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ORIGINAL ARTICLE

The impact of total mesorectal excision in middle and low rectal carcinomas

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Summary

Purpose: *The incidence of locoregional recurrence in rectal cancer has declined since total mesorectal excision (TME) has been widely adopted. The purpose of this study was to investigate the long-term survival and the incidence of locoregional recurrences in patients with middle and low rectal carcinomas undergoing TME.*

Methods: *The medical records of 126 patients with middle and low rectal carcinomas treated from 1987-2007 were retrospectively reviewed. Of them 80 had undergone total mesorectal excision (TME-group) and 46 surgery with conventional methods (CON-group). Clinical variables were correlated to morbidity, hospital mortality, recurrence, sites of recurrence, and survival.*

Results: *The groups were comparable except for type of surgery and sites of recurrence. Five-year overall survival rate for TME group was 75% and for CON-group 47% (p=0.0346). Although the groups were not different for the total number of recurrences, the number of locoregional recurrences was significantly lower in TME group (p=0.004).*

Conclusion: *TME appears to improve long-term survival in patients with middle and low rectal carcinomas. The incidence of locoregional recurrence is also reduced by TME.*

Key words: locoregional recurrence, rectal cancer, survival, total mesorectal excision

Introduction

The standard approaches of abdominoperineal or anterior resection for rectal cancer have both been disappointing because of poor local control and low overall survival. The unacceptable high rates of locoregional recurrence [1] have led to the systemic use of adjuvant treatments such as irradiation [2,3], systemic chemotherapy, or both in various combinations [4]. All these strategies have offered clear reduction in the incidence of locoregional recurrences but the most powerful factor that has undoubtedly offered efficient local control has unequivocally been TME [5,6].

The purpose of this study was to investigate the impact of TME on survival and locoregional recurrence in patients with middle and low rectal carcinomas.

Methods

The records of patients with rectal carcinomas with the lower margin at or below 10 cm from the anal canal on rigid proctosigmoidoscopy, treated from 1987-2006, were retrospectively reviewed. There were 142 patients meeting the above criteria but only 126 had been treated with curative intent. The remaining 16 patients that had been treated with palliative intent were excluded from analysis. Of them 80 had undergone total mesorectal excision (TME group) and 46 conventional surgery (CON-group). The groups were correlated for age, gender, ASA class, physical status, type of surgery, TNM stage, adjuvant chemotherapy, postoperative irradiation, CEA and CA 19-9 serum levels, residual tumor, morbidity, hospital mortality, recurrences, sites of recurrence, and overall survival.

Physical status was assessed according to Karnofsky performance scale. Histopathological data included all the details of the resected specimens about tumor invasion, lymph node infiltration, metastatic lesions, degree of differentiation, and residual tumor. Specimens were staged according to TNM system. Sites of recur-

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rence were assessed as distant (liver, lung, brain, osseous etc) and locoregional (pelvis, and peritoneal surfaces). Preoperative irradiation or neoadjuvant chemotherapy were not used. Postoperative irradiation and/or adjuvant systemic chemotherapy were used in stage III patients.

Patients were assessed with physical examination, hematological and biochemical examinations, tumor markers (CEA, CA 19-9), endoscopy, tumor biopsies, and CT scan of the abdomen, thorax, and pelvis.

Follow-up was accomplished with physical examination, hematological and biochemical examinations, tumor markers (CEA, CA 19-9) at 3 months initially and at 6 month-intervals afterwards. Follow-up assessment included CT scan examination every 6 months and colonoscopy once a year.

Statistical methods

Statistical analysis was made using SPSS (Statistical Package for Social Sciences). The proportions of patients with a given characteristic were compared by chi-square analysis, or Fisher's exact-test. Differences in the means of continuous measurement were tested by Student's t-test. Survival curves were constructed using the Kaplan-Meier method and the comparison of curves was calculated using the log-rank test. Cox regression analysis made possible multiple analysis of survival. Logistic regression analysis was used for multiple analysis of morbidity, hospital mortality and recurrence. A two-tailed p-value < 0.05 was considered statistically significant.

