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10-Year Oncologic Outcomes After Laparoscopic or Open Total Mesorectal Excision for Rectal Cancer

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Abstract

Background

Only few studies have compared laparoscopic total mesorectal excision (LTME) and open total mesorectal excision (OTME) for rectal cancer with follow-up longer than 5 years. The aim of this study was to compare 10-year oncologic outcomes after LTME and OTME for nonmetastatic rectal cancer.

Methods

We conducted a retrospective analysis of a prospective database of rectal cancer patients undergoing LTME or OTME. Statistical analyses were performed on an ‘‘intention-to-treat’’ basis and by actual treatment. Overall survival (OS) and disease-free survival (DFS) were compared by using the Kaplan–Meier method. A multivariable analysis was performed to identify predictors of poor survival.

Results

Between April 1994 and August 2005, a total of 153 LTME patients and 154 OTME patients were included. Similarly, 10-year OS and DFS after LTME and OTME were observed: 76.8 versus 70.6 % ($P = 0.138$) and 69.1 versus 67.6 % ($P = 0.508$), respectively. Conversion to OTME did not adversely affect OS and DFS. Stage-by-stage comparison showed no significant differences between LTME and OTME. No significant differences were observed in local recurrence rates after LTME and OTME (6.5 vs. 7.8 %, $P = 0.837$). Median time until local recurrence was 24.5 (range, 12–56) months after LTME and 22 (6–64) months after OTME ($P = 0.777$). Poor tumor differentiation, lymphovascular invasion, and a lymph node ratio of 0.25 or more were the independent predictors of poorer OS and DFS.

Conclusion

This retrospective study with long follow-up did not show significant differences between the two groups in OS and DFS.

Introduction

Rectal resection combined with total mesorectal excision (TME) is the procedure of choice for the surgical treatment of extraperitoneal rectal cancer [1, 2].

While several randomized clinical trials (RCTs) have shown equivalent long-term survival [3–7] after laparoscopic or open resection for colon cancer, only a few RCTs [8] have evaluated 5-year survival after LTME and OTME, and evidence from comparative studies with a follow-up longer

than 5 years is very limited [9]. In addition, some concerns about the routine use of LTME in rectal cancer patients have been recently raised in the absence of long-term oncologic results [10, 11].

This article reports the 10-year oncologic outcomes in patients undergoing LTME or OTME for nonmetastatic extraperitoneal rectal cancer.

Materials and methods

This is a retrospective analysis of a prospective database of all patients referred to our Institution with rectal adenocarcinoma within 12 cm from the anal verge between April 1994 and August 2005. Exclusion criteria were preoperative or intraoperative evidence of distant metastases, cancer nonresponding to neoadjuvant chemoradiation therapy (CRT), acute bowel obstruction, tumor perforation, synchronous colorectal cancers, T1 cancers treated by transanal endoscopic microsurgery, and previous history of rectal surgery.

The indication for long-course neoadjuvant CRT (45 Gy over 4 weeks in association with systemic 5-fluorouracil intravenous infusion) was discussed in a multidisciplinary setting and offered to patients staged as T3-4N0-2M0.

All patients were operated on by four expert colorectal surgeons following the TME principles described by Heald et al. [1]: two with much experience in advanced laparoscopic surgery performed LTMEs, while the other two surgeons performed OTMEs. Therefore, patients underwent LTME or OTME depending on the operating surgeon. An abdominoperineal resection (APR) was performed when MRI showed tumor involvement of the anatomic anal canal.

LTME was performed using five trocars. After a careful exploration of the peritoneal cavity to detect possible liver or peritoneal metastases, and the pelvis, the sigmoid mesocolon was dissected from the sacral promontory up to the origin of the inferior mesenteric artery that was divided 1 cm from the aorta. Then, the inferior mesenteric vein was identified, dissected, and cut at the level of the ligament of Treitz. Complete mobilization of the splenic flexure was performed in all patients. TME was then started posteriorly after identification of the holy plane. Dissection was continued then laterally and anteriorly down to the pelvic floor, until circumferential rectal mobilization was obtained. In patients undergoing anterior resection (AR), the rectum was divided with a linear endoscopic stapler inserted through the right iliac fossa trocar. The bowel was than exteriorized through a protected suprapubic incision. The descending colon was divided and the anvil of a circular stapler introduced into the lumen of the proximal colon. The colon was then reintroduced into the abdomen and an intracorporeal end-to-end colorectal anastomosis was performed. A hand-sewn coloanal anastomosis was performed in very low rectal cancers. A diverting ileostomy was constructed at the end of the procedure, depending on the surgeon’s assessment of the quality of the anastomosis. Conversion from LTME to OTME was defined as unplanned incision or an incision made longer than that was necessary for specimen retrieval.

Adjuvant chemotherapy (CT) was offered after a clinical oncologic evaluation within 8 weeks after surgery to all patients undergoing neoadjuvant CRT and those with a postoperative diagnosis of stage 2–3 rectal cancer. Five-fluorouracil-based chemo-regimen (5-FU/leucovorin) was used until August 2004, while 5-FU/leucovorin with oxaliplatin regimen was administered since September 2004.

Follow-up protocol included clinical examination, serum carcinoembryonic antigen assay every 3 months, and liver ultrasound every 6 months for the first 2 years, then annually. A CT scan of

chest, abdomen and pelvis was performed every year. A colonoscopy was performed at 1 year, then every 3 years.

Oncologic outcomes included overall survival (OS), disease-free survival (DFS), local recurrence (LR), and distant metastases rates. LR was defined as any recurrence within the pelvis or the perineum diagnosed by pathologic evaluation of the biopsy or surgical specimen, or by radiologic evidence of lesions increasing in size over time.

Outcomes

The primary endpoint of this study was 10-year DFS. Secondary endpoints were OS, LR, and distal metastases rates at 10 years.

