·Colerectal Cancer-related Research·

Prognosis of rectal cancer patients after total mesorectal excision

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[Abstract] **Background and Objective**: Total mesorectal excision (TME) can reduce local recurrence and improve prognosis of rectal cancer. This study was to analyze the clinicopathologic characteristics of rectal cancer, and explore the prognosis factors of rectal cancer after radical TME. **Methods**: From 1990 to 2003, 1056 rectal cancer patients had received radical TME. The impacts of 20 clinicopathologic factors on the prognosis were analyzed with univariate and multivariate method. **Results**: The 3-, 5-, and 10-year overall survival rates were 84.9% (95% CI, 83.8%–86.0%), 73.8% (95% CI, 72.4%–75.2%), and 65.1% (95% CI, 63.4%–66.8%), respectively. Univariate analysis showed that preoperative serum carcinoembryonic antigen (CEA) and CA19-9 levels, tumor gross type, pathologic type, pathologic grade, preoperative bowel obstruction or bowel perforation, T stage, N stage, and first treatment era were associated with the prognosis of rectal cancer. Multivariate analysis showed that N stage, histological type, surgical procedures, and T stage were independent prognostic factors. **Conclusion**: N stage, histological type, surgical procedures, and T stage are independent prognostic factors for rectal cancer patients who received radical TME.

Key words: rectal neoplasm, total mesorectal excision, prognosis, multivariate analysis

The incidence of colorectal cancer is rising year by year in China, and more than 50% of these cases are rectal cancers.[1] Surgery is the main treatment for rectal cancer, but postoperative recurrence rate is high.[2,3] Total mesorectal excision (TME) is a corner stone in the surgical treatment for rectal cancer which can significantly decrease local recurrence rate and improve the prognosis.[4-6] Although the outcomes of treating rectal cancer by TME have been widely reported, large-scale analysis from single center is rare. Herein, we analyzed the long-term efficacy of TME on 1059 rectal cancer patients treated in our hospital during 1990-2003, and investigated influential factors.

Materials and Methods

Clinical data. The overall database of 3174 cases of colorectal cancers treated in Sun Yat-sen University Cancer Center from January 1990 to April 2003 was established. Among them, 1059

(33.4%) patients with rectal cancer were treated by radical TME. They aged from 21 to 95 years, with a median age of 57 years. All these cases were pathologically confirmed as rectal adenocarcinoma. To exclude the influence of other malignant tumors on the long-term efficacy, patients with extra-intestinal cancers, multiple primary colorectal carcinoma, familial adenomatous polyposis and those receiving re-operation due to postoperative recurrence were excluded from our study.

Treatment approaches. All these patients were treated by radical operation. For middle-to-low rectal cancer, the rectum was isolated and tumor was resected according to TME principles. For upper rectal cancer, modified TME (that is, the mesorectum at 5 cm away from the distal end of tumor was resected based on TME principles) was used to remove tumors.

Of the 1059 patients, three (0.3%) died of operation (within three months after TME), 1056 were evaluable for long-term efficacy analysis. Among the latter, 486 (46.0%) underwent anterior resection, 524 (49.6%) underwent abdomino-perineal resection, 25 (2.4%) underwent other operations (Bacon operation, posterior pelvic node dissection, whole pelvic node dissection and Hartmann operation), 21 (2.0%) were unknown for anus preservation.

Observed parameters. A total of 22 clinicopathologic and management parameters were observed, including age, gender, the distance between tumor and anal verge, tumor volume, concomitant intestinal obstruction or perforation before operation, concomitant diabetes, operation pattern, combined organ resection, safety surgical margin, peri-operative blood transfusion, intraoperative chemotherapy, postoperative anastomotic leakage, gross type, histological type, pathologic grade, intestinal infiltration depth (T stage), lymph node involvement (N stage), preoperative serum CEA and CA19-9 levels and time of initial treatment.

Follow-up. All patients were followed-up routinely by mail, telephone call and personal visit every three months in the first two years after operation, every six months in the third-fifth years, and yearly thereafter till death or April 2008. Survival duration was recorded as the time span between operation and time of death. Of the 1059 patients, 65 were lost to follow-up, and the follow-up rate was 93.8%.

Statistical methods. Statistical analyses were performed using software SPSS12.0. Measurement data were shown as mean ± SD. Survival rate was analyzed by Kaplan-Meier method and compared by sequential log-rank test. Those factors with significance in univariate analysis were introduced into Cox regression model for multivariate analysis. Significance level was set to α =0.05.

