Prognosis analysis of patients with resectable T4 colorectal cancer

Wei Chen
Sun Yat-sen University Sixth Affiliated Hospital
Jun-Wen Ye
The Seventh Affiliated Hospital Sun Yat-sen University
Xiao-ping Tan
Guangzhou Medical University Second Affiliated Hospital
Yan Zhang
Sun Yat-sen University Sixth Affiliated Hospital
Jing-Lin Liang
Sun Yat-sen University Sixth Affiliated Hospital
Meijin Huang (hmjin@mail.sysu.edu.cn)
SYSU

Research article

Keywords: Colorectal cancer, Surgery, Prognosis, Resectable

Posted Date: June 26th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-37853/v1

Abstract

Objective: To observe the factors related to survival and prognosis of patients with resectable stage T4 colorectal cancer. Methods : 148 patients with resectable stage T4 colorectal cancer who underwent surgery in the first Affiliated Hospital of Sun Yat-sen University between August, 1994 and December, 2005 were retrospectively analyzed. Univariate and multivariate analyses of associations between clinicopathological variables and survival were analyzed using the Cox regression model.

Results: At the end of December of 2010 or death, the 5-year and 10 years OS rates were 49.0% and 32.2% respectively, the median OS was 25 months. The disease free survival rates (DFS) at 5 and 10 years were 44.2% and 30.3% respectively. In univariate analysis, patients with postoperative pathology lymph node metastasis was associated with the prognosis of patients with OS (all P< 0.01), postoperative adjuvant therapy failed to improve OS and DFS (P>0.05). Postoperative pathology lymph node metastasis was associated with DFS too (all P< 0.01). In multivariate analysis, postoperative pathology lymph node metastasis was independent factor affected OS and DFS in colorectal cancer patients.

Conclusion: Postoperative prognosis of T4 colorectal cancer patients is poor, postoperative pathology lymph node positive was an independent factor affect OS and DFS.

Background

Colorectal cancer is one of the most common malignant tumors in the world, with high mortality. China is a high incidence area for colorectal cancer, with more than half of the world's morbidity and mortality[1]. Surgical resection is one of the main treatment methods for colorectal cancer patients. Early surgical treatment of colorectal cancer is effective, and the 5-year survival rate is as high as 60.5%[2]. Most patients have progressed to the locally advanced during the diagnosis, and lost the opportunity for direct surgery. Even after surgery, it is difficult to achieve complete resection. Advances in surgical techniques and perioperative management have improved patient survival, but surgery alone does not improve outcomes in patients with locally advanced colorectal cancer patients. In order to improve the resection rate, the guidelines[3] recommend that patients with locally advanced colorectal cancer can be treated with neoadjuant chemoradiotherapy and/or chemotherapy combined surgery, and radical chemoradiotherapy is also feasible. However, due to the limited accuracy of preoperative staging and the patient's willingness, some patients were sometimes more liked to undergo surgical resection, and some doctors considered that neoadjuvant therapy may increase the risk and complications of surgery, so they firstly choose surgery, and then determine whether postoperative adjuvant therapy is available according to postoperative pathology results. Patients with stage T4 colorectal cancer have poor prognosis and are

prone to recurrence and distant metastasis. This study was to investigate the prognostic factors affecting patients with postoperative T4 colorectal cancer patients.

Materials And Methods

General information: A retrospective analysis of 148 patients with operative treatment of T4 stage colorectal cancer who underwent surgery in at the first Affiliated Hospital of Sun Yat-sen University between August, 1994 and December, 2005. Inclusion criteria: Postoperative pathological staging revealed neoplasm invasiveness out of the membrane (T4), and the survival time was longer than 2 months. Exclusion criteria: patients who cannot tolerate surgery because of poor cardiopulmonary function; distant metastasis and so on. All patients and their families gave informed consent to the study and signed informed consent. The study was approved by the Ethics Committee of Sun Yat-sen University.