Statistics

Quantitative data are given as median and range. Categorical data are reported as percentages. Proportions were compared using the χ^2 test or the Fisher exact test, where appropriate. Student's *t* test was used to compare normally distributed variables. Univariable OS and DFS rate analyses were performed using the Kaplan–Meier method and the differences between the groups were assessed with the log-rank test.

OS was calculated from the date of surgery to the date of death from any cause. Patients alive were censored at the date of last examination. DFS was calculated from the date of surgery to the date of recurrence. Patients alive with no recurrence were censored at the date of last examination. Time to LR or distant metastases was calculated from the time of surgery to date of recurrence. A multivariable Cox regression analysis was performed to identify predictors of poor OS and poor DFS. Multivariable analysis to detect risk factors for LR after AR was conducted with a logistic regression model. Explanatory variables with univariable $P \leq 0.200$ were included in the multivariable analysis in order to evaluate all potential predictors in the final modeling process.

All analyses were performed on an ''intention-to-treat'' basis (patients who had LTME converted to OTME were analyzed in the LTME group) and by actual treatment (LTME, OTME, and LTME converted to OTME). A level of 5 % was set as the criterion for statistical significance. The data were collected in an Excel spreadsheet. The statistical analysis was performed using SYSTAT Version 10 (Copyright © SPSS Inc., 2000).

Results

Between April 1994 and August 2005, 160 patients underwent LTME and 162 underwent OTME for nonmetastatic extraperitoneal rectal cancer. Two OTME (1.2 %) patients died in the early postoperative period. A total of 13 (4 %) patients were lost to follow-up: 7 LTME patients and 6 OTME patients. Therefore, 153 LTME patients and 154 OTME patients were available for the 10-year oncologic analysis (Fig. 1). The two groups were similar in age, gender, body mass index, use of neoadjuvant CRT, type of procedure performed, anastomotic leakage (AL) rates, pathology, and administration of adjuvant CT (Table 1). Median follow-up was 79 (12–231) months for all LTME patients and 82.5 (12–242) months for all OTME patients ($P = 0.537$). Median follow-up for patients alive at the time of analysis was 132 (120–231) months for LTME patients and 138.5 (120–242) months for OTME ($P = 0.315$).

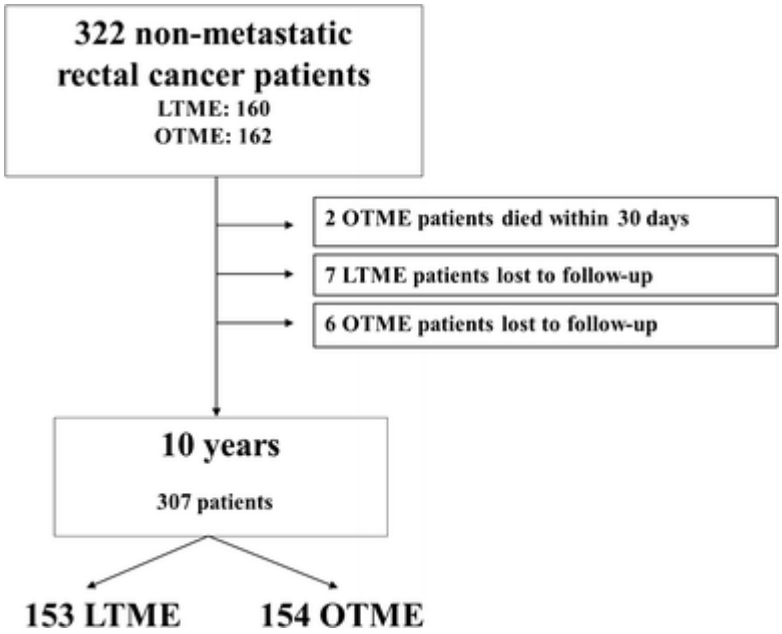

Fig. 1

Study design. *LTME* laparoscopic total mesorectal excision, *OTME* open total mesorectal excision

Table 1

Patients' characteristics

	LTME (*n* = 153)	**OTME (*n* = 154)**	***P* value**
Gender			
Male, *n* (%)	82 (53.6)	93 (60.4)	0.277
Age (years)	66.5 (32–90)	65 (24–87)	0.452
Body mass index (Kg/m^2)	24 (21–31)	24 (20–32)	0.688
Neoadjuvant CRT, n (%)	53 (34.6)	57 (37)	0.753
Surgical procedure, n (%)			0.334
AR	126 (82.4)	119 (77.3)	
APR	27 (17.6)	35 (22.7)	
Conversion to open surgery, *n* (%)	16 (10.5)		
Locally advanced tumor	10 (62.5)		
Technical difficulties	4 (25)		
Morbid obesity	2 (12.5)		
Anastomotic leakage, *n* (%)	10 (7.9)	8 (6.7)	0.905
Positive CRM, *n* (%)	2 (1.3)	3 (1.9)	0.994
Pathology stage, *n* (%)			0.164
1	55 (35.9)	41 (26.6)	
2	42 (27.5)	54 (35.1)	
3	56 (36.6)	59 (38.3)	
Tumor stage, *n* (%)			0.733
1	13 (8.5)	10 (6.5)	

	LTME (*n* = 153)	OTME (*n* = 154)	*P* value
2	50 (32.7)	48 (31.2)	
3	90 (58.8)	96 (62.3)	
Tumor size (cm)	3.2 (2.1–4.5)	3 (2–5)	0.716
Distal resection margin (cm)	2.5 (0.5–4)	2.8 (0.5–4.5)	0.416
Distance from anal verge (cm)	5 (0–7)	5 (0–6)	0.517
Number of lymph nodes harvested	12 (1–23)	11.5 (1–40)	0.608
Adjuvant chemotherapy, *n* (%)	78 (50.9)	85 (55.2)	0.532
5-FU/LV	69	75	
5-FU/LV + oxaliplatin	9	10	

LTME laparoscopic total mesorectal excision, *OTME* open total mesorectal excision, *CRT* chemoradiation therapy, *AR* anterior resection, *APR* abdominoperineal resection, *CRM* circumferential resection margin, *5-FU/LV* five-fluorouracil/leucovorin

Overall survival

The 10-year OS rate on an “intention-to-treat” basis was similar between LTME (76.8 %) and OTME (70.6 %) patients (*P* = 0.138) (Fig. 2a). By actual treatment, similar OS rates were observed for LTME (76.8 %), converted patients (76 %), and OTME patients (70.6 %) (P = 0.371) (Fig. 2b). No differences were found between LTME and OTME for stage 1 (92 vs. 91 %, *P* = 0.850) and stage 2 cancers (85.2 vs. 84.9 %, *P* = 0.870). A trend toward a better OS was observed after LTME for stage 3 cancers (56.8 vs. 43.6 %, *P* = 0.056).

