistics of the USA, the incidence between 1973 and 2005 was only 0.38/1,000,000 person-year in children between 10 and 20 years of age and 802/1,000,000 person-year in adults over 20 years of age.[6] Yang *et al*.[7] reported a review of 270 colorectal cancer patients aged below 20 years in the USA and found that right hemicolon was the most common primary site where tumor occurred, which is consistent with the results of the present study, suggesting that colorectal cancer in the 10–20 years old population might have a predilection for the ileocecal and appendix. On the contrary, it has been reported that rectum is the most common site of colorectal cancer in the whole Chinese population.[8] The present study implies a difference in the location of primary lesions between young people and the overall population with colorectal cancer.

The average time from symptom onset to diagnosis is 3 months. Diagnosis of colorectal cancer has been reported to be delayed in adolescents attributed mainly to the fact that young people are not a high-risk population for this disease.[7] This study summarizes the common symptoms and predilection sites of colorectal cancer in young people aged 10–20 years and may provide an evidence for clinical diagnosis in future cases.

Colorectal cancer is already in the middle or late stage before it is diagnosed in the majority of adolescent patients.[9] In this study, the proportion of patients with disease at Stage III or IV is higher than that reported previously. Besides, most studies reported that the proportion of signet ring cell carcinoma and mucinous adenocarcinoma was higher in the young population, with more aggressive behavior and a poorer prognosis than other subtypes.[9-12] In this study, 7 out of 19 patients have signet ring carcinoma, which is significantly higher than the reported percentage.[11] All

signet ring cell carcinoma patients have T4a tumors and regional lymph node metastasis.

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC), accounts for about 2% of all colorectal cancers.[13] HNPCC is an autosomal dominant genetic disease mainly caused by microsatellite instability (MSI) due to MMR gene defects.[13] The age at onset is younger than 50 years in many patients.[13] On the other hand, approximately 10–15% of sporadic colorectal cancer carry the MSI.[14,15] The dMMR rates are significantly higher in the 30–50 years old and 71–79 years old groups than those in other age groups, and significantly higher in the right hemicolon.[14,15] In our study population, both two patients with dMMR have right hemicolon cancer and no family history of cancer. The proportion of MMR protein deficiency is significantly higher than the reported average of 10–15%, lower than the mutation rate of 31.6% in the 30–50-year-old population, and similar to the mutation rate in the 71–79 years old population.[14,15] Although the number of cases is small, our study suggests that the prevalence of MSI is high in 10–20-year-old patients with colorectal cancer.

In this study, the 3- and 5-year survival rates are 34.9% and 23.2%, respectively. The median survival time is 26 months. The 5-year survival rate in our study is lower than the 40% reported by Sultan *et al*.[8] The lower survival rate in our study might be related to the higher percentage of patients with mucinous adenocarcinoma and signet ring cell carcinoma, as well as the higher percentage of patients with Stage III disease. Our study shows that the prognosis of 10–20-year-old patients is significantly poorer. This may be explained by the delayed diagnosis in young people, leading to advanced stage at the time of diagnosis, little opportunity for radical treatment, and pathological classification.

It is noticeable that as colorectal tumor is rarely occurred in the population of patients who are below 20 years old, the sample size of the present work is small. The primary aim of this study is to describe the clinical and pathological features of this specific subpopulation, whereas the survival analysis depending on factors derived from the small number of patients is not definitive and thus should be taken with caution.

In general, the study summarizes the clinical, pathological, and prognostic characteristics of 10–20-year-old patients with colorectal cancer. The results of this study can be helpful for diagnosing colorectal cancer in this age group.

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Conflicts of interest

There are no conflicts of interest.

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