Results

Survival. In the whole group, the 3-, 5-, and 10-year survival rates were 84.9% (95% confidence interval [CI]: 83.8%-86.0%), 73.8% (95% CI: 72.4%-75.2%) and 65.1% (95% CI: 63.4%-66.8%), respectively, with a median survival duration of 73.5 months. In patients at stages Ⅰ, Ⅱ and Ⅲ, the 5-year survival rates were 89.4% (95% CI: 91.2%-87.6%), 80.0% (95% CI: 77.8%-82.2%) and 56.8% (95% CI: 53.9%-59.7%), respectively.

Local recurrence. Postoperative local recurrence was seen in 103 (9.8%) patients, of which 30 had anastomotic recurrence, 32 had perineal recurrence and 41 had abdomino-pelvic recurrence.

Univariate analysis of prognosis. Perioperative blood transfusion, preoperative serum CEA and CA19-9 levels, preoperative concomitant intestinal obstruction and perforation, gross type, histological type, operation pattern, pathologic grade, intestinal infiltration depth, lymph node involvement and time of initial treatment were influential factors for the prognosis of rectal cancer patients who underwent TME (Table 1).

Multivariate regression analysis of prognosis. Lymph node involvement, histological type, operation pattern, and infiltration depth (T stage) were independent prognostic factors for rectal cancer patients who underwent TME (Table 2).

Table 1 Univariate prognostic analysis of rectal cancer after radical total mesorectal excision (TME)

Variate	Cases number (%)	5-year survival rate(%)	*P* value
Sex			0.254
Male	570(54.0)	72.5± 1.9	
Female	486(46.0)	75.4± 2.0	
Age (years)			0.265
<30	31 (2.9)	66.6± 9.2	
≥30	1 025(97.1)	74.0± 1.4	
Peri-operative infusion			0.006
No	834(79.0)	75.4± 1.6	
Yes	222(21.0)	68.0± 3.2	
Distance from Anal Verge			0.067
Upper (≥ 10 cm)	81 (7.7)	83.8± 4.7	
Middle-lower (<10 cm)	972(92.0)	73.4± 1.5	
Tumor size			0.117
<5 cm	476(45.1)	74.7± 2.1	
≥5 cm	574(54.4)	73.8± 1.9	
Pre-operative serum CEA			0.001
Normal	603(57.1)	77.6± 1.8	
Elevated	192(18.2)	67.4± 3.5	
Pre-operative serum CA19-9			<0.001
Normal	515(48.8)	78.6± 1.9	
Elevated	97 (9.2)	60.4± 5.4	
Pre-operative bowel obstruction or perforation			0.003
No	1 006(95.3)	74.5± 1.4	
Yes	50 (4.7)	61.5± 6.9	
Comorbidity of diabetes			0.446
No	1 000(94.7)	73.8± 1.4	
Yes	56 (5.3)	74.7± 6.1	
Operation procedure			<0.001
Anterior resection (AR)	521(49.3)	79.5± 1.8	
Abdominoperineal resection	481(45.5)	68.6± 2.2	
Safe margin (for AR)			0.169
<2 cm	9 (1.7)	88.9±10.5	
≥2 cm	502(96.4)	80.3± 2.1	
Combined multi-organ resection			0.433
No	963(91.2)	74.3± 1.5	
Yes	93(8.8)	68.8± 5.0	
Intro-operative chemotherapy			0.159
No	537(49.4)	72.2± 2.0	
Yes	509(48.2)	75.5± 2.0	
Anastomotic leakage			0.627
No	1 043(98.8)	73.8± 1.4	
Yes	13(1.2)	73.3±13.2	
Tumor gross type			<0.001
Proliferated	330(31.3)	81.2± 2.2	
Ulcerative	662(62.7)	71.9± 1.9	
Infiltrated	52 (4.9)	51.6± 7.2	
Pathologic type			<0.001
Mucinous component or signet ring cell adenocarcinoma	105(9.9)	53.8± 5.1	
Adenocarcinoma	928(87.9)	76.4± 1.4	
Histological grade			<0.001
Ⅰ	109(10.3)	89.2± 3.1	
Ⅱ	688(65.2)	75.5± 1.7	
Ⅲ	106(10.0)	55.1± 5.0	
T stage			<0.001
T1	65 (6.2)	93.6± 3.1	
T2	330(31.3)	83.0± 2.2	
T3	418(39.6)	68.3± 2.4	
T4	227(21.5)	66.7± 3.2	
N stage			<0.001
N0	684(68.4)	83.7± 1.5	
N1	260(24.6)	60.2± 3.2	
N2	97(9.2)	45.0± 5.3	
First treatment era			0.010
Before 1st, Jan. 1997	385(36.5)	69.5± 2.4	
After 1st, Jan. 1997	671(63.5)	73.6± 1.7	

The data of some patients are incomplete.