Results

The groups were comparable for age, gender, ASA class, performance status, TNM stage, residual tumor, degree of differentiation, morbidity, hospital mortality, adjuvant chemotherapy, postoperative irradiation, CEA, CA 19-9, and number of recurrences. They were different for the type of surgery, because low anterior resections were more frequently performed in the TME group. Locoregional recurrences were more frequently recorded in the CON group (Table 1). The mean age in the TME group was 67.5±10.1 years (range 46-92) and in the CON group 70.3±10.9 years (range 43-93) ($p > 0.05$). Patients were prepared for surgery with mechanical bowel preparation. In the TME and the CON group, 40 low anterior resections, and 8 low anterior resections respectively were protected with proximal loop colostomy. All these operations constituted 75% of the total low anterior resections. All the resected specimens were staged according to TNM system, degree of differentiation, residual tumor. CEA measurements were obtained from all patients but CA 19-9 was obtained only from 60 patients in the TME group and 18 patients in the CON group. Two patients in the TME group and 5 patients in the CON group denied receiving adjuvant chemotherapy. In addition 13 patients in the TME group and 9 patients in the CON group denied receiving postoperative adjuvant chemotherapy.

Table 1. Univariate analysis of patient, tumor and treatment characteristics in both groups

Variable	*TME group n=80*	*CON group n=46*	*p-value*
M/F ratio	44/36	25/21	NS
ASA class			NS
I/II/III	48/29/3	24/17/5	
Karnofsky perf. status			NS
90-100/70-80/50-60	76/3/1	38/7/1	
T			NS
$T_1/T_2/T_3$	6/16/58	4/5/37	
N			NS
$N_0/N_1/N_2$	35/25/20	25/13/8	
M			NS
M_0/M_1	77/3	44/2	
Degree of differentiation			NS
$G_1/G_2/G_3$	25/51/4	17/24/3	
Residual tumor			NS
R_0/R_1	78/2	45/1	
Hospital mortality	5	5	NS
Morbidity	22	15	NS
Adjuvant chemotherapy	38	18	NS
Postoperative irradiation	14	4	NS
Recurrence	16	15	NS
TNM stage			NS
I/II/III/IV	14/21/42/3	8/16/20/2	
Age (years)			NS
<65 vs.>65	28/52	12/34	
CEA (ng/ml)			NS
<5 vs.>5	55/25	25/19	
CA 19-9 (ng/ml)			NS
<35 vs.>35	58/6	18/0	
Sites of recurrence			0.004
Distant vs. locoregional	13/3	4/10	
Type of surgery			0.001
LAR vs. APR	50/30	14/32	

M: male, F: female, LAR: low anterior resection, APR: abdominoperineal resection, ASA: American Society of Anesthesiologists, NS: non significant

Morbidity and hospital mortality

The overall morbidity rate was 29.4% (37 patients). The complications are demonstrated in Table 2. By univariate analysis ASA class (p=0.002), performance status (0.025), and low anterior resection

Table 2. Complications

Complication	*No. of patients*	*%*
Wound infection	9	7.1
Respiratory	8	6.3
Urinary infection	8	6.3
Anastomotic leak	6	4.8
Cardiac arrhythmias	2	1.6
Cerebrovascular accident	2	1.6
Postoperative bleeding	1	0.8
Renal failure	1	0.8

(p=0.023), were related to morbidity. The independent factors that influenced morbidity were ASA class (p <0.001, hazard ratio [HR]=3.368, 95% CI=1.701-6.668), and low anterior resection (p=0.01, HR=3.116, 95% CI=1.31-7.412). The overall hospital mortality rate was 7.9% (10 patients). ASA class (p <0.001) and performance status (p=0.025) were related to hospital mortality by univariate analysis. However, only ASA class (p <0.001, HR=0.119, 95%CI=0.038-0.379) was identified as an independent factor of mortality. The hospital mortality was recorded in ASA III patients with performance status < 50%.

Survival

The 5-year overall survival rate was 65.7% (Figure 1). Five-year survival rate for the TME group was 77% and for the CON group 47.5% (p=0.0343; Figure 2). Univariate analysis showed that despite TME, ASA class (p<0.0001), presence of metastasis (p <0.0001), and stage (p <0.0001) were the factors related significantly to survival (Table 3). In multivariate analysis only M and stage were identified as independent variables of survival (Table 4). Stage by stage 5-year survival rate was 87, 77, 54, and 0% for stages I, II, III, and IV, respectively (Figure 3).