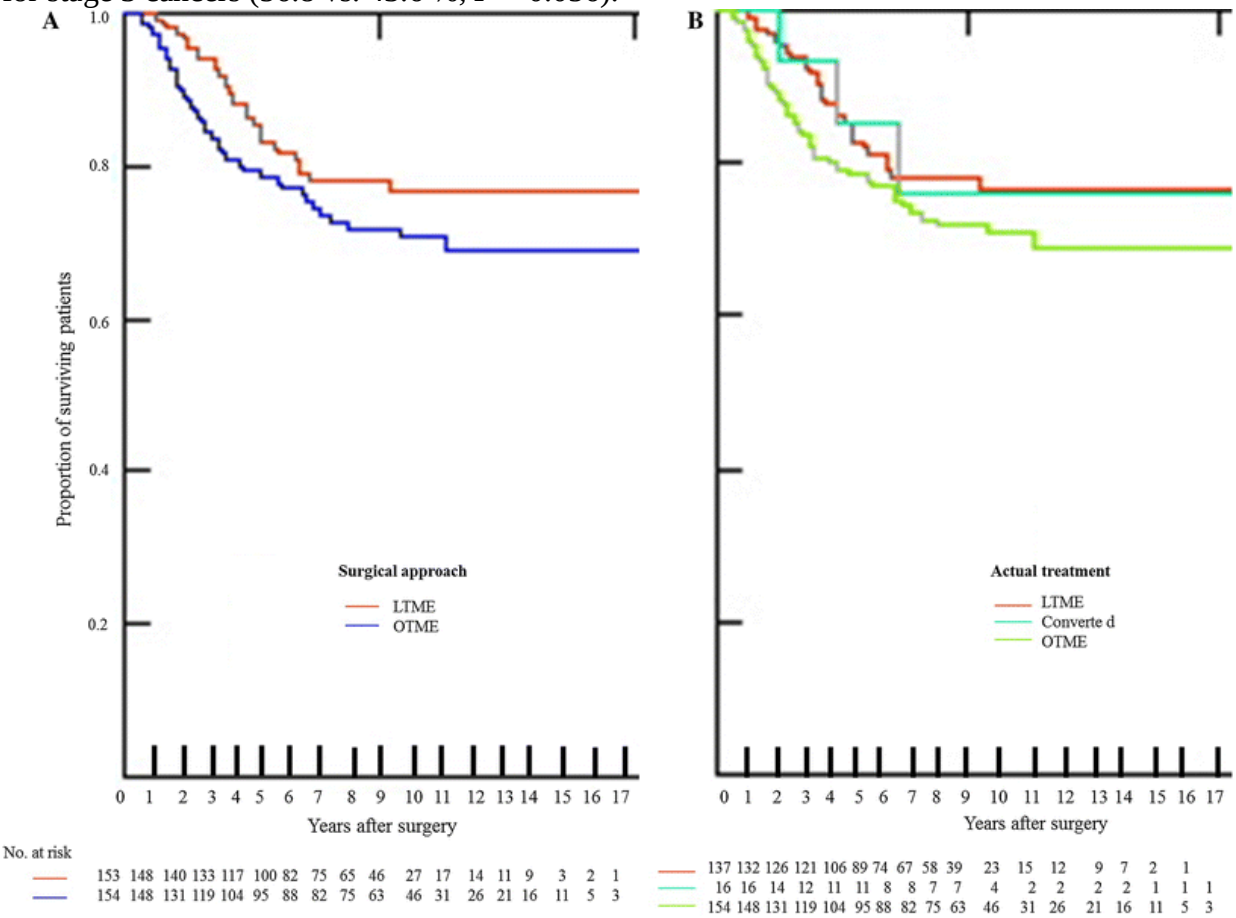

Fig. 2

Overall survival by **a** surgical approach ($P = 0.138$; Log-rank test), **b** actual treatment ($P = 0.371$; Log-rank test). *LTME* laparoscopic total mesorectal excision, *OTME* open total mesorectal excision

At univariable analysis, pT3 stage, poor grade (G3) of tumor differentiation, lymphovascular invasion, and LNR of 0.25 or more were risk factors for a poorer OS (Table 2). A slightly poorer OS was observed after APR than anterior resection (AR), even though the difference was not statistically significant (66.5 vs. 75.6 %, $P = 0.140$). After AR, 10-year OS was 77 % in patients with no AL and 59 % in those who experienced AL ($P = 0.082$).
Table 2

