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Type of Operation does not Affect Survival after Non-curative Resection for Adenocarcinoma of the Rectum at or below the Peritoneal Reflection: a Multivariate Analysis

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Purpose. The purpose of this study was to determine whether the type of operation [sphincter-saving resection (SSR) or abdominoperineal resection (APR)] for primary adenocarcinoma of the rectum at or below the peritoneal reflection affects survival after non-curative surgery.

Methods. This retrospective study included 42 patients who underwent non-curative surgery by the following two types of operation between 1989 and 1998: (1) SSR (n=19 patients) included low anterior resection with either double-stapling technique (n=16) or transanal coloanal anastomosis (n=3); (2) APR (n=23). 'Non-curative' resection implied 'Curability B' and 'Curability C' defined by the Japanese Classification of Colorectal Carcinoma. Outcome measure was disease-specific survival. Univariate and multivariate Cox's regression analyses were used to evaluate data. Median follow-up was 17.2 months at study conclusion.

Results. Disease-specific survival after non-curative surgery did not differ between the two types of operations. Multivariate analyses showed that the type of operation was not a significant independent variable in predicting disease-specific survival after surgery. One variable - 'Curability' - was significant predictor of outcome after surgery.

Conclusions. The type of operation (SSR or APR) did not affect survival after non-curative resection for adenocarcinoma of the rectum at or below the peritoneal reflection.

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Key Words: rectal cancer, sphincter-saving resection, abdominoperineal resection, double-stapling technique, coloanal anastomosis, non-curative resection.

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Introduction

Sphincter-saving resections (SSR) have been performed with increasing frequency in patients with cancer of the lower third of the rectum.[1,2)] Development of circular stapling device or improvement of surgical technique for transanal coloanal anastomosis has made it possible to construct an anastomosis between the colon and the anal canal.[3,4)] Numerous studies have compared the oncologic results of a SSR such as low anterior resection with an abdominoperineal resection (APR).[1)] When a low anterior resection is properly performed with a 2-cm distal resection margin, the low anterior resection can achieve comparable local recurrence and survival rates in comparison to APR.[1,2,5)] Most authors of these studies reported on the oncologic results after curative SSR for cancer of the lower third of the rectum.[6,7)] However, the effect of the type of operation (SSR or APR) on survival after non-curative resection for tumors located in the lower third of the rectum has not been fully discussed.[8)]

In this retrospective review, we compared disease-specific survival after non-curative SSR and APR for adenocarcinoma located in the rectum at or below the peritoneal reflection. The aim of this study was to determine whether the type of operation (SSR or APR) affects survival after non-curative surgery.

Patients and Methods

Patients

Forty-two patients who underwent non-curative resection for primary adenocarcinoma of the rectum at or below the peritoneal reflection between January 1989 and December 1998 at the Nagasaki University Hospital and Sasebo Municipal Hospital were included

in this study. Thirteen were women, and 29 were men. Ages ranged from 44 to 90 years, with a median age of 64.5 years. The patients underwent the following two types of operations for rectal cancer: (i) SSR (SSR group with 19 patients), low anterior resection with either an intrapelvic anastomosis achieved by double-stapling technique[3] (DST) (16 patients) or a transanal coloanal anastomosis[4] (CAA) achieved by hand-sewn suture (3 patients) (ii) APR (APR group with 23 patients). The following groups of patients were excluded from this study: patients who underwent curative surgery; patients who underwent Hartmann resections or total pelvic exenterations; patients with more than one carcinoma of the colon and rectum; patients with other organ malignancies; patients with familial adenomatous polyposis; patients who were treated with local excision; patients who died following postoperative complications occurring within one month of the operation; and patients who were lost to follow-up.

All patients underwent preoperative that included digital and endoscopic examination, biopsy, abdominopelvic computed tomography, and in more recent years endoscopic ultrasonography. None of the patients had received pre- or intra-operative radiotherapy and chemotherapy. Patients received adjuvant cytotoxic chemotherapy after surgery (systemic administration of 5-fluorouracil (5-FU) and/or infusion chemotherapy of 5-FU via proper hepatic artery for liver metastases), and/or oral administration of 5-FU derivatives.

