SAJS
General Surgery

Long-term outcomes after laparoscopic total mesorectal excision for advanced rectal cancer

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Summary

Purpose. The aim of this study was to evaluate the long-term outcomes of laparoscopic total mesorectal excision in the treatment of advanced rectal cancer in a randomised population.

Methods. Between 2001 and 2005, 125 patients (70 males, 55 females, mean age 55.5 (standard deviation (SD) 11) years, range 25 - 81 years) with rectal cancer were evaluated and prospectively followed up in our hospital (mean follow-up 42 (SD 23 months, range 5 - 113 months). The 5-year overall survival rate, 5-year disease-free survival rate and recurrence rate were analysed.

Results. There were 54 cases of cancer defined as UICC stage II and 68 cases defined as stage III. Of these cases, 22 were localised to the upper rectum, 50 to the middle rectum and 53 to the lower rectum. The 5-year overall survival rates were 71.3% and 51% among the stage II and the stage III patients, respectively. The 5-year disease-free survival rates were 59.2% and 45.4% among the stage II and the stage III cancer patients, respectively. The overall recurrence rate was 16.8% (local recurrence rate 11.25%, distant recurrence rate 8%). Multivariate analysis showed that age and size were independent predictors of overall survival (p=0.006 and p<0.001 for stage II and stage III patients, respectively).

Conclusions. Our results suggest good long-term outcomes of laparoscopic surgery in the treatment of rectal cancer. However, this technique should be used with caution in older patients and patients with larger tumours.

Substantial improvements have been made in the treatment of rectal cancer in the past two decades because of earlier diagnosis, improved efficacy and delivery of chemotherapy, and the adoption of advanced surgical techniques such as laparoscopic total mesorectal excision (TME). Laparoscopic TME has several advantages, including shorter recovery time, fewer complications and shorter duration of hospital stay than the standard treatment.[1,2] However, the use of TME for advanced cancers remains controversial, as long-term outcomes have yet to be evaluated.[3] We therefore evaluated the 5-year overall survival rate, 5-year disease-free survival rate and recurrence rate among patients with advanced rectal cancer after surgical treatment by laparoscopic TME.

Materials and methods

Patients

Between January 2001 and July 2005, a total of 125 laparoscopic TME procedures were performed in the Department of General Surgery, General Hospital of Chengdu Military Region, Chengdu, People's Republic of China. Data on patient demographics, oncological details and follow-up status were collected prospectively. The inclusion criterion was a diagnosis of TNM stage II - III cancer. Exclusion criteria were emergency hospitalisation, contraindications to laparoscopic surgery, obesity and previous abdominal surgery.

A tumour was considered to be a primary rectal carcinoma if it was located in the lower third (0 - 5 cm from the anal verge), middle third (6 - 10 cm from the anal verge) or upper third (11 - 15 cm from the anal verge) of the rectum, as measured by rigid rectosigmoidoscopy.

All cases were reviewed by a consortium of staff surgeons, oncologists, anaesthesiologists, pathologists and gastro-enterologists before the operations, all patients gave informed consent, and review board approval was obtained.

Pre-operative work-up

All patients underwent pre-operative tumour staging by contrast medium enema, rectoscopy and colonoscopy with tumour biopsies, endorectal ultrasonography, abdominal ultrasound imaging, an abdominal computed tomography (CT) scan and a chest radiograph. Magnetic resonance imaging (MRI) of the pelvis was performed in selected cases to rule out tumour invasion into adjacent organs.

Neo-adjuvant treatment

Adjuvant treatment was administered to all patients and consisted of six cycles of 5-FU/folinic acid.

Follow-up

All patients underwent rectoscopic and abdominal ultrasound follow-up examinations every 3 months for the first 2 years, every 6 months for the next 3 years, and once a year after 5 years to evaluate tumour recurrence.

Studied data

Patient demographic data and outpatient follow-up were studied. The following data were collected prospectively: age, gender, tumour location, tumour size, and local and distant tumour recurrence. An analysis of the probability of survival was also performed.

Statistical analysis

The chi-square test and Student's t-test were applied when appropriate. A p-value <0.05 was considered to be statistically sig-

nificant. Survival curves were generated using the Kaplan-Meier method. Cox regression was used to perform multivariate analysis of prognostic factors. The SPSS software (version 13.0 for Windows, SPSS, Chicago, IL, USA) was used for statistical analysis.

