RESEARCH ARTICLE

Prognostic Significance of the Mucin Component in Stage III Rectal Carcinoma Patients

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Abstract

Background: Although mucinous adenocarcinoma has been recognized for a long time, whether it is associated with a poorer prognosis in colorectal cancer patients is still controversial. Many studies put emphasis on mucinous adenocarcinoma containing mucin component ≥50%. Only a few studies have analyzed cases with a mucin component <50%. Objectives: This study aimed to analyze the prognostic value of different mucin component proportions in patients with stage III rectal cancer. Materials and Methods: Clinical, pathological and follow-up data of 136 patients with the stage III rectal cancer were collected. Every variable was analyzed by univariate analysis, then multivariate analysis and survival analysis were further performed. Results: Univariate analysis showed pathologic T stage, lymphovascular invasion, and histological subtype were statistically significant for DFS. Pathologic T stage was significant for OS. Histological subtype and lymphovascular invasion were independent prognostic factors in multivariate analysis for DFS, and histological subtype was the only independent prognostic factor for OS. Survival curves showed the survival time of mucinous adenocarcinoma (MUC) was shorter than non-MUC (adenocarcinomas with a mucin component <50% and without mucin component). Conclusions: Histological subtype (tumor with different mucin component) was an independent prognostic factor for both DFS and OS. Patients with MUC had a worse prognosis than their non-MUC counterparts with stage III rectal carcinoma.

Keywords: Mucinous adenocarcinoma - rectal carcinoma - prognostic significance

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Introduction

Colorectal cancer (CRC) is the fourth common carcinoma in China, and the morbidity is also increasing rapidly (Gu et al., 2013). Similar situation also appears in other countries (Abdifard et al., 2013). Accurate prognostic prediction of patients is essential for improved treatment selection. The prognosis of rectal cancer can be influenced by many factors. The TNM system has become the principal method for prognosis assessment (Greene, 2007). However, there are some shortages of it. For example, patients with the same stage in TNM system may have considerably different prognosis. The more accurate staging could be availed by taking histopathological parameters into account.

Mucinous adenocarcinoma (MUC) characterized by abundant of extracellular mucin is a histological subtype of colorectal adenocarcinoma. It is a histological variant that accounts for 4% to 15% of cases of primary colorectal cancer (Leopoldo et al., 2007). In accordance with World Health Organization criteria, mucinous adenocarcinoma is diagnosed when the extracellular mucin cover 50% of the lesion or more (Hamilton et al., 2010). Tumour with less than 50% extracellular mucin is diagnosed as adenocarcinomas with mucin component. Although this histologic subtype has been recognized for longtime, whether it has poorer prognosis in patients with colorectal cancer is still controversial. Some studies believed that mucinous histologic type itself is an important prognostic factor affecting the progression of tumor and outcome of patients with colorectal carcinoma. And the survival rate of patients with mucinous adenocarcinoma could be inferior to the patients with non-mucinous adenocarcinoma (NMC) (Kanemitsu et al., 2003; Verhulst et al., 2012; Biffi et al., 2013; Hugen et al., 2013), while some other studies did not find any adverse prognostic effect (Leopoldo et al., 2007; Farhat et al., 2008; Xie et al., 2009; Langner et al., 2012; Yamaguchi et al., 2012).

Total mesorectal excision operation technology (TME) has improved disease-free survival (DFS) and overall survival (OS) significantly in patients with rectal cancer (Den et al., 2008). Chemotherapy, which is primarily based on 5-fluoruracil, has decreased tumour recurrence in American Joint Cancer Committee (AJCC) Stage III patients (Langner et al., 2012). This study aimed to analyze the prognostic impact of different mucin component in patients with stage III rectal carcinoma in current treatment. We therefore focused on differences in survival in patients with adenocarcinomas with and without mucin.

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Materials and Methods

Patients and pretreatment evaluation

In 2009, a total of 136 patients with the stage III rectal carcinoma who underwent laparoscopic total mesorectal excision (TME) operation technology were collected from the colorectal cancer database of the West China Hospital of Sichuan University, Chengdu, China. All patients had primary rectal carcinoma. 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 (AJCC cancer staging manual, 7th edn, 2010).

Chemoradiotherapy and further adjuvant chemotherapy were performed after the operation. The standard scheduled on the base of patients final pathology, clinical condition and post-operative recovery was made by multidisciplinary team. The total dose of radiotherapy ranged 45 to 50.4 Gy. The schedule of chemotherapy was based on 5-fluorouracil or combination.