Definitions

Tumor location was measured in distance (cm) from the dentate line, which was determined by preoperative rigid or flexible colonoscopy. We confirmed intraoperatively that the lower margins of the tumors were located in the rectum at or below the peritoneal reflection. Macroscopic type of tumor, 'Curability' of surgical resection, and grade of peritoneal dissemination (P1, P2, and P3) and liver metastasis (H1, H2, and H3) were determined according to the Japanese Classification of Colorectal Carcinoma.[9] Tumor size (cm) was documented as the longest diameter of the tumor on gross examination of the fresh specimen. Distal resection margin (cm) was determined on gross examination of the fresh specimen that was spread on a cork specimen board by means of fine needles. Tumor stage and histologic grade were obtained from the pathologic report after surgery. American Joint Committee on Cancer Classification and Stage groupings were used for tumor assessment.[10]

'Curability': 'Curability' of surgical resection was determined both macroscopically and microscopically.[9] The lymph nodes of groups 1, 2, and 3 are referred to as n1, n2, and n3, respectively, based on the extent of lymph node metastasis. Rectal resection on the basis of lymph node dissection was classified as follows: D1, rectal resection with complete removal of group 1 lymph nodes only; D2, rectal resection with complete removal of group 1 and 2 lymph nodes; and D3, rectal resection with complete removal of group 1, 2, and 3 lymph nodes. 'Curability A' indicates that there were no residual tumors and there was a high probability of cure, under the following conditions: (1) 'D' number $\geq$ 'n' number; (2) no metastases in liver, peritoneum, and other distant organs; and (3) surgical margins without histological evidence of malignant cells. 'Curability B' indicates that there were no residual tumors estimated but the patient could not be assessed as 'Curability A' because the patient had one or more of the following conditions: (1) 'D' number <'n' number; (2) excision for metastases in liver, peritoneum, and other distant organs; and (3) surgical margins that histologically showed malignant cells. 'Curability C' indicates that there was definite residual tumor. In this study, 'Curability A' is designated as 'curative' resection, while 'Curability B' and 'Curability C' are considered 'non-curative' resections.

Operative technique

Our policy regarding the resection for cancer of the rectum at or below the peritoneal reflection was as follows. The abdominal portion of the DST[3], CAA[4], or APR was performed using exactly the same techniques, except for transection of the distal rectum or excision of the rectum. We have principally removed lymph nodes at the root of inferior mesenteric artery for patients with stage III/IV tumor, while we did not for patients with stage 0/I/II tumor. Lateral lymph node dissection with removal of the autonomic nerves was performed for patients with stage III/IV tumors, whereas not for patients with stage 0/I/II tumors. The entire mesorectum was routinely mobilized to the pelvic floor in the avascular plane *via* sharp dissection. All patients underwent the total mesorectum excision.[11] The choice of operation (DST, CAA, or APR) depended on the location of the tumor relative to the dentate line and stage. The policy has been to perform the anastomosis in the abdomen by DST whenever possible. If an anastomosis could not then be achieved *per* abdomen, transanal CAA was performed. In DST and CAA, the distal rectum was divided with a 1-cm margin for stage 0/I or a 2-cm distal resection for stage II/III/IV tumors. In the APR, the distal rectum was not transected and the anus and rectum were widely

excised.

Aggressive resection for distant metastases such as liver metastases (H1and H2[9]), peritoneal dissemination (P1[9]), and lung metastasis was performed, whereas resection for para-aortic lymph node metastases (N4[9]) was not.

Follow-up and study endpoints

Follow-up was completed through office records, telephone, or written contact with the patient and/or primary care physician. The patients were examined at three-month intervals for the first three postoperative years and every six months thereafter. Complete clinical examinations were performed and included digital and rectal palpation, as well as total colonoscopy. In addition, the patients underwent periodic metastatic workup using chest and abdominal computed tomography. Follow-up for all patients included in this study was complete and median follow-up was 17.2 (range, 2.5-76.9) months at the conclusion of the study. A minimum of 3-years of follow-up is available for all patients.

