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Research Article

Prognostic Analysis of Patients with Resectable T4 Colorectal Cancer

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Abstract

Background: To observe the factors related to the survival and prognosis of patients with resectable stage T4 colorectal cancer.

Methods: A total of 148 patients with resectable stage T4 colorectal cancer who underwent surgery at the First Affiliated Hospital of Sun Yat-sen University between

August, 1994 and December, 2005 were retrospectively analysed. Univariate and multivariate analyses of the associations between clinicopathological variables and survival were analysed using the Cox regression model.

Results: The follow-up period ended in December 2010 or at patient death; the 5-year and 10-year overall survival (OS) rates were 49.0% and 32.2%, respectively, and the median OS duration was 25 months. The 5-year and 10-year disease-free survival (DFS) rates were 44.2% and 30. 3%, respectively. In univariate analysis, postoperative pathology indicating lymph node metastasis was associated with patient prognosis in terms of OS (all P< 0.01), and postoperative adjuvant therapy failed to improve OS or DFS (P>0.05). Postoperative pathology indicating lymph node metastasis was also associated with DFS (all P< 0.01). In multivariate analysis, postoperative pathology indicating lymph node metastasis was an independent factor affecting OS and DFS in colorectal cancer patients.

Conclusion: The postoperative prognosis of T4 colorectal cancer patients is poor, and postoperative pathology indicating lymph node positivity was an independent factor for OS and DFS.

Keywords: Colorectal cancer; Surgery; Prognosis; Resectable

Abbreviations: CRC- Colorectal cancer; PC- Peritoneal carcinomatosis; CCR- Complete cytoreduction; OS- Overall survival; HIPEC- Hyperthermic intraperitoneal chemotherapy

1. Introduction

Colorectal cancer is one of the most common malignant diseases in the world and has a 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 for colorectal cancer is effective, and the 5-year survival rate is as high as 60.5% [2]. Most patients have progressed to locally advanced disease before getting diagnosed and have lost the opportunity to undergo 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 the outcomes of patients with locally advanced colorectal cancer. To improve the resection rate, the guidelines [3] recommend that patients with locally advanced colorectal cancer can be treated with neoadjuvant chemoradiotherapy and/or chemotherapy combined with surgery, and radical chemoradiotherapy is also feasible. However, due to the limited accuracy of preoperative staging and patient willingness, some patients preferred to undergo surgical resection, and some doctors considered that neoadjuvant therapy may increase the risk and complications of surgery, so some doctors first chose surgery and then determined whether postoperative adjuvant therapy was feasible according to the postoperative pathology results. Patients with stage T4 colorectal cancer have poor prognosis and are prone to developing recurrence and distant metastasis. This study investigated the prognostic factors of patients with postoperative T4 colorectal cancer.

2. Materials and Methods

General information: A retrospective analysis of 148 patients with T4 stage colorectal cancer who underwent surgery at the First Affiliated Hospital of Sun Yat-sen University between August 1994 and December 2005 was performed. The inclusion criteria were as follows: postoperative pathological staging revealed neoplastic invasion out of the membrane (T4), and the survival time was longer than 2 months. The exclusion criteria were as follows: intolerance to surgery because of

poor cardiopulmonary function; distant metastasis and so on. All patients and their families gave informed consent to participate in the study and signed informed consent forms. 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 after surgery for the first year, 6 months for the next 2 years and yearly thereafter. The first review was performed at the hospital one month after the operation. Chest and abdominal CT, routine blood, liver and kidney function tests, tumour marker tests, colonoscopy and other examinations were routinely performed; if necessary, a whole body bone scan and PET-CT were performed to determine whether there was systemic metastasis. Local recurrence was defined as an anastomotic stoma or regional lymph node recurrence. Distant recurrence was defined as positive, distant lymph nodes or distant organ metastasis.

Statistical method: The overall survival (OS) time was from the date of surgery to the date of death or end of follow-up. The disease-free survival (DFS) time was from the date of surgery to the date of tumour recurrence or metastasis. Using SPSS 23.0 software, the Kaplan-Meier method was used to calculate OS and DFS, and the log-rank method was used to test for differences in OS. The Cox model was used for single factor and multifactor analysis, and the $\chi 2$ test was used to analyse the effect of different treatment methods on the survival rate. $P<0.05$ was considered statistically significant.

3. Results

3. 1 Postoperative conditions

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. During the operation, the average number of lymph nodes removed was 13.5 (2~35). Postoperative pathology revealed 85 patients with lymph node metastasis and 63 patients with negative lymph nodes. Postoperative pathology showed that the tumour invaded the adventitia. Postoperative anastomotic leakage was found in 2 cases.