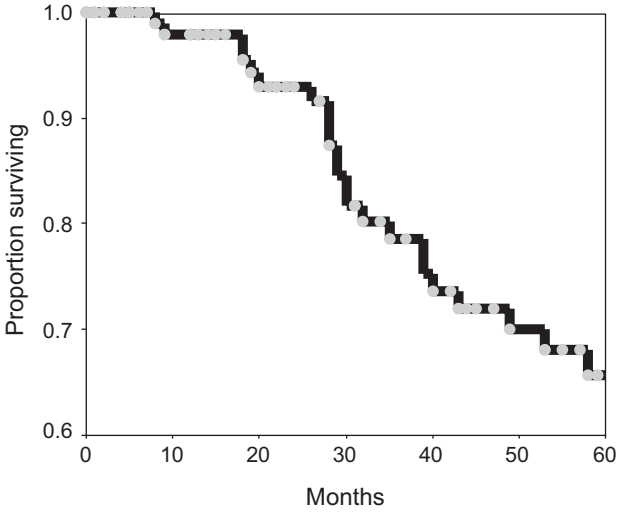

Figure 1. Five-year overall survival.

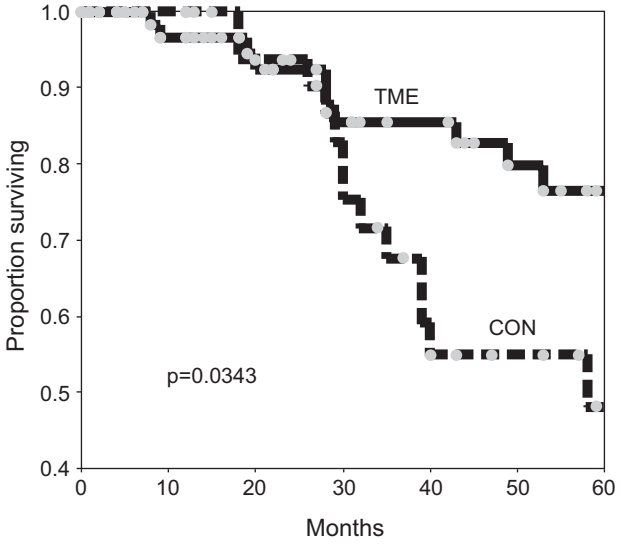

Figure 2. Five-year overall survival for TME and CON groups.

Follow-up

During follow-up 31 patients (24.6%) developed recurrence. Of them 16 (16.3%) were in the TME

Table 3. Univariate analysis of survival

Variable	*p-value*
ASA class	<0.0001
Performance status	NS
Nodal status	NS
Metastasis	<0.0001
Tumor depth	NS
Stage	<0.0001
Degree of differentiation	NS
Postoperative irradiation	NS
Age	NS
Gender	NS
Residual tumor	NS
CEA	NS
CA 19-9	NS
Total mesorectal excision	0.0343
Type of surgery	NS

NS: non significant

Table 4. Multivariate analysis of survival

Variable	*HR*	*p-value*	*95% CI*
Metastasis	5.484	0.0039	1.092-27.54
Stage	2.121	0.0032	1.065-4.221

HR: hazard ratio, CI: confidence interval

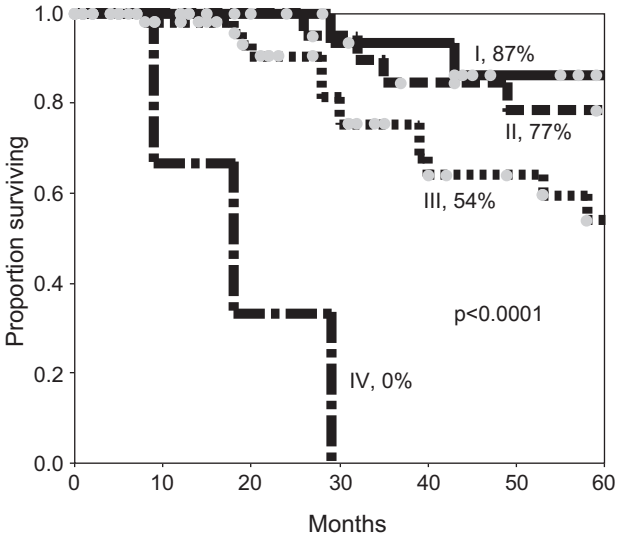

Figure 3. Five-year overall survival by stage (I-IV).