Endpoint of the study was disease-specific survival. Disease-specific survival was defined as the time from the date of operation to the date of rectal cancer death. Data from patients who died of causes other than rectal cancer were censored in the survival analysis.

Statistical analysis

Continuous data were expressed as mean ± standard deviation. Comparison of the continuous data between the two groups was conducted using unpaired t-test. Categorical data were analyzed by χ^2 test or Fisher's exact test. The influence of each variable on the survival time was calculated according to the Kaplan-Meier method,[12] and differences between survival times were tested for significance using the log rank test.[13] The prognostic relevance of a single factor was determined by univariate Cox's regression analysis, whereas clinicopathological factors were analyzed by multivariate Cox' regression analysis.[14] All tests were two-tailed and a P value of less than 0.05 was considered significant.

Results

Comparison of clinicopathological features between the SSR and APR groups

Mean distance between the tumor lower margin and the dentate line (tumor location) in the SSR group was significantly longer that that in the APR group (P<0.0001). Mean tumor size and distal resection margin in the SSR group were significantly shorter than those in the APR group, respectively (P=0.0002 and P =0.031, respectively). However, there were no differences in the other variables (age, gender, macroscopic type, histologic grade, lymphatic and venous invasions, T stage, N stage, M stage, stage, 'Curability', and postoperative chemotherapy) compared between the two groups (Table 1).

Table 1. Comparison of clinicopathological features between SSR and APR groups.

	No. of cancer		
Variable	SSR* (n=19)	APR* (n=23)	P value
Age (years) †	64.7±15.1	63.2±9.1	0.68
Gender			1.00
Female	6 (31.6)	7 (30.4)	
Male	13 (68.4)	16 (69.6)	
Tumor location (cm) †	3.4±1.1	1.3±1.2	<0.0001
Tumor size (cm) †	4.9±1.1	7.2±2.2	0.0002
Distal resection margin (cm) †	2.9±2.4	4.5±2.1	0.031
Macroscopic type‡			0.19
Type 1 or Type 2	15 (79.0)	13 (56.5)	
Type 3 or Type 4	4 (21.0)	10 (43.5)	
Histologic grade			0.55
Well differentiated	5 (26.3)	3 (13.0)	
Moderately differentiated	11 (57.9)	16 (69.6)	
Poorly differentiated	3 (15.8)	4 (17.4)	
Lymphatic invasion			0.43
Absent	5 (26.3)	3 (13.0)	
Present	14 (73.7)	20 (87.0)	
Venous invasion			0.32
Absent	4 (21.1)	9 (39.1)	
Present	15 (78.9)	14 (60.9)	
T stage			0.21
T3	12 (63.2)	9 (39.1)	
T4	7 (36.8)	14 (60.9)	
N stage			1.00
N0	3 (15.8)	3 (13.0)	
N1/N2	16 (84.2)	20 (87.0)	
M stage			0.48
M0	3 (15.8)	6 (26.1)	
M1	16 (84.2)	17 (73.9)	
Stage			0.72
II	1 (5.3)	2 (8.7)	
III	2 (10.5)	4 (17.4)	
IV	16 (84.2)	17 (73.9)	
'Curability'‡			0.75
'Curability B'	8 (42.1)	8 (34.8)	
'Curability C'	11 (57.9)	15 (65.2)	
Postoperative chemotherapy			1.00
No	5 (26.3)	6 (26.1)	
Yes	14 (73.7)	17 (73.9)	

* SSR, sphincter-preserving resection; APR, abdominoperineal resection.
† Age, tumor location, tumor size, and distal resection margin are expressed as means ± standard deviations. Statistical analysis used unpaired t-test.
‡ Macroscopic type and 'Curability' were determined according to the Japanese Classification of Colorectal Carcinoma.[9] See "Patients and Methods".

Factors of non-curative resection and patients' outcome

Clinicopathological factors of non-curative resection are shown in Table 2 (the patients had one or more factors).

Table 2. Factors of non-curative resection

Variables	No. of patients*	
	'Curability B'† (n=16)	'Curability C'† (n=26)
Liver metastasis	7	15
Pulmonary metastasis	0	3
Peritoneal dissemination	0	5
'D' number <'n' number†	3	6
Positive resection margin†		
Surgical cut end (ew)	6	6
Distal cut end (aw)	1	1

*The patient had one or more factors.
†Variables were determined according to the Japanese Classification of Colorectal Carcinoma.[9] See "Patients and Methods".

