

Intestinal obstruction: a factor of worse prognosis of rectal cancer?

Kaiqiang Qin¹, Xiaona Chu¹, Yongjang Wang¹, Liangdong Cheng², Chunqiao Li², Yuanbo Li², Liang Ning², Shikuan Li^{2*}

¹College of medicine, Qingdao University, Qingdao, 266003 China

²Department of Emergency General Surgery, Affiliated Hospital of Qingdao University, Qingdao, 266000, China

Abstract: To assess the relationship between intestinal obstruction and the prognosis of rectal cancer. Data of 151 rectal cancer patients were extracted between January 2010 and October 2015 to survival analyse. The Kaplan-Meier method is used to survival analyse. The log-rank test was executed to compare the survival rate between patients with intestinal obstruction and those without intestinal obstruction. Cox proportional hazards regression analysis was performed to estimate the crude hazard ratio of mortality from colorectal cancer. The χ^2 test was used to compare disordered qualitative variables. The Kruskal Wallis H test was used to compare ordered qualitative variables. The 3-5 years overall survival rate after treatment of patients with intestinal obstruction were shorter than patients without intestinal obstruction respectively. The 3-5 years disease-free survival rate after treatment of patients with intestinal obstruction was lower than patients without intestinal obstruction, respectively. The log-rank test suggested that there were significant difference between the two overall survival curves ($P=0.013$) and two disease-free survival curves ($P=0.047$). Univariate and Multivariate Cox proportional hazards regression analysis suggested that intestinal obstruction decreased overall survival rate ($P<0.05$) instead of disease-free survival rate ($P>0.05$). Intestinal obstruction is a factor of poor prognosis of rectal cancer.

Keywords: Rectal cancer; Intestinal obstruction; Prognosis

Received 29 November 2016, Revised 25 January 2017, Accepted 27 January 2017

*Corresponding Author: Shikuan Li, worldwidth@aliyun.com

1. Introduction

Colorectal cancer is one of the most widespread malignancies worldwide. Colorectal cancer became the third most common cancer globally in 2012 [1]. According 2015 new statistics, colorectal cancer was fifth common cancer of all cancer in China [2]. However, with the aging of our country gradually aggravating and lifestyle gradually westernized, the incidence and mortality of colorectal cancer were increasing [2,3]. In China, unlike in Western countries, rectal cancer accounts for approximately 70% of colorectal cancers [4]. Thus, the importance of rectal cancer had been a public health problem in China. Some factors affecting the prognosis of rectal cancer have been studied. Rectal cancer is a complex clinical problem, and high risks of mortality were associated with advanced-stage tumours, elevated preoperative serum carcinoembryonic antigen, poorer grade histological differentiation [3,5-7]. In the present study, we assessed the prognosis of rectal cancer patients with and without intestinal obstruction. In order to study the relationship between intestinal obstruction and the prognosis of rectal cancer, we used existing data in the affiliated Hospital of Qingdao University, Qingdao, China. Other variables that might affect the survival of rectal cancer patients were also extracted, including age, sex, family history of rectal cancer, ASA score, tumor size, morphological classification, histological differentiation, lymphatic metastasis, recurrence or metastasis, cancer staging.

2. Materials and Methods

2.1. Patients

A total of 151 patients with rectal cancer that underwent radical surgery at Affiliated Hospital of Qingdao University, Qingdao, China from January 2010 to January 2015 were enrolled in our database. Their clinical cases and follow-up data were recorded. The data included age, sex, family history of rectal cancer, ASA score, tumor size, morphological classification, histological differentiation, lymphatic metastasis, cancer stage, nodes, date of surgery, date of recurrence. With intestinal obstruction group was consisted of all rectal cancer with intestinal obstruction patients ($n=75$). Without intestinal obstruction group was consisted of patients random checked by random number method of all rectal cancer without intestinal obstruction patients ($n=76$). The 7th editions of the Union for International Cancer Control (UICC) classification [8] were used to categorize rectal carcinomas. Rectal cancer was defined as cancer with a distal margin of 15 cm from the anal verge measured with a rigid endoscope.

2.2. Follow-up duration

All patients were followed up at 25 days after operation, 3 moth intervals for the first 2 years, and 6 moth intervals for 3-5 years. The primary following up endpoint was death. The secondary following up endpoint was recurrence or metastasis. Overall

survival time was defined as from time of operation to time of death. Disease-free survival was defined as

from time of operation to time of recurrence or metastasis.