Table 2 Multivariate prognostic analysis of rectal cancer after TME

Variate	β	SE	*P* value	Exp(β)	95% CI for Exp(β)
N stage	0.869	0.118	<0.001	2.385	1.893–3.003
Pathologic type	0.761	0.256	0.003	2.141	1.296–3.537
Operation procedure	0.523	0.178	0.003	1.687	1.189–2.392
T stage	0.320	0.112	0.004	1.377	1.106–1.714

while in other histology group, the prognosis was significantly improved. Therefore, in patients with adverse histology, surgical advancement alone is not enough to improve their prognosis, and multimodality therapy and strict follow-up should be attempted to improve their survival.

3.2 Correlation of surgery-related factors to prognosis

The prognosis is better in female patients with rectal cancer than in male patients.[10] Generally, male pelvic cavity is narrower than female pelvic cavity; moreover, anatomic structures such as prostate gland and seminal vesicles further restrict the operation and surgical extent. Therefore, the risk of surgical treatment failure is higher in males than in females. However, Ding et al.[11] found that gender affected anal preservation, rather than prognosis, and thus adverse anatomic factors were considered to influence choice of surgical procedure, but did not significantly affect prognosis. We also found that gender was not a prognostic factor. With TME principles, compliance to direct vision and sharp dissection principles, even in a narrow male palvic cavity, may be an important step to decrease the influence of gender on prognosis.

The safety margin in rectal cancer operations has always been controversial. Different from the "5 cm principle"[12] and "negative margin theory", TME procedures consider complete resection of 5 cm of mesorectum at distal end of tumor as equally important as the resection of 2 cm of intestine from distal end of tumor.[4, 5] Our study compared the influence of different safety margins of 2 cm, 3 cm and 4 cm on the prognosis, and revealed no significant difference. Since most studies suggested that cancer infiltration at the distal end was majorly limited within 1 cm, whether or not "2 cm principle" is the bottom line of safety margin in rectal cancer has yet to be confirmed. Nonetheless, in our study, only 9 patients had the margin of <2 cm (>1 cm). Therefore, the influence of a safety margin of <2 cm on the prognosis has to be further evaluated by large scale studies.

The influence of operation patterns on the prognosis of rectal cancer is also controversial. Although all the rectal tumors were isolated and removed according to TME principles during the abdomino-perineal resection in our study, multivariate analysis showed that operation pattern was an independent prognostic factor, with poorer prognosis for patients received abdomino-perineal resection than for those received anterior resection. Traditionally, it was considered that the musculus levator ani and adipose tissue in the fossa ischiorectalis were highly susceptible to postoperative recurrence, therefore, to ensure complete resection, abdomino-perineal resection should be used for lower rectal cancer.[6] However, Heald et al.[6] found that the prognosis of patients received abdomino-perineal resection was even poorer than that of those with Dukes C disease. Such poor prognosis had mainly resulted from that the pelvic floor was impaired by abdomino-perineal resection and perineal tissues was directly exposed to tumor cells and became a nice hotbed for tumor cells to implant, once free tumor cells entered these tissues via the anus that was not well closed or the tore intestine, recurrence may occur. Therefore, they believed that abdomino-perineal resection had potential risk and should be avoided as much as possible. Ragtegoal et al.[7] found that the high local recurrence rate of patients who received abdomino-perineal resection was the result of a high CRM invasion rate, which was the real reason why the destiny of lower rectal cancer was not modified even if APR was performed. Our study showed the percentage of abdomino-perineal resection significantly decreased since 1997, which also explained the improved prognosis for rectal cancer surgeries during this period via another aspect. Of course, some scientists also believed that abdomino-perineal resection could produce as good efficacy as anterior resection, as long as TME principles and standardized surgical approaches were adhered to.[13] This showed that different doctors from different centers might have vastly varied opinions regarding surgical procedures for rectal cancer and their influence on the prognosis. Hence, based on the accordance to general TME principles, different centers should be prudent in selecting surgical

Discussion

Rectal cancer is one of the common malignant tumors in China, with an increasing incidence. Due to the anatomic features of pelvic cavity, rectal cancer is prone to invade adjacent tissues and can not be resected by radical operation; on the other hand, the resection extent of rectal cancer can not be as extensive as that of colon cancer. Therefore, the recurrence rate after traditional operations for rectal cancer was as high as 18%-49%.[2, 3] In 1982, Heald et al.[4] reported firstly that TME could significantly decrease postoperative local recurrence and improve prognosis of rectal cancer. In more than 20 years, TME-based operations for rectal cancer are widely used worldwide. Currently, TME has been a standard operation for rectal cancer. Herein, we explored the prognostic factors of rectal cancer patients who underwent TME.

