RESEARCH ARTICLE

Prognostic Analysis of Schistosomal Rectal Cancer

Meng Wang, Yuan-Chuan Zhang, Xu-Yang Yang, Zi-Qiang Wang*

Abstract

Background: Schistosomiasis is an infectious disease that affects more than 230 million people worldwide, according to conservative estimates. Some studies published from China and Japan reported that schistosomiasis is a risk factor for colorectal cancer in Asia where the infective species is *S. japonicum*. Hoqwever, there have been only few reports of prognosis of patients with schistosomal rectal cancer SRC. Objectives: This study aimed to analyze differences in prognosis between SRC and non-schistosomal rectal cancer(NSRC) with current treatments. Materials and Methods: A retrospective review of 30 patients with schistosomal rectal cancer who underwent laparoscopic total mesorectal excision operation (TME) was performed. For each patient with schistosomal rectal cancer, a control group who underwent laparoscopic TME with non-schistosomal rectal cancer was matched for age, gender and tumor stage, resulting in 60 cases and controls. Results: Univariate analysis showed pathologic N stage (*P*=0.006) and pathologic TNM stage (*P*=0.047) statistically significantly correlated with disease-free survival (DFS). Pathologic N stage (*P*=0.014), pathologic TNM stage (*P*=0.002), and with/without schistosomiasis (*P*=0.026) were statistically significantly correlated with overall survival (OS). Schistosomiasis was the only independent prognostic factor for DFS and OS in multivariate analysis. Conclusions: The prognosis of patients with schistosomal rectal cancer is poorer than with non-schistosomal rectal cancer.

Keywords: Schistosomiasis - rectal cancer - laparoscopic resection - prognosis

Asian Pac J Cancer Prev, **15 (21)**, 9271-9275

Introduction

Colorectal cancer (CRC) is the fourth most common carcinoma in China, and the morbidity was increasing rapidly (Gu et al., 2013). Similar situation also appeared in other countries (Greene, 2007). No single risk factor accounted for most cases of colorectal cancer. Many risk factors had been identified and established in epidemiological studies: family history of colorectal cancer, inflammatory bowel disease, smoking, excessive alcohol consumption, high consumption of red and processed meat (Brenner, 2014). And some evidence suggested that infection with Helicobacter pylori, Fusobacterium, and other potential infectious agents might be associated with an increased risk of colorectal cancer (McCoy et al., 2013; Inoue et al., 2014).

Schistosomiasis was an infectious disease that affected more than 230 million people worldwide, according to conservative estimates (Vos et al., 2012). Three main species of schistosomes infected human beings, Schistosoma haematobium, Schistosoma mansoni, and Schistosoma japonicum. S japonicum was located to Asia, primarily the China and Philippines (Colley et al., 2014). By the end of 2010, approximately 65 million individuals in China were at risk of infection and 325, 824 cases were diagnosed as schistosomiasis (Liao et al., 2013). Schistosomiasis was considered closely related with the development of malignancy in the bladder (Zaghloul, 2012), rectum (Matsuda et al., 1999). Some studies published from China (Xu and Su, 1984) and Japan (Ishii et al., 1994) reported that schistosomiasis was a risk factor for colorectal cancer in Asia where the infective species was S. japonicum. One study had reported that there were more substitution mutations at CpG dinucleotides in schistosomal rectal cancer than in non-schistosomal rectal cancer (Zhang et al., 1998). But few studies reported the prognosis of patients with schistosomal rectal cancer.

Total mesorectal excision operation technology (TME) had significantly improved disease-free survival (DFS) and overall survival (OS) for patients with rectal cancer (How et al., 2011). Chemotherapy which was primarily based on 5-fluoruracil had decreased the recurrence of tumour on American Joint Cancer Committee (AJCC) Stage III patients (Cihan et al., 2011). This study aimed to analyze the difference of prognosis between schistosomal rectal cancer (SRC) and non-schistosomal rectal cancer (NSRC) in current treatment.