Univariable and multivariable analysis of risk factors for overall survival

Variable	***N* 307**	**Univariable analysis**		**Multivariable analysis**	
		Hazard ratio (95 % CI)	***P* value[a]**	**Hazard ratio (95 % CI)**	***P* value[a]**
Age[b]					
>65	154	1			
≤65	153	1.08 (0.64–1.84)	0.789		
Gender					
Female	132	1			
Male	175	1.16 (0.68–1.98)	0.683		
Surgical approach					
LTME	137	1			
Converted	16	1.21 (0.61–2.68)	0.771		
OTME	154	1.43 (0.84–2.43)	0.225		
Type of surgical procedure					
AR	245	1			
APR	62	1.52 (0.84–2.77)	0.201		
Grade of tumor differentiation					
G1–2	255	1		1	
G3	52	3.35 (1.59–7.06)	0.002	7.27 (1.81–29.20)	0.005
pT staging					
T1–T2	121	1		1	
T3	186	3.86 (2.01–7.42)	<0.001	3.07 (0.77–12.29)	0.113
Number of lymph nodes					
≥12	136	1			
<12	171	1.29 (0.75–2.24)	0.408		
Lymph node ratio					
0	192	1		1	
0.01–0.24	61	1.43 (0.69–2.95)	0.335		
≥0.25	54	10.42 (5.01–21.66)	<0.001	6.07 (1.81–20.36)	0.004
Lymphovascular invasion					
Absent	231	1		1	
Present	76	11.44 (4.99–26.17)	<0.001	10.56 (3.57–31.25)	0.001
Neoadjuvant CRT					

Variable	*N* 307	Univariable analysis		Multivariable analysis	
		Hazard ratio (95 % CI)	*P* value[a]	Hazard ratio (95 % CI)	*P* value[a]
No	197	1		1	
Yes	110	0.37 (0.26–0.89)	0.023	0.43 (0.16–1.18)	0.103
Adjuvant chemotherapy					
No	144	1		1	
Yes	163	0.51 (0.35–0.88)	0.019	0.33 (0.09–1.17)	0.085

[a]Cox regression analysis. 95 % CI = 95 % confidence interval

[b]Median age of the study population

LTME laparoscopic total mesorectal excision, *OTME* open total mesorectal excision, *AR* anterior resection, *APR* abdominoperineal resection

Poor grade of differentiation, lymphovascular invasion, and a LNR of 0.25 or more were found to be independent predictors of poorer OS (Table 2).

Disease-free survival

The 10-year DFS for all stages on an “intention-to-treat” basis was 69.1 % after LTME and 67.6 % after OTME ($P = 0.508$) (Fig. 3a). By actual treatment, the DFS rate was 70.4 % for LTME, 57.3 % for converted patients, and 67.6 % for OTME patients ($P = 0.559$) (Fig. 3b). No significant differences were observed in a stage-by-stage comparison between the two groups (stage 1: 87.1 vs. 76.4 %, $P = 0.199$; stage 2: 69.7 vs. 85.8 %, $P = 0.126$; stage 3: 48.7 vs. 44.2 %, $P = 0.298$).

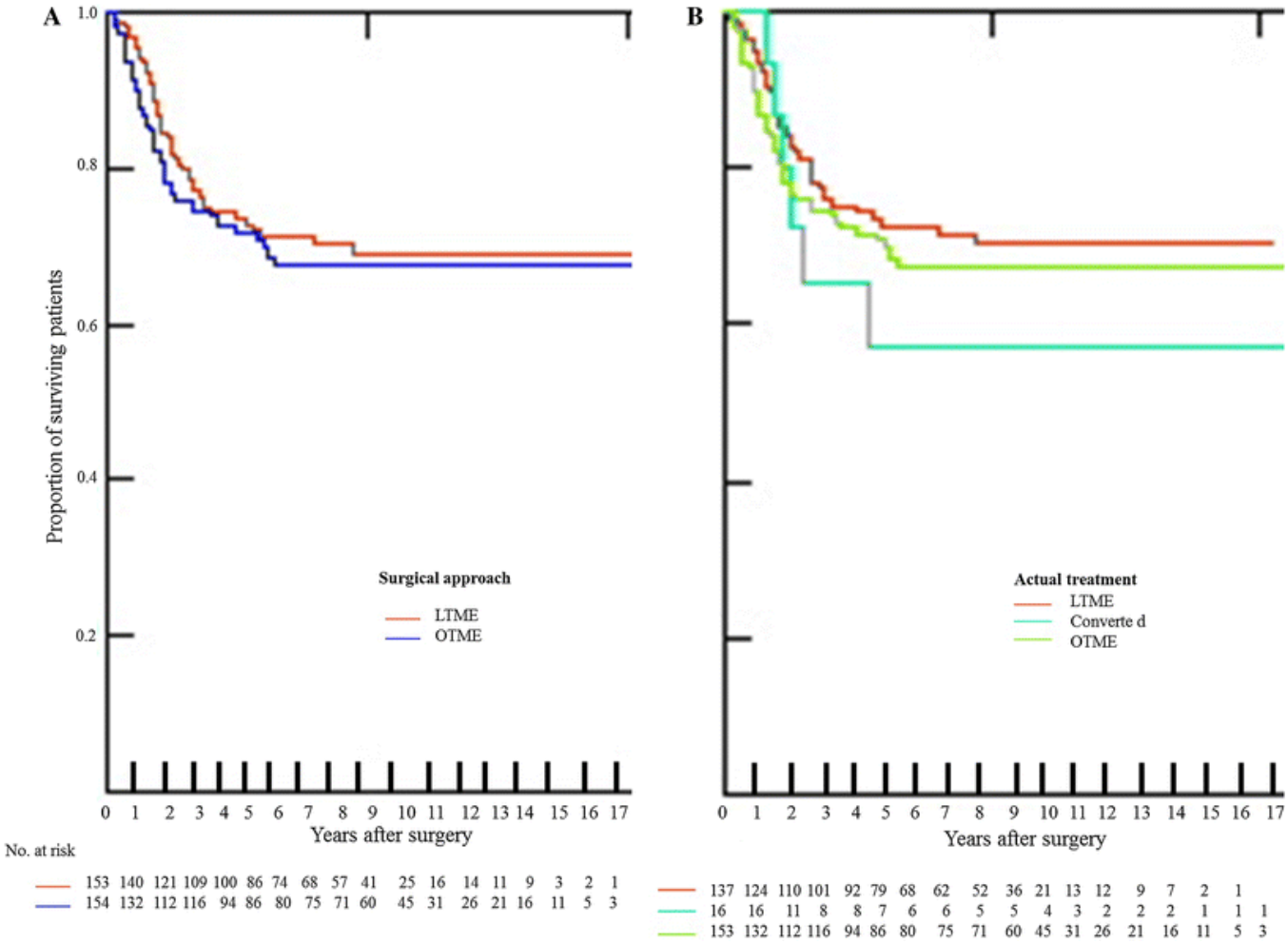

Fig. 3

Disease-free survival by **a** surgical approach (P = 0.508; Log-rank test), **b** actual treatment (P = 0.559; Log-rank test). *LTME* laparoscopic total mesorectal excision, *OTME* open total mesorectal excision