Surgical technique

Each patient was placed in a steep Trendelenburg position, with the head and right side tilting down. The surgeon stood at the patient's right side. Laparoscopic exploration was performed by creating a pneumoperitoneum using CO_2 to a maximum pressure of 14 mmHg. A 5-port technique was used, and ports were placed under direct vision of a flexible videoscope. Scissors, the LigaSure and a harmonic scalpel were used for dissection. We first dissected the inferior mesenteric artery (IMA) at the origin, being careful to protect the pre-aortic sympathetic neural plexus. The dissection was extended to the inferior mesenteric vein (IMV). Both the IMA and IMV were ligated near their origins with a linear vascular stapler or clips. An incision was then made at the right leaf of the sigmoid mesocolon, and the avascular plane between the visceral and parietal pelvic fascia was entered. Along this plane, the left gonadal vessels and ureter were safely explored and protected. For middle- or lower-third rectal tumours, the rectum and its mesentery were sharply dissected along the anatomical space between the visceral and parietal endopelvic fascia, until the anal hiatus of the pelvic diaphragm was reached. The pelvic autonomic nerves, including the superior hypogastric nerves, the autonomic branches of S2 - S4 autonomic branches, and the pelvic autonomic nerve plexus were identified and preserved. For upper-third rectal tumours, the mesorectum was separated up to 5 cm below the lesion. When the pelvic dissection was complete, the distal end was cut using endoscopic linear staplers and an Endo-GIA-type mechanical suturing device.

The specimen was extracted via a plastic wound protector through a small incision in the left lower quadrant. Transection of the proximal bowel was performed extracorporeally. A standard double-stapling technique was used to perform tension-free intracorporeal anastomosis. In cases of very low-lying cancer, a hand-sewn colo-anal anastomosis was done. For abdominoperineal resection, the sigmoid colon was divided, and TME was completed during the abdominal phase of rectal dissection. The specimen was extracted through the perineum after perineal dissection in a standard fashion. Finally, an end-colostomy was constructed at a preplanned site.

Results

Patient demographics and tumour characteristics

The patients were 70 men and 55 women, with a mean age of 55.5 years (range 25 - 81 years). The distribution of tumour location was as follows: upper (*N*=22, 17.6%), middle (*N*=50, 40%) and lower (*N*=53, 42.4%). Among all cases, 54 and 71 cancers were defined as UICC stage II and stage III, respectively. The mean tumour size was 3.9 cm (range 2 - 7 cm). Double-stapling anastomosis was performed in 72 cases, hand-sewn colo-anal anastomosis in 29, and a diverting stoma in 24. Patient demographics and tumour characteristics are set out in Table I.

Tumour recurrence

Patients were followed up for a median of 38 months (range 5 - 113 months). Fourteen patients developed local recurrence (11.2%), stage II in 6 (11.1%) and stage III in 8 (11.2%). No significant difference was observed between the two groups (p=0.978). There was no port-site metastasis in any case. Eight patients developed distant recurrence (6.4%), of which 3 and 5 cases were stage II and stage III, respectively, with no significant difference between the two groups (p=0.737). In cases of distant recurrence in the liver or lung, surgical treatment was used when possible. Otherwise they were treated systemically or regionally (liver) (Table II).

Survival rate

The overall 5-year survival rates were 71.3% and 51% for stage II and stage III cancers, respectively. There was a significant difference between survival in the stage II and stage III groups (log-rank test, p=0.035, Fig. 1). The survival functions indicated that in the first 24 months there was little difference in survival between the two groups; however, after 2 years, survival rates decreased rapidly, with the stage III group survival rate declining more precipitously than stage II group survival rate. The 5-year disease-free survival rates were 59.2% in the stage II group and 45.4% in the stage III group (Fig. 2).

Multivariate analysis

Gender, tumour size, patient age and tumour location were found to be significantly associated with overall survival in a univariate analysis. These factors were then applied to a multivariate model, which identified patient age and tumour size as negative predictors for survival (Table III).