Follow-up and review: The patients were followed up every 3 months for the first year, 6-monthly for the next 2 years and yearly thereafter after surgery. The first review was performed at the hospital one month after the operation. Routine review of chest and abdomen CT, blood routine, liver and kidney function, tumor markers, colonoscopy and other examinations, if necessary, whole body bone scan and PET-CT to see if there is systemic metastasis. Local recurrence: anastomotic stoma or regional lymph nodes recurrence. Recurrence in the distance: distant lymph nodes or distant organ metastasis.

Statistics method: The overall survival time (OS) is from the date of surgery to the death or follow-up deadline. The disease free survival time (DFS) is from the date of surgery to the date of tumor recurrence or metastasis. Using spss 23.0 software, Kaplan-Meier method was used to calculate OS and DFS, and Log-rank method was used to test; Cox model was used for single factor and multifactor analysis, and $\chi 2$ test was used to analyze the effect of different treatment methods on survival rate. $P < 0.05$ was considered statistically significant.

Result

Postoperative condition

The whole group was followed up until December 2010. Among the 148 patients, 84 were male and 64 were female. The patients were 17 to 86 years old and the median age was 64 years old. During the operation, the average lymph node was removed by 13.5 (2 ~ 35). Postoperative pathology revealed 85 cases with lymph node metastasis and 63 cases with negative lymph nodes. Postoperative pathology: all showed that the tumor invaded the adventitia. Postoperative anastomotic leakage was found in 2 cases.

The Postoperative Survival Rate

The 5- and 10-year survival rates were 49.0% and 32.2% in the whole group and the median survival was 58.8 months. Cox univariate analysis showed that postoperative pathological lymph node metastasis were associated with OS ($P < 0.05$). The gender, age, obstruction, tumor site, liver metastasis,histological grade, family history, postoperative adjuvant therapy were not associated with OS($P > 0.05$). Cox multivariate analysis showed that postoperative lymph node metastasis was an independent factor influencing patient survival. Compared with postoperative lymph node-negative patients, the risk of death in patients with lymph node was increased by 1.213 times (95% Cl: 0.845–1.564, $P = 0.045$). See Table 1.

Table 1
Cox proportional hazards model univariate and multivariate analyses of individual parameters for correlations with overall survival (OS)

Variable	Univariate analysis		Multivariate analysis		*P*
	10 year- OS	P value	HR	CL (95%)	
Gender		0.557			
Female	87.6				
Male	81.6				
Age (y)		0.103			
≥65	82.4				
<65	83.8				
Obstruction		0.270			
No	81.5				
Yes	64.3				
Tumor site		0.117			
Rectal	72.7				
Colon	86.2				
N stage		0.000			0.045
N0	74.5		1		
N1-N2	60.7		1.213	0.845–1.564	
Liver metastasis		0.285			
No	82.7				
Yes	66.7				
Histological grade		0.571			
Well	90.9				
Moderately	77.1				
Poorly	65.2				
Family history		0.415			
No	84.0				

Variable	Univariate analysis		Multivariate analysis		*P*
	10 year- OS	P value	HR	CL (95%)	
Yes		50.2	0.531		
Postoperative adjuvant therapy		60.1			
No		74.5			
Yes					

Postoperative Disease-free Survival Rate

The DFS at 5 and 10 years after surgery of the whole group were 44.2% and 30.3%, respectively, and the median DFS was 45.2 months. The gender, age, obstruction, tumor site, liver metastasis, histological grade, family history, postoperative adjuvant therapy were not associated with DFS ($P > 0.05$). Cox multivariate analysis showed that postoperative pathological lymph node positive is an independent factor affecting DFS in patients. Compared with postoperative pathologically node-negative patients, lymph node-positive patients had a 1.425 times increased risk of tumor recurrence or metastasis (95% CI: 0.974–1.836, both $P < 0.01$). See Table 2.