3. 2 Postoperative survival rate

The 5- and 10-year survival rates were 49.0% and 32.2%, respectively, in the whole group, and the median survival duration was 58.8 months (Figure 1). Cox univariate analysis showed that postoperative pathology indicating lymph node metastasis was associated with OS ($P<0.05$). Sex, age, obstruction, tumour site, liver metastasis, histological grade, family history, and 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 patients with negative lymph nodes postoperatively, those with positive lymph nodes had a 1.213 higher risk of death (95% Cl: 0.845-1. 564, $P=0.045$). See Table 1.

3. 3 Postoperative disease-free survival rate

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

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		0.27			
No	81.5				
Yes	64.3				
Tumor site		0.117			
Rectal	72.7				
Colon	86.2				
N stage		0			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				
Yes	50.2	0.531			
Postoperative adjuvant therapy					
No					
Yes	60.1				
	74.5				

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- 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				
Yes	52.1	0.764			
Postoperative adjuvant therapy					
No					
Yes	63.1				
	75.2				

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

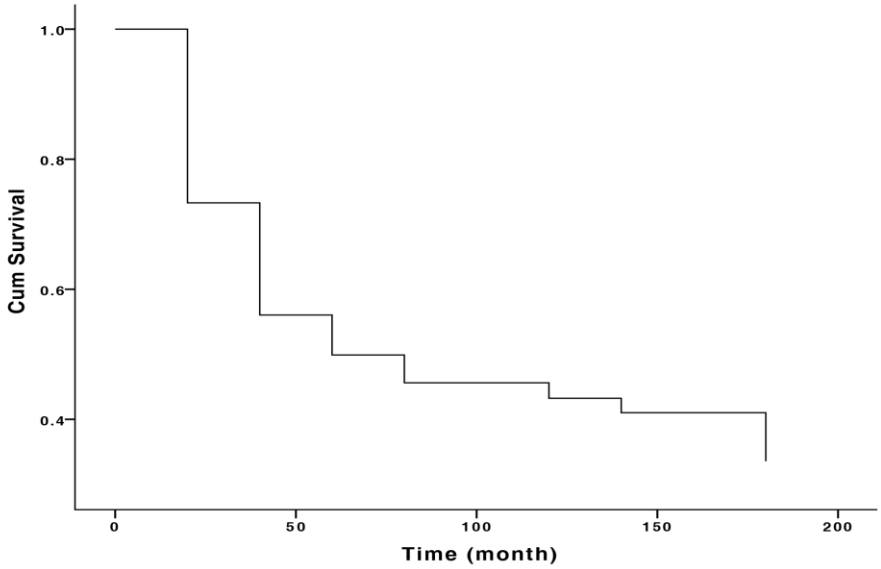

Figure 1: Survival curve for T4 CRC patients undergone surgery.

4. Discussion

In the 1970s, the surgical treatment of patients with T4 stage colorectal cancer mainly involved nutritional ostomy and palliative resection. With the continuous advancement of surgery and anaesthesia technology, patient management in the perioperative period has been gradually strengthened. The surgical resection rate of patients with T4 colorectal cancer is gradually increasing, but the survival rate of these 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. The previous study showed that among 240 patients with T4 colorectal cancer, 77 patients received postoperative adjuvant chemotherapy [6]. The results showed that patients with T4 tumours who received postoperative chemotherapy had significantly better survival with respect to 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.

This 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 duration of 58.8 months, and poor overall survival. The main reasons for the 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 tumour is invasive, and local recurrence or distant metastasis can easily occur after surgery.

The 5-year and 10-year disease-free survival rates were 44.2% and 30.3%, respectively, and the median DFS duration was 45.2 months. More than one-third of the patients had tumour progression within 1 year after surgery, so R0 resection of the tumour was performed. Controlling 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 tumours and prolong patient survival. In terms of reducing the postoperative recurrence rate and improving postoperative survival, a previous study found that postoperative adjuvant therapy can improve OS in patients with advanced colorectal cancer and prolong DFS [7-13]. However, in our study, postoperative adjuvant chemotherapy did not lead to improved OS and DFS (both P>0.05) compared surgery alone. This may because the colorectal cancer and T stage were too advanced, and there were micro-metastases in the lymph nodes. Conventional pathological diagnostic techniques have a limited role in the diagnosis of micro-metastasis, resulting in inaccurate postoperative staging. There were only a few cases in this study, which may 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.

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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 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.

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