Discussion

Over the past 20 years there have been major advances in the treatment of rectal cancer. These improvements have been mirrored

TABLE I. PATIENT DEMOGRAPHICS AND TUMOUR CHARACTERISTICS (*N*=125)

Variable	
Mean age (range) (yrs)	**55.5 (25 - 81)**
Gender (*N*)	
Male	**69**
Female	**53**
Stage (*N*)	
II	**54**
III	**68**
Location in rectum (*N*)	
Upper third	**22**
Middle third	**50**
Lower third	**53**
Size (mean (SD)) (cm)	**3.96 (1.19)**

TABLE II. LOCAL AND DISTANT RECURRENCE ACCORDING TO TNM STAGE

	Local recurrence (*N* (%))	Distant recurrence (*N* (%))
Stage II	**6 (11.1)**	**3 (5.5)**
Stage III	**8 (11.2)**	**5 (7)**
Total	**14 (11.2)**	**8 (6.4)**

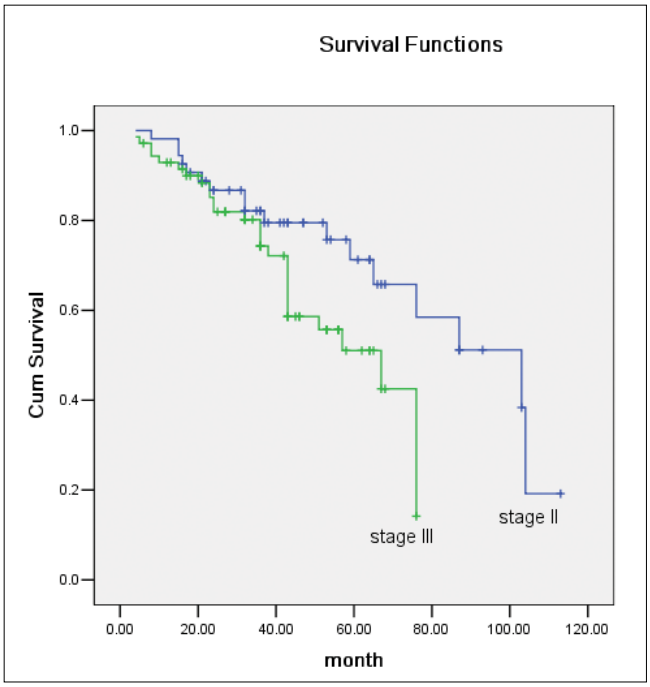

Fig. 1. Five-year overall survival rates according to stage.

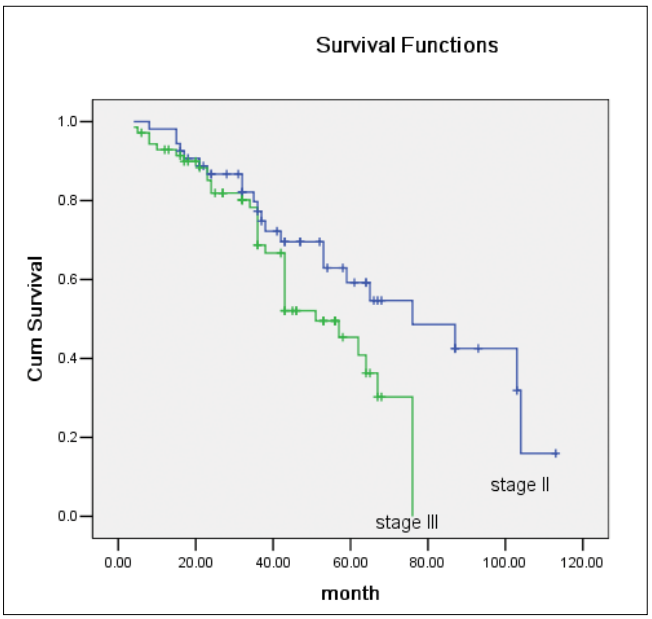

Fig. 2. Five-year disease-free survival rates according to stage.

by a considerable reduction in the rate of local recurrence and an improvement in overall patient survival.[4,5] Laparoscopic surgery is a minimally invasive procedure that has substantially improved the surgical treatment of rectal cancer.[6] The short-term advantages of this procedure (e.g. fewer postoperative complications, faster recovery of stomal function and shorter hospital stay) have been confirmed in previous studies.[7-9] However, the use of laparoscopic surgery for the treatment of rectal cancer has developed slowly, particularly owing to uncertainty regarding its long-term efficacy.