Table 2
Cox proportional hazards model univariate and multivariate analyses of individual parameters for correlations with disease-free survival (DFS)

Variable	Univariate analysis		Multivariate analysis		*P*
	10 year- DFS	P *value*	HR	CL(95%)	
Gender		0.436			
Female	83.2				
Male	75.3				
Age (y)		0.201			
≥65	81.2				
<65	79.5				
Obstruction		0.316			
No	80.2				
Yes	60.3				
Tumor site		0.281			
Rectal	71.2				
Colon	83.1				
N stage		0.014		0.032	
N0	73.1		1		
N1-N2	57.2		1.425	0.974–1.836	
Liver metastasis		0.132			
No	80.2				
Yes	60.1				
Histological grade		0.231			
Well 87.2					
Moderately 73.1					
Poorly 40.1					
Family history		0.531			
No	82.1				

Variable	Univariate analysis		Multivariate analysis		*P*
	10 year- DFS	P *value*	HR	CL(95%)	
Yes	52.1	0.764			
Postoperative adjuvant therapy	63.1				
No	75.2				
Yes					

Discussion

In the 1970s, surgical treatment of patients with T4 stage colorectal cancer mainly took nutritional ostomy and palliative resection. With the continuous advancement of surgery and anesthesia technology, the management of perioperative period is gradually strengthened. The surgical resection rate of patients with T4 colorectal cancer is gradually increased, but the survival rate of patients is still not high. According to reports in the literature, the 5-year survival rate of patients with T4 stage colorectal cancer is 0%[4, 5]. Although patients with stage T4 colorectal cancer have a poor prognosis after surgery, surgical treatment is still feasible in patients with resectable colorectal cancer. Andreas et al [6] found that 240 patients with T4 colorectal cancer, 77 patients received postoperative adjuvant chemotherapy. The results showed that patients with a T4 tumor who received postoperative chemotherapy had a highly significant survival benefit in respect of overall survival ($p < 0.001$) and recurrence-free survival ($p = 0.008$). This suggests that surgical treatment is still important in patients with resectable T4 colorectal cancer.

The study selected patients who underwent surgery between August, 1994 and December, 2005. All patients had a 10-year survival rate of 32.2%, a median survival of 58.8 months, and poor overall survival. The main reasons for poor prognosis in patients with colorectal cancer are roughly divided into two aspects. First, the accuracy of preoperative staging is not high, and patients do not receive standardized treatment. Second, the tumor is invasive, and it is easy to local recurrence or distant metastasis after operation.

The 5-year and 10-year disease-free survival rates were 44.2% and 30.3%, respectively, and the median DFS was 45.2 months. More than one-third of the patients had tumor progression within 1 year after surgery, so R0 resection of the tumor was performed. And control of postoperative recurrence or metastasis is the key to improving survival. Regarding T4 stage colorectal cancer, the probability of achieving complete R0 resection in a single operation is not high. Even if R0 resection is achieved, the 5-year survival rate is not satisfactory. Studies have shown that neoadjuvant chemoradiotherapy /chemotherapy can improve the resection rate of locally advanced resectable tumors and prolong patient survival. In terms of reducing postoperative recurrence rate and improving postoperative survival, the study found that postoperative adjuvant therapy can improve OS in patients with advanced colorectal cancer and prolong DFS in patients [7–13]. However, in our study, postoperative adjuvant chemotherapy

did not improve OS and DFS (both P > 0.05) compared with patients who underwent surgery alone. It may be that the patient's T stage was late, and there was a micrometastasis in the lymph nodes of the colorectal cancer. Conventional pathological diagnostic techniques have limited role in the diagnosis of micrometastasis, resulting in inaccurate postoperative staging. There are fewer cases in this study, which may also cause statistical errors.

This study found that after T4 stage colorectal cancer surgery, lymph node positive was an independent factor affecting OS and DFS (P < 0.01). Compared with postoperative lymph node-negative patients, lymph node-positive patients had worse OS and DFS. During the follow-up period of this study, more than half of the patients had local recurrence or distant metastasis. Liver metastasis was also an independent factor affecting OS (both P < 0.001). This study also has certain limitations. First: the number of patients selected was limited, and 148 patients were included in the study. Second, the study was retrospectively analyzed and still required multicenter prospective clinical trials and longer follow-up to confirm.