'Curability B': Of 7 patients underwent hepatectomies for liver metastases with curative intent, 2 patients are alive with disease-free (77.0 and 36.6 months after surgery), while 5 patients died with hematogenous metastases [median follow-up, 21.0 (range, 4.1-25.8) months]. All of 3 patients who had a factor of "D number < n number"[7] died of disease [median follow-up, 16.4 (range, 9.5-50.0) months]. Of 7 patients who had a positive resection margin, 3 patients are alive with disease-free [median follow-up, 40.3 (range, 39.6-44.6) months], whereas 4 patients died of disease [median follow-up, 43.0 (range, 16.4-75.7) months].
'Curability C': All patients died of disease [median follow-up, 12.5 (range, 2.5-38.1) months].

Comparison of survival time after non-curative surgery between the SSR and APR groups

Disease-specific survival time after non-curative surgery between the SSR and APR groups did not differ (P=0.45). The cumulative 5-year disease-specific survival rates were 13.2% in the SSR group and 9.3% in the APR group (Fig. 1).

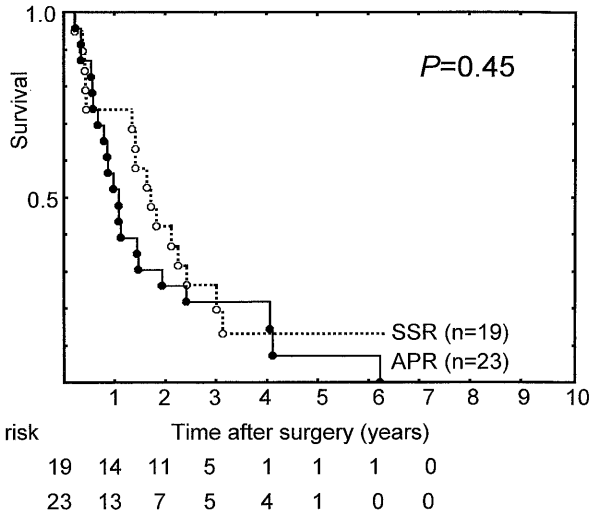

Figure 1. Disease-specific survival curve in 42 patients who underwent non-curative resection for cancer of the rectum at or below the peritoneal reflection according to the type of operation. SSR, sphincter-preserving resection. APR, abdominoperineal resection.

Cox's regression analysis to determine the prognostic value of type of operation

To assess the effects of different variables on disease-specific survival in 42 patients who underwent non-curative resection for rectal cancer, the Cox's regression analysis was conducted. We excluded variables such as T stage, N stage, and M stage from this analysis to avoid the problem of collinearity. However, we included the remaining 13 variables (age, gender, tumor location, tumor size, distal resection margin, macroscopic type, histological grade, lymphatic and venous invasions, stage, postoperative chemotherapy, type of operation, and 'Curability'). Univariate Cox's regression analysis indicated that lymphatic invasion, stage, and 'Curability' were associated with short survival of the patient. Multivariate Cox's regression analysis revealed that only one independent variable - 'Curability' - was found to be significant for predicting survival (Table 3).

Discussion

The effect of the type of operation on survival after non-curative resection for tumors located in the lower third of the rectum has not been fully discussed.[8] Bokey et al.[8] reported that the nature of the operation [SSR (high, low, or extended low anterior resection) and APR] performed had no independent effect on survival in patients with all stages. The current study

Table 3. Prognostic variables for disease-specific survival after non-curative resection in Cox's regression analysis (n=42).