Materials and Methods

Patients and pretreatment evaluation

In 2009, a total of 33 consecutive schistosomal rectal cancer patients underwent curative surgery. Among them, 3 patients were lost to follow-up and were excluded from this study. A retrospective review of 30 patients with schistosomal rectal cancer who underwent laparoscopic

*Department of Gastroenterological Surgery, West China Hospital, Sichuan University, Chengdu, China *For correspondence: hxwangm@126.com*

TME was performed. Clinical information was collected from the database of the West China Hospital of Sichuan University, Chengdu, China. This project was registered with the Institutional Ethics Committee of West China Hospital, Sichuan University.

For each patient with schistosomal rectal cancer, a control group of 30 patients with non-schistosomal rectal cancer who underwent laparoscopic TME was matched for age, gender and tumor stage, resulting in 60 cases and controls.

To establish the diagnosis and determine staging, patients underwent digital rectal examination, complete blood cell count, liver function analysis, serum carcinoembryonic antigen, colonoscopy with biopsy, magnetic resonance imaging of the pelvis, computed tomography (CT) of the abdomen and chest. Bone scan, and F-18 deoxyfluoroglucose positron emission tomography were performed when required.

Treatment

All patients underwent laparoscopic TME by one colorectal surgeon who was experienced in colorectal and laparoscopic advanced surgery. All of operations followed the principle: adequate resection margins, en bloc high ligation of the inferior mesenteric artery (IMA) and lymphadenectomy. All circumferential margins were cleared. The number of positive lymph nodes and total number of retrieved lymph nodes were recorded. The pathologic stage was determined according to the seventh edition of the American Joint Committee on Cancer (AJCC) staging manual.

Follow-up and response evaluation

Patients were followed up every 3 months for first 2 years, every 6 months for the next 3 years. The examinations included complete blood cell count, liver function analysis, CEA levels, abdominal ultrasound, interval imaging and colonoscopic examinations. CT of chest, CT or MRI of abdominal and pelvic part, were performed annually.

We defined the local recurrence as the recurrent disease in the pelvis. The distant recurrence was defined as the recurrence outside the pelvis. The enteroscope was performed for biopsy when it was required. Disease-free survival (DFS) was the time from the surgery to the local or distant failure. Overall survival (OS) was calculated from surgery to death induced by all causes or end of follow up.

Statistical analysis

Present study was a retrospective case-control study and the case-to-control ratio was 1:1. The chi-square test or t-test was used for comparison of two groups. Kaplan-Meier method was used to draw the survival curves. Survival of all patients was analyzed by each variable: age, gender, smoking, drinking, obesity, pathologic TNM stage, pathologic T stage, pathologic N stage, tumor with/without schistosome, CEA, tumor location (Distance from anal verge), tumor size, lymphovascular invasion. The comparison of the survival curves was performed by log-rank test. A multivariable Cox regression analysis was performed to identify predictive factors of DFS and OS. Every variable was analyzed by univariate analysis, in order to cover all potentially important predictors, then variables with $P \leq 0.10$ in univariate analysis were included in multivariable analysis. Statistical analysis was performed by SPSS version 21. Statistical significance was stated as two tailed $P<0.05$.

Results

Demographic data

The study included 60 patients including 36 males and 24 females. The mean age at diagnosis was 63.67 (41-85) years for all patients, 63.87 (45-85) years for the SRC group, and 63.47 (41-81) years for the NSRC group. Males constituted 57% of the patients in both groups. Some risk factors accounts for most cases of colorectal cancer such as smoking, drinking and obesity were also analyzed (Brenner, 2014). In this analysis, we defined obesity as BMI greater than or equal to 25. And they were summarized in Table 1.