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. The routine imaging included the CT of chest, the 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

Kaplan-Meier method was used to draw the survival curves. The comparison of the survival curves was performed by log-rank test. A multivariable Cox regression analysis was performed to identify predictive factors of disease-free survival and overall survival. Every variable was analyzed by univariate analysis, in order to cover all potentially important predictors, then variables with P≤0.10 in univariate analysis were included in multivariable analysis. This level was chosen to incorporate all potentially important predictor variables in the final modeling process. All sets of variables were analyzed: age, gender, pathologic T stage, differentiation, tumor size, lymphovascular invasion, histological subtype (with different proportion of extracellular mucin component: ≥50%, <50%, 0%). Statistical analysis was performed by SPSS version 21. Statistical significance was stated as two tailed $p < 0.05$.

Results

The clinical and pathological characteristics of 136 patients (male 74, female 62) were summarized in Table 1. The median age was 57 (21-85years), and median follow-up time was 50 (7-58months). According to the difference of tumor extracellular mucin proportion, we divided the patients into three groups of histological subtype. 18 (13.2%) patients were mucinous adenocarcinoma (mucin proportion≥50%), 27 (19.9%) patients were adenocarcinomas with mucin component (mucin proportion: <50%), and 91 (66.9%) patients were adenocarcinoma without mucin component (mucin proportion: 0%).

Analysis of prognostic factors for survival

Univariate analysis showed pathologic T stage (p=0.02), lymphovascular invasion (p=0.02), and histological subtype (p=0.01) were statistically significant for DFS, but only pathologic T stage (p=0.02) was statistically significant for OS. When we took p<0.10 as statistically significant, lymphovascular invasion (p=0.06) and histological subtype (p=0.09) also had statistically significant for OS. The survival time of patients with lymphovascular invasion was shorter than non-invasion,

Table 1. Clinical and Pathologic Characteristics

Characteristic		No. of patient	%
Gender	male	74	54.4
	female	62	45.6
Age, yr	Median	57	42.6
	<60	74	54.4
	≥60	62	45.6
Tumor size, cm	Median	3.7	2.6
	<5	30	22.1
	≤5	106	77.9
Differentiation	Well	3	2.2
	Moderate	116	85.3
	Poorly	17	12.5
Pathologic T stage	T1	4	2.9
	T2	15	11
	T3	33	24.3
	T4a	81	59.6
	T4b	3	2.2
LVI	Positive	22	16.2
(lymphovascular invasion)	Negative	114	83.8
Histological subtype	≥50%	18	13.2
(mucin proportion)	<50%	27	19.9
	0%	91	66.9

Table 2. Univariate Analysis of Factors for DFS and OS

Characteristic	No. of patient	4-yr DFS, %±SE	4-yr OS, %±SE
Gender			
Male	74	54.0±5.8	61.4±5.7
Memale	62	44.9±6.3	57.5±6.3
		p=0.23	*p*=0.35
Age, yr			
<60	74	48.6±5.8	58.7±5.8
≥60	62	51.4±6.4	56.7±6.5
		p=0.89	*p*=0.97
Tumor size, cm			
<5	30	49.4±9.2	60.0±8.9
≤5	106	49.9±4.9	59.7±4.8
		p=0.81	*p*=0.99
Differentiation			
Well	3	100±0.0	100±0.0
Moderate	116	51.6±4.7	61.8±4.5
Poorly	17	29.4±11.1	36.8±12.3
		p=0.12	*p*=0.15
Pathologic T stage			
T1	4	50.0±25.0	50.0±25.0
T2	15	60.0±12.6	66.7±14.9
T3	33	54.5±8.7	62.6±8.6
T4a	81	48.0±5.6	57.6±5.5
T4b	3	0	0
		p=0.02	*p*=0.02
LVI			
Positive	22	31.2±10.0	45.5±10.6
Negative	114	53.4±4.7	63.5±4.5
		p=0.02	*p*=0.06
Histological subtype (mucin proportion)			
≥50%	18	16.7±8.8	44.4±11.7
<50%	27	48.1±9.6	58.2±9.6
0%	91	57.0±5.2	65.7±5.0
		p=0.01	*p*=0.09