	Univariate analysis		Multivariate analysis	
Variables	HR (95% CI)*	*P* value	HR (95% CI)*	*P* value
Age (+10 years)	1.01 (0.98-1.04)	0.50	1.00 (0.95-1.04)	0.83
Gender				
Female	1		1	
Male	1.50 (0.72-3.1)	0.28	0.99 (0.33-2.97)	0.99
Tumor location (+1.0 cm)	1.02 (0.83-1.25)	0.82	1.02 (0.65-1.59)	0.93
Tumor size (+1.0 cm)	1.19 (1.00-1.41)	0.050	1.17 (0.90-1.52)	0.25
Distal resection margin (+1.0 cm)	0.96 (0.84-1.11)	0.60	0.98 (0.74-1.29)	0.88
Macroscopic type†				
Type 1 or Type 2	1		1	
Type 3 or Type 4	1.21 (0.61-2.39)	0.59	1.60 (0.53-4.81)	0.41
Histological grade				
Well differentiated	1		1	
Moderately differentiated	1.66 (0.67-4.12)	0.27	1.38 (0.43-4.39)	0.59
Poorly differentiated	2.73 (0.87-8.56)	0.085	2.69 (0.46-15.75)	0.27
Lymphatic invasion				
Absent	1		1	
Present	2.74 (1.06-7.09)	0.038	1.38 (0.34-5.63)	0.65
Venous invasion				
Absent	1		1	
Present	1.04 (0.49-2.20)	0.91	0.94 (0.31-2.81)	0.91
Stage				
II/III	1		1	
IV	2.94 (1.20-7.21)	0.018	2.55 (0.63-10.40)	0.19
Postoperative chemotherapy				
No	1		1	
Yes	1.06 (0.49-2.26)	0.89	0.43 (0.16-1.16)	0.094
Type of operation‡				
SSR	1		1	
APR	1.28 (0.66-2.48)	0.46	0.77 (0.13-4.48)	0.77
'Curability'†				
'Curability B'	1		1	
'Curability C'	5.11 (2.18-11.96)	0.0002	4.43 (1.30-14.44)	0.017

* HR, hazard ratio; CI, confidence interval.
† Macroscopic type and 'Curability' were determined according to the Japanese Classification of Colorectal Carcinoma.[9] See "Patients and Methods".
‡ SSR, sphincter-preserving resection; APR, abdominoperineal resection.

revealed that 'Curability' of surgical resection[9] was only an independent predictor for disease-specific survival after non-curative surgery, whereas the type of operation was not. In this study, non-curative resection includes both 'Curability B' and 'Curability C' (refer to "Patients and Methods"). Therefore, we believe that aggressive resection for stage III/IV tumors of the rectum located at or below the peritoneal reflection should possibly be performed, even if the tumor has non-curative factors such as liver metastasis and/or invasion into adjacent organs. In addition, a SSR could also be recommended for such patients with stage III/IV tumors, if the procedure can be properly performed with an adequate distal resection margin. This is because the SSR may not affect disease-specific survival after non-curative surgery, as revealed in this study.

A SSR in this study included two types of operation (DST and CAA). In studies with long-term follow-up, low anterior resection with DST for rectal cancer provided acceptable local recurrence and survival rates comparable with those noted with APR.[3] In addition, CAA using transanal manual sutures for selected rectal tumors provided a good treatment for rectal cancer without compromising local control or survival.[4,15] The level of the tumor is still probably the most important factor influencing the type of operation in patients with resectable low rectal cancer.[6] It has been demonstrated

that a distal resection margin of 2 cm[16] or less[17] in SSRs do not compromise survival or local recurrence in carefully selected patients with rectal cancers.[1] In the current study, distal margin clearance with a 1-cm or a 2-cm distal resection margin for stage 0/I or stage II/III/IV tumor, respectively, was performed. As a result, in the current study, the type of operation (SSR or APR) did not affect survival after non-curative resection.

Current evidence suggests that at the time of surgery, patients with colorectal cancer have viable tumor cells in the bowel lumen and that these cells are capable of implanting and causing tumor growth.[18,19] Irrigation of the rectal stump before anastomosis after resection for carcinoma has been an accepted colorectal surgical practice.[18] We have routinely used rectal washout using diluted povidone iodine solution during SSR.

In conclusion, the type of operation (SSR or APR) did not affect disease-specific survival after non-curative surgery. The results suggest that SSRs (DST or CAA), given appropriate execution of procedures, will provide a good quality of life without a permanent colostomy for patients with cancer of the rectum at or below the peritoneal reflection.

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