Local control has been one of the objectives pursued in the surgical treatment of rectal cancer. Before the development of TME, 50% of rectal cancer patients had local recurrence within

TABLE III. MULTIVARIATE ANALYSIS OF OVERALL SURVIVAL AMONG RECTAL CANCER PATIENTS

	HR	95% CI	*p*
Size >4 cm	**1.853**	**1.374 - 2.498**	**0.000**
Age >75 yrs	**0.961**	**0.934 - 0.988**	**0.006**
Gender	**1.554**	**0.851 - 2.961**	**0.181**
Tumour location	**1.563**	**0.959 - 2.548**	**0.073**

HR = hazard ratio; CI = confidence interval.

1 year after rectal resection.[10] In addition, 65 - 80% of patients developed local lesions around the rectum, particularly within the mesorectum.[11] In these cases, local recurrence was inevitable if the mesorectal excision was not complete. In the early 1980s, Heald and colleagues laid out the principles of TME and reported a local recurrence rate of 4% after 10 years in patients treated with this technique.[12] A local recurrence rate of approximately 7% after laparoscopic TME for advanced rectal cancer has also been reported.[13-15] This result is roughly the same as that observed with the open technique. In our study, the local recurrence rate after treatment with laparoscopic TME was 11.2%, and most of these cases occurred within the first 2 years after the operation. These findings are similar to those reported in previous studies. The distant recurrence rate was found to be 6.4%. Neo-adjuvant chemoradiotherapy seems to provide an advantage for local control of cancer recurrence. Sauer *et al.*[16] reported that the 5-year cumulative incidence of local relapse was 6% among patients assigned to pre-operative chemoradiotherapy and 13% in the postoperative treatment group (p=0.006). These results showed that pre-operative chemoradiotherapy improves local control of cancer recurrence. However, the National Surgical Adjuvant Breast and Bowel Project (NSABP) R-03 trial found no difference in the 5-year local recurrence rate between patients treated pre-operatively versus postoperatively with chemoradiotherapy.[17] In addition, pre-operative chemoradiotherapy may delay definitive treatment, allow distant/sanctuary site seeding, and reduce compliance with postoperative adjuvant chemoradiation.[18] Further evaluation of the benefit of pre-operative chemoradiotherapy is therefore necessary.

Another long-term indicator of successful surgical treatment of rectal cancer that we were concerned about was survival rate. A 5-year overall survival rate for advanced rectal cancer of 58 - 73% has been reported, and the disease-free survival rate for advanced rectal cancer was 45 - 75.1% in patients treated with the open technique.[19-22] Theoretically, no difference should have been observed between open and laparoscopic technique survival rates had the laparoscopic TME surgery been executed in the same manner as the open TME. In one study, the 5-year overall survival rate for rectal cancer after laparoscopic TME was 65%.[23] In another study it was 64%, and no difference was found between the open and laparoscopic groups.[24] Our data showed that the 5-year overall survival rates were 71.3% and 51% for stage II and stage III, respectively, and that the 5-year disease-free survival rates were 59.2% and 45.4% in stage II and stage III, respectively. Results from the literature and our study indicate that there is no significant difference between laparoscopic and open TME survival rates.

For our laparoscopic procedure, we found that the best technique was to identify the space between the visceral and parietal fascia; furthermore, laparoscopic rectal resection allowed magnification and accurate identification of structures and tissues in the narrow pelvic cavity. The unique advantages of laparoscopy allow excellent implementation of the TME technique for rectal cancer resection.

A multivariate analysis was performed to identify prognostic factors. Consistent with results reported in the literature,[19,25] our study showed that 5-year survival rates differed significantly between stage II and stage III cancer cases. TNM stage was found to be a significant prognostic factor. Tumour size >4 cm and age >75 years were negatively correlated with survival. Our results therefore suggest that laparoscopic TME should be used with caution in older patients and patients with large tumours, although we did not find randomised controlled trials in the literature to support this.

In conclusion, the long-term outcomes of laparoscopic TME in the treatment of rectal cancer were good, with the exception of cases of older patients and patients with large tumours, in which care should be taken when deciding on type of treatment. Future randomised comparative studies are necessary to confirm these results.

Conflict of interest. The authors declare that they have no conflicts of interest.

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