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

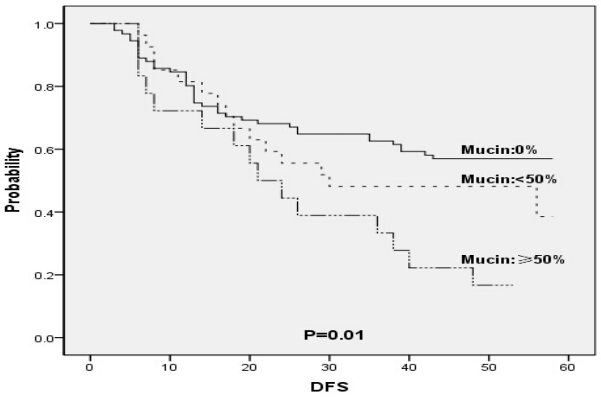

Figure 1. The 4-DFS Curve According to Histological Subtype. The 4-DFS rates were 57.0±5.2%, 48.1±9.6%, 16.7±8.8% with Increasing Mucin Component (*p*=0.01)

and reduced with increasing of the depth of tumor invasion and extracellular mucin proportion. Age, gender and differentiation showed no statistically significant for both DFS and 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. Pathologic T stage, lymphovascular invasion and histological subtype were included. In multivariate analysis for DFS, histological subtype ($p<0.01$) and lymphovascular invasion ($p=0.02$) were independent prognostic factors. In multivariate analysis for OS, histological subtype ($p=0.04$) was the only independent prognostic factor for stage III rectal carcinoma. The results were showed in Table 3.

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

Variable	DFS		OS	
	HR (95% CI)	*p*-valu	HR (95% CI)	*p*-value
LVI				
Negative	1		1	
Positive	2.06 (1.12-3.82)	0.02	1.89 (0.96-3.71)	0.07
Pathologic T stage		0.14		0.13
T1	1		1	
T2	1.08 (0.22-5.29)	0.93	0.59 (0.11-3.26)	0.54
T3	1.24 (0.28-5.58)	0.78	0.97 (0.21-4.43)	0.97
T4a	1.34 (0.32-5.64)	0.69	1.05 (0.25-4.4)	0.95
T4b	6.48 (0.97-43.3)	0.05	4.68 (0.69-31.6)	0.11
Histological subtype (mucin proportion)		0		0.04
0%	1		1	
<50%	1.48 (0.80-2.71)	0.21	1.33 (0.68-2.61)	0.4
≥50%	2.96 (1.58-5.58)	0	2.47 (1.23-4.99)	0.01

*DFS, disease-free survival; OS, overall survival; LVI, lymphovascular invasion; HR, hazard ratio; CI, confidence interval

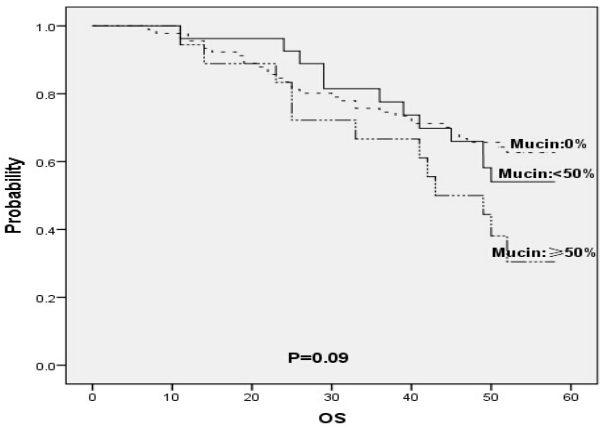

Figure 2. The 4-OS Curve According to Histological Subtype. The 4-OS rates were 65.7±5.0%, 58.2±9.6%, 44.4±11.7% with Increasing Mucin Component (*p*=0.09)

Survival analysis of patient with different histological subtype

Survival curve of patients with different histological subtype for DFS and OS were showed in Figure 1 and 2. Intuitively, the survival curve of patient with adenocarcinomas containing mucin component (mucin proportion: <50%) was more close to the survival curve of patient with adenocarcinoma without mucin (mucin proportion: 0%). The survival curve of patient with

mucinous adenocarcinoma (mucin proportion: ≥50%) was obviously diverse from other two groups. The survival time of MUC group was obviously shorter than non-mucinous adenocarcinoma (HR=2.47, 95%Cl: 1.23-4.99). Further survival analysis of the two groups (adenocarcinoma with and without mucin component) was performed, and the survival curve had no significant difference between the two groups for both DFS (p=0.35) and OS (p=0.61). This means that the survival time of patients with mucinous adenocarcinoma was inferior to that of patients with non-mucinous adenocarcinoma, and the survival time of patients with adenocarcinomas containing mucin component and without mucin component was similar.