In the univariable analysis, pT3 rectal cancer, G3 tumor differentiation, lymphovascular invasion, and a LNR of 0.25 or more were found to be risk factors for a poorer DFS (Table 3). A slightly poorer OS was observed after APR than AR, even though the difference was not statistically significant (60.6 vs. 70.7 %, P = 0.147). In the group of patients undergoing AR, 10-year DFS was 72.6 % in those without AL and 48.1 % in those who experienced AL (P = 0.015).

Table 3

Univariable and multivariable analysis of risk factors for disease-free survival

Variable	***N* 307**	**Univariable analysis**		**Multivariable analysis**	
		Hazard ratio (95 % CI)	***P* value[a]**	**Hazard ratio (95 % CI)**	***P* value[a]**

Variable	*N* 307	Univariable analysis		Multivariable analysis	
		Hazard ratio (95 % CI)	*P* value[a]	Hazard ratio (95 % CI)	*P* value[a]
Age[b]					
>65	154	1			
≤65	153	1.11 (0.68–1.81)	0.709		
Gender					
Female	132	1			
Male	175	1.08 (0.65–1.77)	0.802		
Surgical approach					
LTME	137	1			
Converted	16	1.25 (0.51–4.13)	0.574		
OTME	154	1.09 (0.67–1.78)	0.803		
Type of surgical procedure					
AR	245	1		1	
APR	62	1.52 (0.87–2.67)	0.182	1.23 (0.42–3.62)	0.705
Grade of tumor differentiation					
G1–2	255	1		1	
G3	52	4.77 (2.26–10.07)	<0.001	10.86 (2.66–44.29)	0.001
pT staging					
T1–T2	121	1		1	
T3	186	2.87 (1.65–5.01)	<0.001	3.07 (0.83–11.33)	0.093
Number of lymph nodes					
≥12	136	1		1	
<12	171	1.48 (0.89–2.46)	0.158	1.346 (0.42–3.62)	0.440
Lymph node ratio					
0	192	1		1	
0.01–0.24	61	1.21 (0.61–2.39)	0.595		
≥0.25	54	9.12 (4.38–18.99)	<0.001	8.99 (2.55–31.70)	<0.001
Lymphovascular invasion					
Absent	231	1		1	
Present	76	7.94 (3.69–17.09)	<0.001	6.68 (2.35–18.97)	<0.001
Neoadjuvant CRT					
No	197	1		1	
Yes	110	0.36 (0.29–0.75)	0.012	0.45 (0.17–1.21)	0.113
Adjuvant chemotherapy					
No	144	1		1	
Yes	163	0.58 (0.35–0.97)	0.040	0.38 (0.12–1.25)	0.111

[a]Cox regression analysis. 95 % CI = 95 % confidence interval

[b]Median age of the study population

LTME laparoscopic total mesorectal excision, *OTME* open total mesorectal excision, *AR* anterior resection, *APR* abdominoperineal resection, *CRT* chemoradiation therapy

In the multivariable analysis, poor grade of tumor differentiation, lymphovascular invasion, and a LNR of 0.25 or more were the independent predictors of poorer DFS (Table 3).

Local recurrence

At 10 years, 10 (6.5 %) LTME patients and 12 (7.8 %) OTME patients developed LR ($P = 0.837$). The median time between surgery and LR was 24.5 (range, 12–56) months after LTME and 22 (6–64) months after OTME ($P = 0.777$). Two (12.5 %) of the 16 patients undergoing LTME converted to OTME developed a LR compared to 8 (5.8 %) of the 137 patients who had the TME completed laparoscopically ($P = 0.281$). Only 2 OTME patients experienced LR after the first 5 years of follow-up. No differences were observed between patients treated by AR and those treated by APR (6.8 vs. 8.5 %; $P = 0.829$).

In patients who had undergone AR, administration of adjuvant CT, lack of lymphovascular invasion, and a distal resection margin of 1 cm or more were associated with a lower risk of LR. AL did not adversely affect the oncologic outcomes in these patients (OR = 1.49, 95 % CI 0.31–8.79, $P = 0.525$) (Table 4).

Table 4

Univariable and multivariable analysis of risk factors for local recurrence after anterior resection

Variable	***N* 245**	**Univariable analysis**		**Multivariable analysis**	
		OR (95 % CI)	***P* value**	**OR (95 % CI)**	***P* value**
Age[a]					
>65	128	1		1	
≤65	117	1.65 (0.19–3.38)	0.182	1.09 (0.17–4.97)	0.923
Gender					
Female	108	1			
Male	137	1.03 (0.33–2.82)	0.970		
Surgical approach					
LTME	114	1			
Converted	12	1.39 (0.16–5.45)	0.562		
OTME	119	1.02 (0.36–2.92)	0.988		
Grade of tumor differentiation					
G1–2	204	1			
G3	41	1.65 (0.41–6.92)	0.888		
pT staging					
T1–T2	104	1			
T3	141	1.05 (0.33–2.77)	0.927		
Number of lymph nodes					
≥12	117	1			
<12	128	1.38 (0.46–4.17)	0.787		
Lymph node ratio					