group and 14 (30.4%) in the CON group (p >0.05). Stage (p=0.021), use of adjuvant chemotherapy (p=0.022), and lymph node status (p=0.05) were found to be related to the development of recurrence by univariate analysis. Multivariate analysis identified only stage (p=0.004, HR=0.377, 95% CI=0.194-0.734) as an independent factor of recurrence. Locoregional recurrences in the TME group were recorded in 3 (3.8%) patients and in 10 patients (21.7%) in the CON group. The total number of recurrences was not different between the two groups. The incidence of locoregional failures in the TME group was significantly lower compared to that recorded in the CON group (p=0.004).

Discussion

The groups were comparable except for type of surgery and the incidence of locoregional failures. Low anterior resection was more frequently performed in the TME group. The Basingstoke experience has proved that abdominoperineal resection is rarely required and only for ultra-low rectal tumors [6]. Current studies support the evidence that the distal margin of resection is less important than previously thought in regard both to the incidence of locoregional failures and to overall survival [7].

TME was initially used by Heald et al. and a significant reduction in abdominoperineal resections was achieved. It also became clear that the incidence of locoregional recurrence was reduced without further preoperative or postoperative treatment [6] and that the circumferential margin of resection was one of the most important factors of recurrence [8].

The Swedish trial [2] showed that preoperative irradiation offered a clear benefit in reducing the locoregional recurrence rate. The Stockholm II short course of preoperative radiotherapy was the first large randomized controlled trial to suggest improved 5-year survival rate [9,10]. The Dutch trial was the second controlled randomized trial that reconfirmed the low incidence of locoregional recurrences with preoperative radiotherapy but failed to show improved survival [3]. In addition, it failed to show downstaging of the tumor which seems to be achieved by long-course preoperative radiotherapy in only 40% of the patients [11]. Preoperative short-course irradiation with TME has currently been adopted as the standard of care for middle and low rectal carcinomas with the intent of decreasing the locoregional recurrences and preserving the normal route of the gastrointestinal tract by increasing the number of low anterior resections [12].

The stage of disease has been proved to be the most significant prognostic variable of survival in the published literature and has been reconfirmed in the present study both by univariate and multivariate analysis [13,14].

Although TME was not identified as an independent variable of survival, the 5-year survival rate was 77% in the TME group vs. 47.5% in the CON group, indicating that this method offers a clear survival benefit [15,16].

The morbidity rate of 29.4% is similar to that reported by others [15,16]. ASA class and the performance of low anterior resection were found to influence morbidity. Low anterior resection is complicated by anastomotic failure in 8-17% of the cases [5,16]. However, if low anterior resection is performed with extensive mobilization of the splenic flexure, high ligation of the inferior mesenteric artery close to the aorta, high ligation of the inferior mesenteric vein at the inferior border of the pancreas, and protected by temporary loop colostomy, then the anastomotic failure is not anticipated to exceed 4% [17]. In the present study 75% of the patients with low anterior resection had their anastomosis protected by colostomy and as a consequence only 4.8% of them were complicated by anastomotic leak. It is important to note that anastomotic failures were recorded in patients that had not undergone temporary protective colostomy.

The hospital mortality was quite high (7.9%) but it was related to poor ASA class and poor performance status.

The incidence of recurrence was not different between the groups. However, in the TME group only 3.8% of locoregional recurrences were recorded even though adjuvant treatments were rarely used. In con-

trast, in the CON group the incidence of locoregional recurrences was as high as 21.7%. It is conceivable that surgery alone plays a major role in the control of locoregional disease. It has been demonstrated that the incidence of locoregional recurrences in potentially curative ultra low anterior resection for carcinomas of the lower third of the rectum using stapled coloanal anastomosis does not exceed 3.5%, and 5-year survival rate in curative and palliative resections is 81% [17].

Conclusion

TME appears to be the most important clinical variable in reducing the incidence of locoregional recurrence. It also appears to offer a survival benefit in patients with middle and low rectal carcinomas and is associated with acceptable morbidity and mortality.

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