Table 1a Comparison of demographic characteristics of rectal cancer patients with and without intestinal obstruction n (%)

Characteristics	Intestinal	Without Intestinal	Chi-Square	P
Age				
≤ 35	1(1.3)	0(0)		
36-59	23(30.7)	29(38.2)	H=1.794	0.180
60-74	34(45.3)	38(50)		
≥ 75	17(22.7)	9(11.8)		
Sex				
Male	39(52.0)	52(68.4)	$\chi^2=4.251$	0.039
Female	36(48.0)	24(31.6)		
Family history				
Positive	13(17.3)	6(7.9)	$\chi^2=3.075$	0.080
Negative	62(82.7)	70(92.1)		
ASA				
1	6(8)	3(3.9)	H=0.579	0.447
2	43(57.3)	53(69.7)		
3	23(30.7)	20(26.3)		
4	3(4)	0(0)		
5	0(0)	0(0)		
Tumor size				
≥ 5cm	47(62.5)	27(35.5)	$\chi^2=11.127$	0.001
<5cm	28(37.5)	49(64.5)		
Morphological classification				
Ulcer type				
infiltrative type	66(88)	59(77.6)	$\chi^2=5.931$	0.052
protrude type	3(4)	1(1.3)		
Histological differentiation grade				
Well	6(8)	16(21.1)		
Moderate	5(6.7)	10(13.2)	H=4.424	0.035
Poor	54(72)	58(76.3)		
	16(21.3)	8(10.5)		

P values were made by chi-squared test.

2.3. Statistical analysis

All data were recorded and analyzed using SPSS version 21.0. The Kaplan-Meier method was used to calculate survival curves. The log rank test was used to compare differences in survival. Univariate hazard ratios and significant and independent predictors of disease-specific survival and overall survival were identified by Univariate and Multivariate Cox proportional hazards regression analysis (using the 'Forward Condition' method). Statistical significance

was defined as $P < 0.05$.

3. Results

3.1. Analysis of rectal cancer patients

The compare and analysis of clinical characteristics of rectal cancer patients with and without intestinal obstruction was showed in Table 1a, b.

Table1b Comparison of demographic characteristics of rectal cancer patients with and without intestinal obstruction n (%)

Characteristics	Intestinal obstruction	without intestinal obstruction	chi-square test	P
Lymphatic metastasis				
Positive	37(49.3)	28(36.8)	$\chi^2=2.402$	0.121
Nagetive	38(50.7)	48(63.2)		
Lymphnode ratio				
<0.09	40(53.3)	54(71.1)		
0.09-0.18	8(10.7)	5(6.6)	H=3.929	0.048
>0.18,<0.34	13(17.3)	5(6.6)		
≥ 0.34	14(18.7)	12(15.8)		
Depth of infiltration				
Tis	0(0)	2(2.6)		
T1	0(0)	5(6.6)		
T2	2(2.7)	19(25)	H=10.778	0.001
T3	42(56)	28(36.8)		
T4a	29(38.7)	17(22.4)		
T4b	2(2.7)	5(6.6)		
TMN stage				
0	0(0)	2(2.6)		
I	2(2.7)	21(27.6)		
IIa	27(36)	18(23.7)		
IIb	6(8)	4(5.3)	H=12.483	0.000
IIc	0(0)	1(1.3)		
IIIa	1(1.3)	3(3.9)		
IIIb	17(22.7)	17(22.4)		
IIIc	11(14.7)	9(11.8)		
IVa	11(14.7)	1(1.3)		
IVb	0(0)	0(0)		
Recurrence or metastasis				
Positive	24(35.8)	13(18.8)	$\chi^2=4.949$	0.026
Nagetive	43(64.2)	56(81.2)		
Missing	15			
CEA				
≤ 5 ng/mL	33(44)	56(73.7)	$\chi^2=13.744$	0.000
> 5 ng/mL	42(56)	20(26.3)		

P values were made by chi-squared test. CEA: Carcinoembryonic antigen.TNM: Tumor node metastasis.

3.2. Overall survival analysis

The 3-5 years overall survival rate after treatment were 77.9%, 53.4% for patients with intestinal obstruction and 90.4%, 78.2% for without intestinal obstruction. The log rank test was used to compare the overall survival rates of patients with intestinal obstruction and patients without intestinal obstruction, and a statistically significant difference

was found (P=0.013). (Table 2, Figure 1). Univariate Cox proportional hazards regression analysis revealed that intestinal obstruction significantly decreased Overall survival rate (RR=2.877, P=0.018). Multivariate Cox proportional hazards regression analysis revealed that intestinal obstruction was an Independent risk factor for Overall survival rate (RR=3.290, P=0.026) (Table 3).

Table 2 Overall survival analysis with the Kaplan-Meier method

	Average overall survival time(month) (95%CI)	overall survival rate%		χ^2 (df)	P ¹
		3year	5year		
With intestinal obstruction	58.280 (51.33, 65.23)	77.9	53.4	6.188 (1)	0.013
Without intestinal obstruction	70.343 (65.09, 75.59)	90.4	78.2		

Survival analysis using the Kaplan-Meier method. CI, confidence interval; χ^2 , chi-squared; df, degrees of freedom. ¹Log-rank test.