Variable	*N* 245	Univariable analysis		Multivariable analysis	
		OR (95 % CI)	*P* value	OR (95 % CI)	*P* value
0	145	1			
0.01–0.24	59	0.51 (0.43–1.89)	0.202		
≥0.25	41	1.34 (0.36–4.99)	0.714		
Lymphovascular invasion					
Absent	180	1		1	
Present	65	4.14 (1.10–15.55)	0.009	6.79 (3.41–18.06)	0.004
Distal resection margin					
>1 cm	182	1		1	
≤1 cm	63	3.41 (1.18–9.83)	0.031	7.24 (0.81–11.05)	0.077
Anastomotic leak					
No	227	1			
Yes	18	1.49 (0.31–8.79)	0.525		
Neoadjuvant CRT					
No	173	1		1	
Yes	72	0.36 (0.13–1.04)	0.079	0.41 (0.08–2.05)	0.275
Adjuvant chemotherapy					
No	119	1		1	
Yes	126	0.19 (0.05–0.71)	0.007	0.10 (0.04–0.20)	0.003

95 % CI = 95 % confidence interval

[a]Median age of the study population

LTME laparoscopic total mesorectal excision, *OTME* open total mesorectal excision, *CRT* chemoradiation therapy

Distant metastases

Distant metastases developed in 34 (22.2 %) LTME patients and in 35 (22.7 %) OTME patients ($P = 0.975$). The median time between surgery and distant recurrence was 20 (range, 4–94) months after LTME and 12 (range, 3–62) months after OTME ($P = 0.077$). Distant metastases occurred after more than 5 years from surgery in 2 LTME and in 2 OTME patients. No differences were observed among patients undergoing AR (22 %) or APR (23.9 %) ($P = 0.860$).

In the group of patients undergoing AR, a trend toward a higher rate of distant metastases was observed if AL occurred (38.9 vs. 19.3 %, OR = 2.67, 95 % CI 0.98–7.29, $P = 0.066$).

No patient developed both local and distant recurrence.

Discussion

To date, there is very limited evidence regarding the oncologic outcomes beyond 5 years after LTME [9, 12–14]. The results of this comparative study did not show significant differences in oncologic outcomes at 10-year follow-up after LTME and OTME for nonmetastatic extraperitoneal rectal cancer. Similarly, the MRC CLASICC Trial group did not find significant differences in both

OS and DFS after LTME or OTME after a median follow-up of 62.9 months [9]. Recently, Brachet Contul et al. [14] have reviewed 132 patients undergoing LTME for mid- and lower rectal cancer. With a median follow-up of 73 months, OS and DFS rates were 73 and 71 % at 10 years. The 10-year LR rate was 4.1 %, with all cases occurring within the first 5 years. Distant metastases developed in 18.2 % of patients (9.1 % after the first 5 years of follow-up). These data are similar to those we have observed in this study: all LR occurred within 5 years after LTME, while 5.9 % of distant metastases were observed after more than 5 years from LTME.

There are few and controversial data about the impact of conversion from LTME to OTME on long-term survival. Most studies have a short-follow-up [15, 16]. Our results show similar 10-year outcomes in patients undergoing LTME, OTME, or converted TME, and these findings are consistent with those reported in the MRC CLASICC trial [9], suggesting that other factors rather than conversion itself might influence the long-term survival of converted patients.

Several studies have shown better 5-year survival in lymph nodes positive colorectal cancer patients undergoing laparoscopic than open surgery, suggesting that reduced surgical trauma and preservation of immune function might play a role in reducing or delaying tumor recurrence. Longer follow-up data are limited [4]. The better OS after LTME than OTME for stage 3 rectal cancer that we previously reported at 5 years [17] was confirmed also at 10 years after surgery. However, the long-term results of larger comparative studies, including COLOR II trial [18], are needed to better clarify if the laparoscopic approach is associated with improved survival in this subgroup of patients.

The current evidence regarding the oncologic safety of APR in the treatment of low-lying rectal cancers is controversial [19]. We observed slightly worse OS and DFS after APR than AR; however, APR was not independently associated with poorer OS and DFS. LR rates were similar after AR and APR. Our findings are similar to those reported in the MRC CLASICC Trial and are consistent with the results recently published by Kim et al. [20] who found similar LR rates after APR and AR (9.5 and 4.5 %, respectively); in a multivariable analysis, APR was not associated with LR and did not jeopardize OS and DFS.

While the impact of involved CRMs on survival of rectal cancer patients is well established [21], the association between close distal margin and LR after AR for extraperitoneal rectal cancer is unclear [22–25]. We observed that a distal resection margin of 1 cm or less after AR was associated with increased LR rate. Distal rectal transection is a critical step during AR for low-lying rectal cancer and the achievement of a clear distal margin can be very challenging in male patients with a narrow pelvis, in obese patients and in the presence of locally advanced tumor. During the last 10 years, some surgical innovations have led to a progressive decrease in the distance between the tumor and the anal verge considered suitable for a sphincter saving procedure. Rullier et al. [26] have demonstrated that intersphincteric resection allows to achieve a complete TME with clear distal margins in 98 % of cases and negative CRMs in 89 % of patients, without adverse impact on long-term survival. More recently, a transanal approach to distal rectal cancer, i.e., transanal TME has been proposed. A few studies have compared the short-term outcomes after transanal TME and LTME [27]. Prospective studies with long follow-up will assess the long-term oncologic results of this approach.

The influence of colorectal AL on long-term survival in rectal cancer patients remains uncertain [28–33]. In our study, AL was associated with poor 10-year survival and a high risk of distant metastases. The mechanisms of these poor outcomes are under evaluation. Some authors have speculated that the inflammation secondary to AL might promote proliferation, migration, and invasion capacity of cancer cells [34–36]. In addition, the need for a reoperation often reduces the

likelihood of receiving adjuvant CT that is known to be beneficial to reduce the risk of cancer recurrence [37].