Correlations of clinicopathologic features to prognosis. Using the year of 1997 as the cut-off date of first treatment, the patients were divided into two groups to reveal the efficacy differences between two periods. Univariate analysis showed that the efficacy in the patients firstly treated after 1997 was better than that in those firstly treated before 1997, but multivariate analysis showed no difference. Further stratified analysis by staging suggested that the influence of initial treatment time was only seen in patients at stages Ⅰ and Ⅱ, whereas survival improvement was not obvious in patients at stage Ⅲ. With more experience and more proficient skills in performing TME, the prognosis of patients at relatively early stages can be further improved by proper operations surgical procedures, but surgical advancement alone is obviously inadequate for improving the survival of the patients with advanced disease.

In our study, lymph node involvement and tumor infiltration depth, also known as two basic components of TNM staging system of rectal cancer, were independent prognostic factors. As lymph node involvement occurs and tumor infiltration depth increases, the risk of distant metastasis increases; on the other hand, circumferential resection margin (CRM) in the rectum decreases as well, therefore, the risk of local tumor recurrence might be increased. Nagtegaal et al.[7] found that local recurrence rates were 38% in patients with a CRM of < 1 mm, 16% in those with a CRM of ≤ 2 mm and 5.8% in those with a CRM of > 2 mm. Hence, when applying TME principles, it is extremely important to ensure the integrity of CRM. But for those with locally advanced disease, CRM is often small, or even already invaded, the possibility of treatment failure is thus increased. This also explains why the prognosis of stage Ⅲ patients is not improved with surgical advancement.

Tumor histology is also an independent prognostic factor of rectal cancer after TME, with significantly poorer prognosis for patients with poorly differentiated adenocarcinoma, mucinous adenocarcinoma and signet ring cell carcinoma than for those with other adenocarcinomas.[8, 9] The adverse biological behaviors of mucinous adenocarcinoma and signet ring cell carcinoma are driven by that mucopolysaccharide from mucinous adenocarcinoma interferes with tumor cell recognition by host immune cells, which is seen as the absence of inflammatory cell infiltration around cancer cells and the inhibition on host immune function, thus the tumor tends to grow invasively and often invades the nerve, blood vessels and lymphatic ducts. Clinically, they are more frequently seen and progress rapidly in young patients with rectal cancer, with a high lymph node metastasis rate and peritoneal dissemination rate. In our study, lymph node metastasis rate was as high as 58.3% in adverse histology group, with a 5-year survival rate of 52.6%, which was significantly lower than those with other histological types (76.4%). To further investigate the influence of surgical advancement on the prognosis in these subgroups of patients, we performed a stratified analysis to compare the prognosis of two histological types at different periods, and found that the prognosis was not significantly different between different periods in adverse histology group, that is, the prognosis did not improve with surgical advancement;

procedures based on patients situation and their own experience.

Anastomotic leakage is the main complication of TME procedures, with an incidence of as much as 7.1-24%.[14, 15] In our study, incidence of anastomotic leakage was 2.5%, and preventive fistulizaiton performed in only three (0.6%) patients, both of which were lower than those reported by foreign literatures.[5, 14-16] It was believed this might be related to the way we handle the root of inferior mesenteric artery. Different from the high ligation of inferior mesenteric artery in traditional approach, we used a "high dissection and low ligation" for the inferior mesenteric artery, that is, dissection of adjacent lymphatic and adipose tissue started from the root of inferior mesenteric artery toward the distal end of the artery, and ended at lower margin of the root of left colic artery, and then sigmoid artery and superior rectal artery were resected. By using such approach, lymphatic and adipose tissue could be dissected to the extent possible while ensuring maximum blood supply.

Uni-variate analysis suggested peri-operative blood transfusion, CEA and CA19-9 levels before surgery, concomitant intestinal obstruction or perforation before surgery, gross tumor category, pathological grading and time of initial treatment related to prognosis, however, the influence on prognosis by these factors was decreased with the introduction of N stage, histology, surgical procedure and T stage, and thus these factors were not included into the multi-variate regression analysis, which indicated the influence of these factors on prognosis was indirect. For instance, CEA level was related to the disease course; as the disease advanced, especially when liver metastasis and distant metastasis were developed, serum CEA level would be significantly increased. The study by Chapman et al.[17] demonstrated that, in overall population with colon-rectal cancer, elevated CEA level before surgery was a predictor for poor prognosis, but once disease stage was under control, CEA level was no longer a prognostic factor.

In conclusion, CEA and CA19-9 levels before surgery, concomitant intestinal obstruction and perforation before surgery, tumor histology, pathological grading, intestinal infiltration depth, lymph node involvement and time of initial treatment were influential factors for prognosis of TME procedures in rectal cancer. Among these factors, N stage, histology, surgical procedure and T stage were independent prognostic factors for TME procedures. Due to the retrospective nature of our study, prognostic factors for TME procedures in rectal cancer, as well as the conclusion on their relative risk, have yet to be further confirmed by large-scale prospective studies.

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