Table 3 Investigate the relationship between intestinal obstruction and the prognosis in rectal cancer with Cox proportional hazards regression analysis

	Univariate Cox			Multivariate Cox		
	RR(95%CI)	Wald χ^2	P	RR(95%CI)	Wald χ^2	P
Intestinal Obstruction	2.877 (1.203, 6.881)	5.636	0.018	3.290 (1.150, 9.413)	4.933	0.026

RR,relative risk. CI, confidence interval.

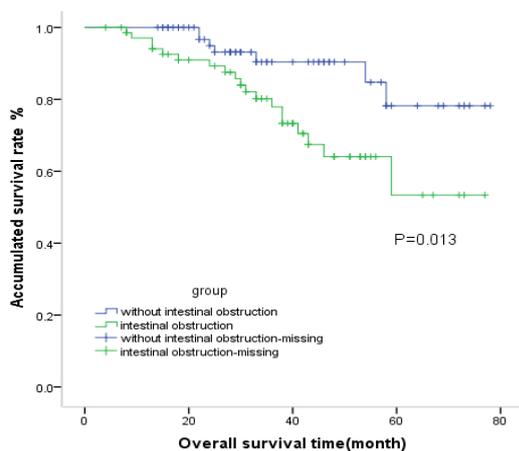


Figure 1. Comparison of Overall survival curves.

3.3. Disease-free survival analysis

The 3-5 years disease free survival rate after treatment was 66%, 60.4% for patients with intestinal obstruction and 83.3%, 69.2% for with intestinal obstruction. The log rank test was used to compare the overall survival rates of patients with intestinal obstruction and patients without intestinal obstruction, and a statistically significant difference was found (P=0.047) (Table 4, Figure 2). Univariate Cox proportional hazards regression analysis revealed that the relation of intestinal obstruction and disease-free survival rate was not statistical significance (P=0.055). Multivariate Cox proportional hazards regression analysis revealed that the relation of intestinal obstruction and disease-free survival rate was not statistical significance (P=0.404).

Table 4 Disease-free survival analysis with the Kaplan-Meier method

	Average disease-free survival time (month) (95%CI)	Disease-free survival rate%		χ^2 (df)	P ¹
		3year	5year		
With intestinal obstruction	52.247 (44.228, 60.265)	66.0	60.4	3.932 (1)	0.047
Without intestinal obstruction	62.864 (55.773, 69.954)	83.3	69.2		

Survival analysis using the Kaplan-Meier method.CI, confidence interval; χ^2 , chi-squared;df, degrees of freedom. ¹Log-rank test.

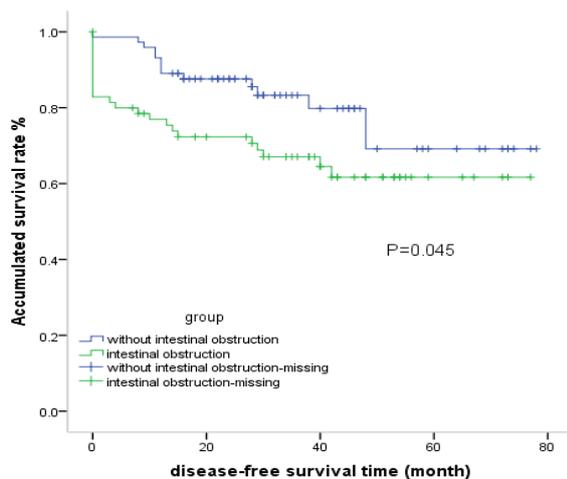


Figure 2. Comparison of disease-free survival curves.

4. Discussion

Some factors have been identified in relation to rectal cancer, such as age, family history of rectal cancer, ASA score, morphological classification, histological differentiation, lymphatic metastasis, recurrence or metastasis, cancer staging [3,5-7]. The study focused on investigating intestinal obstruction as an important factor affecting the prognosis of rectal cancer. Some studies have reported an incidence of intestinal obstruction of 10 to 29% in colorectal cancer patients [3,4]. Although the number of patients with intestinal obstruction is not large, the presence has been suggested to be relation to worse outcomes.