We found a LNR of 0.25 or greater as independent risk factors for poor OS and DFS. LNR has a stronger prognostic value than the number of metastatic lymph nodes and the number of lymph nodes retrieved in the surgical specimen [38–41]. Preoperative CRT significantly reduces the number of lymph node harvested [42–47]. Some large retrospective series have reported that 5-year survival significantly decreases as LNR increases [38, 39, 48]. However, the clinical implication of these findings is limited since there is lack of consensus on the most accurate LNR cut-off value to identify the patients at higher risk of tumor recurrence. We were able to stratify the study population according to the cut-off point of 0.25 that we had previously identified as predictor for poor survival at 5 years after LTME [49]. Further large prospective studies with long follow-up are needed to confirm the accuracy of this threshold value in predicting long-term prognosis in rectal cancer patients.

We acknowledge that the study has some limitations. First, this is a single-institution study. Therefore, our results may not be generalized. Second, it is not a RCT with inherent selection bias. However, this study included two large groups of patients who were similar in terms of demographic and tumor-related characteristics; the only study comparing LTME and OTME with a larger number of patients is the MRC CLASICC trial. Furthermore, all surgical procedures were performed by experienced colorectal surgeons following the same oncologic criteria.

Conclusion

The long-term results of this retrospective study did not show significant differences in OS and DFS in patients undergoing LTME or OTME for extraperitoneal rectal cancer. Poor grade of tumor differentiation, lymphovascular invasion, and a LNR of 0.25 or more are independent predictors of poorer OS and DFS.

References

1. 1.

   MacFarlane JK, Ryall RDH, Heald RJ (1993) Mesorectal excision for rectal cancer. Lancet 341:457–460

2. 2.

   Heald RJ, Moran BJ, Ryall RDH et al (1998) The Basingstoke experience of total mesorectal excision, 1978–1997. Arch Surg 133:894–899

3. 3.

   Fleshman J, Sargent DJ, Green E, et al.; Clinical Outcomes of Surgical Therapy Study Group (2007) Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group trial. Ann Surg 246:655-662; discussion 662-664

4. 4.

Lacy AM, Delgado S, Castells A et al (2008) The long-term results of a randomized clinical trial of laparoscopy-assisted versus open surgery for colon cancer. Ann Surg 248:1–7

5. 5.

Buunen M, Veldkamp R, Hop WC et al (2009) Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomized clinical trial. Lancet Oncol 10:44–52

6. 6.

Kuhry E, Schwenk W, Gaupset R et al (2008) Long-term outcome of laparoscopic surgery for colorectal cancer: a cochrane systematic review of randomised controlled trials. Cancer Treat Rev 34:498–504

7. 7.

Jayne DG, Thorpe HC, Copeland J et al (2010) Five-year follow-up of the Medical Research Council CLASICC trial of laparoscopically assisted versus open surgery for colorectal cancer. Br J Surg 97:1638–1645

8. 8.

Arezzo A, Passera R, Salvai A et al (2015) Laparoscopy for rectal cancer is oncologically adequate: a systematic review and meta-analysis of the literature. Surg Endosc 29:334–348

9. 9.

Green BL, Marshall HC, Collinson F et al (2013) Long-term follow-up of the Medical Research Council CLASICC trial of conventional versus laparoscopically assisted resection in colorectal cancer. Br J Surg 100:75–82

10. 10.

Fleshman J, Branda M, Sargent DJ et al (2015) Effect of laparoscopic-assisted resection vs open resection of stage II or III rectal cancer on pathologic outcomes. The ACOSOG Z6051 randomized clinical trial. JAMA 314:1346–1355

11. 11.

Stevenson ARL, Solomon MJ, Lumley JW et al (2015) Effect of laparoscopic-assisted resection vs open resection on pathological outcomes in rectal cancer. The ALaCaRT randomized clinical trial. JAMA 314:1356–1363

12. 12.

Dulucq JL, Wintringer P, Stabilini C et al (2005) Laparoscopic rectal resection with anal sphincter preservation for rectal cancer. Surg Endosc 19:1468–1474

13. 13.

Ng KH, Chung-Kei D, Cheung HY et al (2009) Laparoscopic resection for rectal cancers. Lessons learned from 579 cases. Ann Surg 249:82–86

14. 14.

Brachet Contul R, Grivon M, Fabozzi M et al (2014) Laparoscopic total mesorectal excision for extraperitoneal rectal cancer: long-term results of a 18-year single-center experience. J Gastrointest Surg 18:796–807

15. 15.

Agha A, Fürst A, Iesalnieks I et al (2008) Conversion rate in 300 laparoscopic rectal resections and its influence on morbidity and oncological outcome. Int J Colorectal Dis 23:409–417

16. 16.

Rottoli M, Bona S, Rosati R et al (2009) Laparoscopic rectal resection for cancer: effects of conversion on short-term outcome and survival. Ann Surg Oncol 16:1279–1286

17. 17.

Morino M, Allaix ME, Giraudo G et al (2005) Laparoscopic versus open surgery for extraperitoneal rectal cancer: a prospective comparative study. Surg Endosc 19:1460–1467

18. 18.

Bonjer HJ, Deijen CL, Abis GA et al: COLOR II Study Group (2015) A randomized trial of laparoscopic versus open surgery for rectal cancer. N Engl J Med 372:1324–1332

19. 19.

How P, Shihab O, Tekkis P et al (2011) A systematic review of cancer related patient outcomes after anterior resection and abdominoperineal excision for rectal cancer in the total mesorectal excision era. Surg Oncol 20:e149–e155

20. 20.

Kim JC, Yu CS, Lim SB et al (2013) Abdominoperineal resection and low anterior resection: comparison of long-term oncologic outcome in matched patients with lower rectal cancer. Int J Colorectal Dis 28:493–501

21. 21.

Nagtegaal ID, Quirke P (2008) What is the role for the circumferential margin in the modern treatment of rectal cancer? J Clin Oncol 26:303–312

22. 22.

Kim YW, Kim NK, Min BS et al (2009) Factors associated with anastomotic recurrence after total mesorectal excision in rectal cancer patients. J Surg Oncol 99:58–64

23. 23.