Clinical characteristics of the tumor

The mean size of tumor was 4.27cm for SRC versus

Table 1. Clinical and Pathologic Characteristics

Characteristic	Schistosome		t/x^2	*P*-value
	Positive (N=30)	Negative (N=30)		
Gender				
male	18	18	/	/
female	12	12		
Age, year	63.87±9.20	63.47±9.42	0.166	0.868
Tumor size, cm	4.27±1.62	3.33±1.31	2.449	0.017
Distance from anal verge, cm				
<5	10	8	0.656	0.466
≥5,<8	6	5		
≥8	14	17		
CEA, ng/ml				
<5	18	16	0.271	0.602
≥5	12	14		
Pathologic T stage				
T1	1	1	0.433	0.933
T2	3	3		
T3	5	7		
T4a	21	19		
Pathologic N stage				
N0	12	12	2.617	0.624
N1a	11	8		
N1b	3	6		
N2a	4	3		
N2b	0	1		
TNM stage				
I	3	3	/	/
IIB	9	9		
IIIA	1	1		
IIIB	15	15		
IIIC	2	2		
LVI(lymphovascular invasion)				
Positive	3	3	/	/
Negative	27	27		
Smoking				
Yes	11	7	1.249	0.264
No	19	23		
Drinking				
Yes	10	5	2.185	0.139
No	20	25		
Obesity				
Yes	7	4	0.958	0.321
No	23	26		

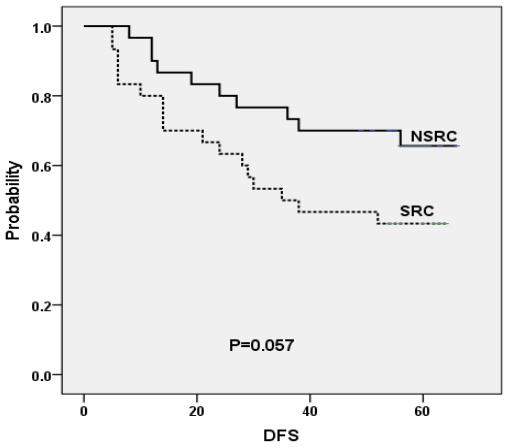

Figure 1. The 4-DFS Curve of SRC and NSRC. The 4-DFS rates were 46.7±9.1% and 70.0±8.4% , respectively (p=0.057)

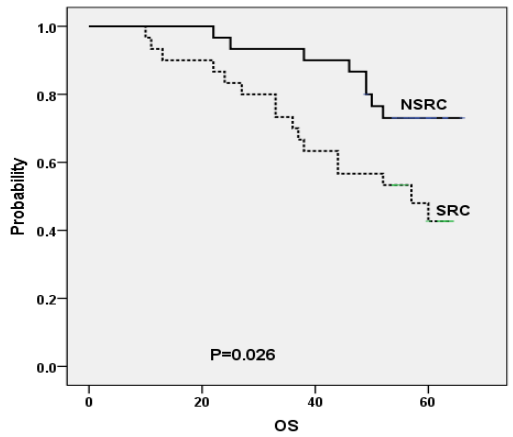

Figure 2. The 4-OS Curve of SRC and NSRC. The 4-OS rates were 63.3±8.8% and 86.7±6.2% , respectively (p=0.026)

3.33cm for NSRC group (P=0.017). The size of tumor in SRC group was larger than NSRC group. Both SRC and NSRC groups showed similar distributions of tumor location (P=0.466). Abnormal carcinoembryonic antigen (CEA) level was defined as a CEA level exceeding 5ng/ml. There were no significant difference between two groups of the CEA level (P=0.602).

With respect to pT classification, 2 tumors were classified pT1 (SRC 1 versus NSRC 1), 6 pT2 (SRC 3 versus NSRC 3), 12 pT3 (SRC 5 versus NSRC 7), and 40 pT4 (SRC 21 versus NSRC 19), respectively. Lymph node metastasis was detected in 36 cases. With respect to pN classification, 24 were classified pN0 (SRC 12 versus NSRC 12), 19 pN1a (SRC 11 versus NSRC 8), 9 pN1b (SRC 3 versus NSRC 6), 7 pN2a (SRC 4 versus NSRC 3) and 40 pT4 (SRC 21 versus NSRC 19), respectively. There were no significant difference of the pT and pN classification between two groups (P=0.933&0.624). The two groups were same in terms of the TNM stage: 3 patients were classified I, 9IIB, 1 IIIA, 15 IIIB and 2 IIIC, respectively. The details were showed in Table 1.