Discussion

Although mucinous adenocarcinoma (MUC) had been recognized for a long time (Symonds et al., 1976), but the clinical characteristics of rectum mucinous adenocarcinoma, especially the prognosis remains controversial. Whether it behaves progressively or protectively was still controversial. Researches on the prognostic significance of mucinous histology had provided inconsistent results. Some studies had suggested that MUC had a worse prognosis compared with non-MUC (Kanemitsu et al., 2003; Verhulst et al., 2012; Biffi et al., 2013). Others reported no differences (Leopoldo et al., 2007; Farhat et al., 2008; Xie et al., 2009; Langner et al., 2012; Yamaguchi et al., 2012). In present study, we found patient with MUC had a worse prognosis than non-MUC (both adenocarcinomas containing mucin component and without mucin component) in all patients with stage III rectal carcinoma.

The accuracy of the results can be affected by many factors. Firstly, differences in the criteria used to define MUC might explain some of these conflicts. Depending on the study, MUC has been defined as tumour with mucin component of at least 50% or >60% (Wu et al., 1996). In accordance with World Health Organization criteria, a histological diagnosis of MUC was made when extracellular mucin accounted for >50% of the lesion in this study.

The second was that patients with different TNM stages were used for comparison. Langner et al. suggested that recording of mucinous differentiation should be used as an indicator of mismatch repair deficiency, but not for prognostic stratification (Langner et al., 2012). Patients with stage I-III were included in that study. And patients with N0 stage (n=212) were obviously more than patients with N1 (n=83) or N2 (n=79) stages. Only patients with stage III rectal cancer were included in this study which was based on the hypothesis that the prognosis of patients with mucinous adenocarcinoma was various in different TNM stages.

In addition, many studies paid close attention to the mucinous adenocarcinoma whose extracellular mucin is 50% or more than 50%, but ignored the characteristic of the adenocarcinomas with extracellular mucin component less than 50%. Kanemitsu et al. thought that mucinous histologic type itself was an important prognostic factor affecting the tumor progression and outcomes of patients with colorectal carcinoma (Kanemitsu et al., 2003). Patients with tumour which extracellular mucin was less than 50% were not analyzed alone in that study. To analyze the prognostic impact of different mucin component, patients with mucinous adenocarcinoma, adenocarcinoma, and adenocarcinomas with mucin component were all included in present study.

The results of this study showed that histological subtype (with different mucin component) was an independent prognostic factor for both DFS and OS in patient with stage III rectal carcinoma. It had highlighted specific characteristics of rectal mucinous adenocarcinoma, which distinguished it from adenocarcinomas and adenocarcinomas with mucin component. And the survival characteristic of patients with rectal adenocarcinomas with mucin component (extracellular mucin<50%) was more similar to adenocarcinoma. Univariate analysis showed histological subtype was statistically significant for DFS. But it was not statistically significant for OS. However, a divergence between the overall survival Kaplan-Meier curves seemed to emerge, and it might be statistically significant for OS in longer follow-up.

Manas et al. viewed when compared with non-mucinous adenocarcinoma, mucinous tumors presented more peritoneal spreading, infiltrating through all layers of the intestinal wall, more lymph node involvement, greater frequency of the advanced stage disease, a lower rate of curative resection, and lower overall 5-year survival rates. Chen et al. thought that compared to patients with non-mucinous adenocarcinomas, mucinous adenocarcinoma patients with later TNM staging made up a big percentage. These conclusions were similar with ours. The next step for the research needs to solve two issues. Firstly, after a median follow-up of 50 months, there was no significant difference between adenocarcinomas with mucin component <50% and without mucin component on disease-free survival and overall survival. However, a divergence between the disease-free survival and the overall survival Kaplan-Meier curves seemed to emerge after 2 years. It might become evident with longer follow-up. Secondly, there were no specific treatment programs for patient with mucinous rectal cancer. Further studies were required to make specific therapeutic program for patients with mucinous rectal carcinoma.

The present study had the shortcomings of a retrospective analysis with small patient sample size. However, it was sufficient to evaluate the prognostic value of adenocarcinomas with different extracellular mucin component. In conclusion, histological subtype (with different mucin component) was an independent prognostic factor for both DFS and OS of patient with stage III rectal carcinoma. Mucinous adenocarcinoma characterized by clinicopathological features was distinct from adenocarcinomas and adenocarcinomas with mucin component.

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