Moore HG, Riedel E, Minsky BD et al (2003) Adequacy of 1-cm distal margin after restorative rectal cancer resection with sharp mesorectal excision and preoperative combined-modality therapy. Ann Surg Oncol 10:80–85

24. 24.

Rutkowski A, Bujko K, Nowacki MP et al (2008) Distal bowel surgical margin shorter than 1 cm after preoperative radiation for rectal cancer: is it safe? Ann Surg Oncol 15:3124–3131

25. 25.

Nash GM, Weiss A, Dasgupta R et al (2010) Close distal margin and rectal cancer recurrence after sphincter-preserving rectal resection. Dis Colon Rectum 53:1365–1373

26. 26.

Rullier E, Laurent C, Bretagnol F et al (2005) Sphincter-saving resection for all rectal carcinomas. The end of the 2-cm distal rule. Ann Surg 241:465–469

27. 27.

Fernández-Hevia M, Delgado S, Castells A et al (2015) Transanal Total Mesorectal Excision in Rectal Cancer: short-term Outcomes in Comparison With Laparoscopic Surgery. Ann Surg 261:221–227

28. 28.

den Dulk M, Marijnen CA, Collette L et al (2009) Multicentre analysis of oncological and survival outcomes following anastomotic leakage after rectal cancer surgery. Br J Surg 96:1066–1075

29. 29.

Mirnezami A, Mirnezami R, Chandrakumaran K et al (2011) Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. Ann Surg 253:890–899

30. 30.

Smith JD, Paty PB, Guillem JG et al (2012) Anastomotic leak is not associated with oncologic outcome in patients undergoing low anterior resection for rectal cancer. Ann Surg 256:1034–1038

31. 31.

Kulu Tarantino I, Warschkow R et al (2015) Anastomotic Leakage Is Associated with Impaired Overall and Disease-Free Survival after Curative Rectal Cancer Resection: a Propensity Score Analysis. Ann Surg Oncol 22:2059–2067

32. 32.

Espín E, Ciga MA, Pera M et al: the Spanish Rectal Cancer Project (2015) Oncological outcome following anastomotic leak in rectal surgery. Br J Surg 102:416–422

33. 33.

Kang J, Choi GS, Oh JH et al (2015) Multicenter analysis of long-term oncologic impact of anastomotic leakage after laparoscopic total mesorectal excision. The Korean Laparoscopic Colorectal Surgery Study Group. Medicine (Baltimore) 94:e1202

34. 34.

Chuang DS, Paddison JS, Booth RJ et al (2006) Differential production of cytokines following colorectal surgery. ANZ J Surg 76:821–824

35. 35.

Lee YS, Choi I, Ning T et al (2012) Interleukin-8 and its receptor CXCR2 in the tumour microenvironment promote colon cancer growth, progression and metastasis. Br J Cancer 106:1833–1841

36. 36.

Salvans S, Mayol X, Alonso S et al (2014) Postoperative peritoneal infection enhances migration and invasion capacities of tumor cells in vitro. An insight into the association between anastomotic leak and recurrence after surgery for colorectal cancer. Ann Surg 260:939–944

37. 37.

Biagi JJ, Paphael MJ, Mackillop WJ et al (2011) Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. JAMA 305:2335–2342

38. 38.

Rosenberg R, Friederichs J, Schuster T et al (2008) Prognosis of patients with colorectal cancer is associated with lymph node ratio. A single-center analysis of 3026 patients over a 25-year time period. Ann Surg 248:968–978

39. 39.

Peschaud F, Benoist S, Julié C et al (2008) Prognosis of Patients With Colorectal Cancer Is Associated With Lymph Node Ratio A Single-Center Analysis of 3026 Patients Over a 25-Year Time Period. Ann Surg 248:1067–1073

40. 40.

Ceelen W, Van Nieuwenhove Y, Pattyn P (2010) Prognostic value of the lymph node ratio in stage III colorectal cancer: a systematic review. Ann Surg Oncol 17:2847–2855

41. 41.

Persiani R, Biondi A, Gambacorta MA et al (2014) Prognostic implications of the lymph node count after neoadjuvant treatment for rectal cancer. Br J Surg 101:133–142

42. 42.

Wichmann MW, Muller C, Meyer G et al (2002) Effect of preoperative radiochemotherapy on lymph node retrieval after resection of rectal cancer. Arch Surg 137:206–210

43. 43.

Nagtegaal ID, van de Velde CJ, van der Worp E et al (2002) Macroscopic evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control. J Clin Oncol 20:1729–1734

44. 44.

Luna-Perez P, Rodrıguez-Ramırez S, Alvarado I et al (2003) Prognostic significance of retrieved lymph nodes per specimen in resected rectal adenocarcinoma after preoperative chemoradiation therapy. Arch Med Res 34:281–286

45. 45.

Baxter NN, Morris AM, Rothenberger DA et al (2005) Impact of preoperative radiation for rectal cancer on subsequent lymph node evaluation: a population-based analysis. Int J Radiat Oncol Biol Phys 61:426–431

46. 46.

Sermier A, Gervaz P, Egger JF et al (2006) Lymph node retrieval in abdominoperineal surgical specimen is radiation time-dependent. World J Surg Oncol 4:29

47. 47.

Rullier A, Laurent C, Capdepont v et al (2008) Lymph nodes after preoperative chemoradiotherapy for rectal carcinoma: number, status, and impact on survival. Am J Surg Pathol 32:45–50

48. 48.

Kim YS, Kim JH, Yoon SM et al (2009) Lymph node ratio as a prognostic factor in patients with stage III rectal cancer treated with total mesorectal excision followed by chemoradiotherapy. Int J Radiat Oncol Biol Phys 74:796–802

49. 49.

Allaix ME, Arezzo A, Cassoni P et al (2013) Metastatic lymph node ratio as a prognostic factor after laparoscopic total mesorectal excision for extraperitoneal rectal cancer. Surg Endosc 27:1957–1967