Survival analysis

Median follow-up duration was 49.8 months (range 10 to 66 months). The 4-year DFS rate in SRC and NSRC group were 46.7±9.1% and 70.0±8.4% (P=0.057). The 4-year OS rate in SRC and NSRC group were 63.3±8.8% and 86.7±6.2% (P=0.026). The DFS and OS curves according two groups were showed in Figure 1 and 2, respectively.

Table 2. Univariate Analysis of Factors for DFS and OS

Characteristics	No. of patient	4-yr DFS %±SE	P-value	4-yr OS %±SE	P-value
Gender					
Male	36	61.1±8.1	0.397	75.0±7.2	0.418
Female	24	54.2±10.2		66.7±9.6	
Age, yr					
<60	18	50.0±11.8	0.48	66.7±11.1	0.476
≥60	42	61.9±7.5		73.8±6.8	
Tumor size, cm					
<5	43	62.8±7.4	0.31	76.7±6.4	0.237
≥5	17	47.1±12.1		58.8±11.9	
CEA, ng/ml					
<5	34	61.8±8.3	0.507	79.4±6.9	0.186
≥5	26	53.8±9.8		61.5±9.5	
Schistosome					
Positive	30	46.7±9.1	0.057	63.3±8.8	0.026
Negative	30	70.0±8.4		86.7±6.2	
Pathologic T stage					
T1	2	100	0.118	100	0.062
T2	6	100		100	
T3	12	66.7±13.6		75.0±12.5	
T4a	40	47.5±7.9		65.0±7.5	
Pathologic N stage					
N0	24	79.2±8.3	0.006	87.5±6.8	0.014
N1a	19	52.6±11.5		52.6±11.5	
N1b	9	22.2±13.9		77.8±13.9	
N2a	7	57.1±18.7		57.1±18.7	
N2b	1	100		100	
Distance from anal verge,cm					
<5	18	61.1±11.5	0.388	72.2±10.6	0.422
≥5, <8	11	72.7±13.4		81.8±11.6	
≥8	31	51.6±9.0		67.7±8.4	
LVI					
Positive	6	50.0±20.4	0.547	50.0±20.4	0.428
Negative	54	59.3±6.7		74.1±6.0	
TNM stage					
I	6	100	0.024	100	0.002
IIB	18	72.2 ±10.6		83.3±8.8	
IIIA	2	100		100	
IIIB	30	43.3±9.0		63.3±8.8	
IIIC	4	25.0±21.7		25.0±21.7	
Smoking					
Yes	18	66.7±11.1	0.47	69.0±7.1	0.469
No	42	54.8±7.7		77.8±9.8	
Drinking					
Yes	15	66.7±12.2	0.292	73.3±11.4	0.55
No	45	55.6±7.4		66.7±7.0	
Obesity					
Yes	11	54.5±15.0	0.961	72.7±13.4	0.951
No	49	59.2±7.0		71.4±6.5	

*DFS, disease-free survival; OS, overall survival; LVI, lymphovascular invasion

Univariate analysis was performed in the whole 60 patients. It showed pathologic N stage (P=0.006) and pathologic TNM stage (P=0.024) were statistically significantly correlated with DFS. Pathologic N stage (P=0.014), pathologic TNM stage (P=0.002), and with/without schistosomiasis (P=0.026) were statistically significantly correlated with OS. The details were showed in Table 2.

Then, multivariate analysis was performed to assess the prognostic value of factors with P<0.10 in univariate analysis for DFS and OS. Smoking, drinking, obesity and other factors were not included in multivariate analysis. The results were showed in Table 3. Factors of schistosomiasis, pathologic N stage and pathologic TNM

Table 3. Multivariate Analysis of the Prognostic Factors for DFS and OS

Variable	DFS		OS	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Schistosome				
Negative	1		1	
Positive	3.147 (1.359-7.290)	0.007	3.661 (1.458-9.193)	0.006
Pathologic T stage	/	/	/	0.297
Pathologic N stage	/	0.064	/	0.758
TNM stage	/	0.336	/	0.15

DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval

stage were included in multivariate analysis for both DFS and OS. Pathologic T stage was also included in OS for $P<0.10$ in univariate analysis. Multivariate analysis showed schistosomiasis was only independent prognostic factor for both DFS ($P=0.007$) and OS ($P=0.006$)

Discussion

Schistosomiasis was an ancient human disease with effects worldwide, particularly in the poorest communities. Research on schistosomal rectal cancer had progressed very fast in recent years. Mariana et al. reported the first case of signet ring cell carcinoma of the rectum occurring in the context of chronic infection by S japonicum (Canepa et al., 2012). Wei Liu et al. reported that history of colonic schistosomiasis was a probable independent risk factor for the development of colorectal neoplasias. Renli Zhang et al. reported that there were more substitution mutations at CpG dinucleotides in schistosomal rectal cancer than in non-schistosomal rectal cancer (Zhang et al., 1998). However, few studies reported the prognosis of patients with schistosomal rectal cancer.

In this report, we matched SRC and NSRC patients for age, gender, and pTNM stage of disease. Moreover, we also found that patients in two groups were similar in terms of tumor location (distance from anal verge), pathologic T stage, pathologic N stage and CEA level. However, we noted that the tumor size of SRC was larger than NSRC. In this analysis, there were no patients with signet-ring adenocarcinoma or mucinous adenocarcinoma. All tumors were adenocarcinoma. One article reported the first case of signet ring cell carcinoma of the rectum occurring in the context of chronic infection by S japonicum (Canepa et al., 2012). Abe and co-workers reported a patient with a sessile polyp in the rectum, further histological evaluation revealed a hyperplastic polyp and calcified Schistosoma eggs in the submucosa (Abe et al., 2006). Liu et al. reported one mucinous adenocarcinoma caused by colonic schistosomiasis (Liu et al., 2013).

To evaluate the prognosis of the patients with SRC, univariate and multivariate analysis were applied in this study. Schistosomiasis was the only independent prognostic factor for both DFS and OS in multivariate analysis. Zhang et al. tested patterns of p53 mutations in SRC on the assumption that schistosomiasis japonica might affect carcinogenesis in the colon and rectum. They found that there were more substitution mutations at CpG dinucleotides in SRC than in NSRC (Zhang et al., 1998). It was probably the cause of poor prognosis in patients with SRC.

Unlike other cancers, such as lung cancer, no single risk factor accounted for most cases of rectal cancer. Apart from age and male sex, the following risk factors had been identified and established in epidemiological studies: Smoking, drinking, obesity and so on. But they were not statistically significantly correlated with DFS and OS in this study. Maybe the reason was the sample size was too small.

There were some effective drugs against Schistosoma. Praziquantel was one of choices for schistosomiasis (Colley et al., 2014). But it was uncertain that patients could benefit from the use of drugs against Schistosoma before or after the operation. There were no specific treatment programs for patient with schistosomal rectal cancer. In this study, TNM stage was a most important indicator for making treatment plan.

This study was different from previous ones. Firstly, previous studies had focused on the epidemiological and clinicopathological characteristics of patients with SRC. Xu et al. reported an epidemiological study about schistosoma japonicum and colorectal cancer in China (Xu et al., 1984). Liu et al. described clinicopathological characteristics of colonic schistosomiasis based on endoscopic findings (Liu et al., 2013). This study reported the poor prognosis of patients with SRC in current treatment. Secondly, multivariate analysis was performed in this study. So this conclusion was more persuasive. In addition, we matched patients for age, gender, and TNM stage of disease at presentation. Moreover, patients in two groups were similar in clinicopathological characteristics (tumor location, pathologic T stage, pathologic N stage and CEA level), which added the consistency of the baseline and comparability between groups. It made the survival analysis result more meaningful.

Soliman et al. reported that intestinal schistosomiasis should be considered as a precancerous condition for development of colonic dysplasia and cancer as a consequence of chronic inflammation that altered inflammatory, antioxidant and fucosylation status associated schistosomiasis (Soliman et al., 2014). Liu et al. described clinicopathological characteristics of colonic schistosomiasis based on endoscopic findings (Liu et al., 2013). This study concluded that the prognosis of patients with SRC was poorer than NSRC. The present study had shortcomings of a retrospective analysis with small sample size, further studies were required to confirm the conclusion by larger sample size and make specific therapeutic program for patients with Schistosomiasis-related rectal carcinoma.