In this study, disease-free survival and overall survival of rectal cancer patients were analyzed respectively. The patients without intestinal obstruction in our cohort had a longer median overall survival time (70.342 months) than those with intestinal obstruction (58.280 months), a longer median disease-free survival time (62.864 months) than those with intestinal obstruction (52.247 months). Patients without intestinal obstruction had higher 3-5 years overall survival rate (90.4%, 78.2%) compared patients with intestinal obstruction (77.9%, 53.4%). Patients without intestinal obstruction had higher 3-5 years disease-free survival rate (83.3%, 69.2%) compared patients with intestinal obstruction (66.0%, 60.4%). The log-rank test revealed that there were significant difference between the two overall survival curves ($P=0.013$) and two disease-free survival curves ($P=0.047$). Univariate Cox proportional hazards regression analysis indicated that ratio for death from rectal cancer with intestinal obstruction was 2.877 times higher than patients without intestinal obstruction ($P=0.01$). Multivariate Cox proportional hazards regression analysis

revealed that ratio for death from rectal cancer with intestinal obstruction was 3.290 times higher than patients without intestinal obstruction ($P=0.026$), which was similar with Mohd Azri Mohd Suan's study [9]. Univariate and Multivariate Cox proportional hazards regression analysis revealed that the relation of intestinal obstruction and disease-free survival rate was not statistical significance ($P>0.05$). Intestinal obstruction was an independent risk factor for overall survival instead of disease-free survival.

There are several possible reasons for poor survival outcomes among rectal cancer patients with intestinal obstruction. It has been studied that patients with intestinal obstruction already present at an advanced stage of cancer and elder (more than 60 years old), which agreed on our study. This situation leads to poor nutritional dynamics and other biochemical imbalances that increase the mortality of rectal cancer [9,10]. Our study showed intestinal obstruction increased Lymphatic metastasis ($P<0.05$). Intestinal obstruction may also increase micro-metastasis to the nearby mesenteric lymph nodes. This micro-metastasis in the lymph nodes is not easily detected. In fact, Gusterson [11] revealed that only 1% of pathologists are able to identify a small metastatic focus of cancer that metastases to the regional lymph nodes. Such failure to find micro-metastases may lead to under-staging the tumour and under-treatment of the patient, which may contribute to the poor survival rate.

This study had several limitations. Firstly, the authors were unable to all variables into account, such as sites of obstruction, operation mode, Radiotherapy and chemotherapy, Perineural invasion, perforation, surgical intervention, which has been done in other studies [3,9,12].

In conclusion, overall survival time and disease-free survival time of rectal cancer patients with obstruction were shorter than those without intestinal obstruction, and the difference between the two groups was significant. Therefore, patients should seek medical treatment as soon as clinical symptoms appear, in order to improve the outcomes of rectal cancer.

References

- [1] International Agency for Research on Cancer. GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012. [Cited 2015 Apr 30]. Available from: <http://globocan.iarc.fr/Default.aspx>.
- [2] Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015[J]. CA: a cancer journal for clinicians, 2016, 66(2):115-132.
- [3] Yuan Y, Li MD, Hu HG, et al. Prognostic and survival analysis of 837 Chinese colorectal

- cancer patients[J]. World journal of gastroenterology, 2013, 19(17):2650-2659.
- [4] Zhao DB, Wu YK, Shao YF, et al. Prognostic factors for 5-year survival after local excision of rectal cancer[J]. World journal of gastroenterology, 2009, 15(10):1242-1245.
- [5] Chen W, Tan XP, Ye JW, et al. Effect of bowel obstruction on stage IV colorectal cancer[J]. Molecular and clinical oncology, 2014, 2(2):308-312.
- [6] Huh JW, Kim YJ, Kim HR. Ratio of metastatic to resected lymph nodes as a prognostic factor in node-positive colorectal cancer[J]. Annals of surgical oncology, 2010, 17(10):2640-2646.
- [7] Zhang S, Gao F, Luo J, et al. Prognostic factors in survival of colorectal cancer patients with synchronous liver metastasis[J]. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland, 2010, 12(8):754-761.
- [8] Hong KD, Lee SI, Moom HY. Lymph node ratio as determined by the 7th edition of the American Joint Committee on Cancer staging system predicts survival in stage III colon cancer[J]. Journal of surgical oncology, 2011, 103(5):406-410.
- [9] Mohd suan MA, Tan WL, Soelar SA, et al. Intestinal obstruction: predictor of poor prognosis in colorectal carcinoma?[J]. Epidemiology and health, 2015, 37:e2015017.
- [10] Yang XF, Pan K. Diagnosis and management of acute complications in patients with colon cancer: bleeding, obstruction, and perforation[J]. Chinese journal of cancer research = Chung-kuo yen cheng yen chiu, 2014, 26(3):331-340.
- [11] [11] Occult axillary lymph-node micrometastases in breast cancer[J]. Lancet (London, England), 1990, 336(8712):434-435.
- [12] Song P, Qin K, Chu X, et al. Erratum to: Different site, different clinical outcomes in perforated colorectal cancer?[J]. International journal of colorectal disease, 2016, 31(11):1805.