Declarations

Acknowledgements

Funding for this trial was generously provided by Sun Yat-sen University.

Funding

This study was supported by the Guangdong Natural Science Foundation（2014A030310021）

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

WC, JLL, JWY, XPT, YZ and MJH contributed to the study design, data collection, data analysis and interpretation, drafting of the manuscript, approval of the final manuscript, and supervision. All authors approved the final version of the manuscript.

Ethics approval and consent to participate

The study was conducted in compliance with all national and international ethical standards for research with humans. All study procedures were approved by the Research Ethics Board of t*he Six Affiliated Hospital*, *Sun Yat-sen University* and patients gave written informed consent before being enrolled.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

References

1. Arnold M, Mónica S, Sierra LM, et al. Global patterns and trends in colorectal cancer incidence and mortality[J]. Gut. 2016;66(4):683–91.
2. Yang ZF, Wu DQ, Wang JJ, et al. Short- and long-term outcomes following laparoscopic vs open surgery for pathological T4 colorectal cancer: 10 years of experience in a single center[J]. World J Gastroenterol. 2018;24(1):76–86.
3. Benson RA, Venook AP, Alhawary MM, et al. NCCN Guidelines Insights: Colon Cancer, Version 2.2018[J]. Journal of the National Comprehensive Cancer Network Jnccn. 2018;16(4):359–69.
4. Laohavinij S, Maneechavakajorn J, Techatanol P. Prognostic factors for survival in colorectal cancer patients[J]. Journal of the Medical Association of Thailand = Chotmaihet thangphaet. 2010;93(10):1156–66.
5. Jeong WK, Shin JW, Baek SK. Oncologic outcomes of early adjuvant chemotherapy initiation in patients with stage III colon cancer[J]. 2015,89(3):124–130.
6. Andreas T, Michael G, Janine H, et al. Benefit of adjuvant chemotherapy in patients with T4 UICC II colon cancer[J]. Bmc Cancer. 2015;15(1):1–9.
7. Dehal A, Graffbaker AN, Vuong B, et al. Neoadjuvant Chemotherapy Improves Survival in Patients with Clinical T4b Colon Cancer[J]. Journal of Gastrointestinal Surgery Official Journal of the Society for Surgery of the Alimentary Tract. 2017;152(5):1–8.
8. Capussotti L, Vigano' L, Ferrero A, et al. Timing of Resection of Liver Metastases Synchronous to Colorectal Tumor: Proposal of Prognosis-Based Decisional Model[J]. Ann Surg Oncol. 2007;14(3):1143–50.
9. Veerasarn V, Phromratanapongse P, Lorvidhaya V, et al. Preoperative capecitabine with pelvic radiotherapy for locally advanced rectal cancer (phase I trial)[J]. Journal of the Medical Association of Thailand = Chotmaihet thangphaet. 2006;89(11):1874–84.
10. Michael M, Zalcberg JR. Adjuvant Therapy for Colorectal Cancer[J]. Cancer Forum. 2014;38(1):44–52.
11. Niloofar A, Mosalaei A, Shapour O, et al. Role of external irradiation in high-risk resected colon cancer[J]. Indian J Cancer. 2005;42(3):133–7.
12. Schrag D. Evolving Role of Neoadjuvant Therapy in Rectal Cancer[J]. Curr Treat Options Oncol. 2013;14(3):350–64.
13. Denost Q, Kontovounisios C, Rasheed S, et al. Individualizing surgical treatment based on tumour response following neoadjuvant therapy in T4 primary rectal cancer[J]. European Journal of Surgical

Oncology the Journal of the European Society of Surgical Oncology the British Association of Surgical Oncology. 2017;43(1):92–9.