In conclusion, the prognosis of patients with SRC was poorer than NSRC. Larger studies in patients with SRC with matching for stage and grade were warranted to examine the impact of schistosomiasis on survival.

References

Abe Y, Inamori M, Fujita K, et al (2006). Gastrointestinal: rectal polyp associated with schistosomiasis. *J Gastroenterol Hepatol*, **21**, 1216.

Brenner H, Kloor M, Pox CP. (2014). Colorectal cancer. *Lancet*, **383**, 1490-502.
Canepa M, Fanta PT, Weidner N, Peterson MR (2012). Schistosomiasis and signet ring cell carcinoma of the rectum. *Ann Diagn Pathol*, 16, 385-7.
Cihan S, Uncu D, Babacan NA, et al (2011). Adjuvant modified FOLFOX-4 in patients with stage III rectum adenocarcinoma. *Asian Pac J Cancer Prev*, **12**, 967-70.
Colley DG, Bustinduy AL, Secor WE, King CH (2014). Human schistosomiasis. *Lancet*, **383**, 2253-64.
Greene FL (2007). Current TNM staging of colorectal cancer. *Lancet Oncol*, **8**, 572-3.
Gu J, Chen N (2013). Current status of rectal cancer treatment in China. *Colorectal Dis*, **15**, 1345-50.
How P, Shihab O, Tekkis P, et al (2011). A systematic review of cancer related patient outcomes after anterior resection and abdominoperineal excision for rectal cancer in the total mesorectal excision era. *Surg Oncol*, **20**, 149-55.
Inoue I, Kato J, Tamai H, Iguchi M, Maekita T, Yoshimura N, Ichinose M (2014). Helicobacter pylori-related chronic gastritis as a risk factor for colonic neoplasms. *World J Gastroenterol*, **20**, 1485-92.
Ishii A, Matsuoka H, Aji T, et al (1994). Parasite infection and cancer: with special emphasis on Schistosoma japonicum infections (Trematoda). A review. *Mutat Res*, **305**, 273-81.
Liao XC, Huang WH, Wu GC (2013). Epidemic monitoring of schistosomiasis in Huangchang Village, Shashi District, from 2005 to 2010. *Zhongguo Xue Xi Chong Bing Fang Zhi Za Zhi*. **25**, 543-4.
Liu W, Zeng HZ, Wang QM, e al (2013). Schistosomiasis combined with colorectal carcinoma diagnosed based on endoscopic findings and clinicopathological characteristics: a report on 32 cases. *Asian Pac J Cancer Prev*, **14**, 4839-42.
Matsuda K, Masaki T, Ishii S, (1999). Possible associations of rectal carcinoma with Schistosoma japonicum infection and membranous nephropathy: a case report with a review. *Jpn J Clin Oncol*, **29**, 576-81.
McCoy AN, Araujo-Perez F, Azcarate-Peril A, et al (2013). Fusobacterium is associated with colorectal adenomas. *PLoS One*, **8**, 53653.
Soliman NA, Keshk WA, Shoheib ZS, Ashour DS, Shamloula MM (2014). Inflammation, oxidative stress and L-fucose as indispensable participants in schistosomiasis-associated colonic dysplasia. *Asian Pac J Cancer Prev*, **15**, 1125-31.
Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C et al (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*, **380**, 2163-96.
Xu Z, Su DL (1984). Schistosoma japonicum and colorectal cancer: an epidemiological study in the People's Republic of China. *Int J Cancer*, **34**, 315-8.
Zaghloul MS (2012). Bladder cancer and schistosomiasis. *J Egypt Natl Canc Inst*, **24**, 151-9.
Zhang R, Takahashi S, Orita S, et al (1998). p53 gene mutations in rectal cancer associated with schistosomiasis japonica in Chinese patients. *Cancer Lett*, **131**, 215-21.