

Outcomes of patients with abdominoperineal resection (APR) and low anterior resection (LAR) who had very low rectal cancer

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Abstract

We compared the oncological outcomes of sphincter-saving resection (SSR) and abdominoperineal resection (APR) in 409 consecutive patients with very low rectal cancer (i.e., tumors within 3 cm from the anal verge); 335 (81.9%) patients underwent APR and 74 (18.1%) underwent SSR. The APR group comprised higher proportions of men (67.5% vs 55.4%, $P = .049$) and advanced-stage patients ($P < .001$). Preoperative chemoradiotherapy (PCRT) was more frequently administered in the SSR group (83.8% vs 52.8%, $P < .001$). Overall, the systemic and local recurrence rates were 29.1% and 6.1%, respectively. On stratification according to PCRT and pathologic stage, the mode of surgery did not affect the recurrence type. Moreover, recurrence-free survival (RFS) did not differ according to the mode of surgery in different cancer stages. RFS was associated with ypT and ypN stages in patients who received PCRT, while pN stage, lymphovascular invasion (LVI), and circumferential resection margin (CRM) involvement were risk factors for RFS in those who did not receive PCRT. Notably, SSR was not found to be a risk factor for RFS in either subgroup. Patients who were stratified according to cancer stage and PCRT also showed no differences in RFS according to the mode of surgery. Our results demonstrate that, regardless of PCRT administration, SSR is an effective treatment for very low rectal cancer, while CRM is an important prognostic factor for patients who did not receive PCRT.

Abbreviations: APR = abdominoperineal resection, CRM = circumferential resection margin, DFS = disease-free survival, ISR = intersphincteric resection, LVI = lymphovascular invasion, OS = overall survival, PCRT = preoperative chemoradiotherapy, PNI = perineural invasion, RFS = recurrence-free survival, SSR = sphincter-saving resection.

Keywords: abdominoperineal resection, oncological outcomes, preoperative chemoradiotherapy, rectal cancer, sphincter-saving resection

1. Introduction

Decades ago, low rectal cancer was a challenge for surgeons, with abdominoperineal resection (APR) being the standard treatment. However, advancements in surgical techniques such as ultra-low anterior resection and intersphincteric resection (ISR), enabled patients with low rectal cancer to undergo surgery without sacrificing the anal sphincter.^[1–3]

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The distal resection margin, which is an important determinant of local recurrence as well as survival, can be as short as 1 cm when total mesorectal excision is used.^[4–6] Downstaging and lower local recurrences after preoperative chemoradiotherapy (PCRT) also contribute to the success rates of sphincter-saving resection (SSR).^[7,8] Furthermore, the development of anastomotic devices has also simplified surgeries and shortened their durations, even for tumors located very low in the rectum.^[9,10]

When SSR is performed for very low rectal tumors that are close to the anal sphincter complex, the distal boundary of the resection is located in the anal canal. While small-scale studies have shown ISR to be generally safe,^[3,11,12] the oncological safety profile of the resection of very low rectal tumors with ambiguous external anal sphincter involvement and uncertain circumferential resection margin (CRM) remains unclear. Moreover, the clinicopathological heterogeneity of patients renders it difficult to interpret the currently published data.

Therefore, we aimed to identify the factors affecting the oncologic outcomes of SSR and APR, and to compare these modalities in various patient subgroups.

2. Methods

2.1. Patients

We retrospectively reviewed the medical records of the Asan Medical Center tumor registry to identify patients who underwent radical surgery for rectal cancer between January

2000 and December 2010. We excluded patients who presented with pathological stage IV cancer, or were lost to follow-up. This study was approved by the Institutional Review Board of the Asan Medical Center.

Patients who underwent PCRT received external beam radiation therapy (median dose, 50.4 Gy). Intravenous fluorouracil-based chemotherapy or capecitabine was administered as concomitant chemotherapy. At 6 to 8 weeks after PCRT completion, patients underwent radical resection (SSR or APR) according to the principles of total mesorectal excision. In patients who received PCRT, pathologic responses were evaluated in the resected specimens using the tumor regression grade scored using a 5-tier system: total regression with no residual tumor cells and only fibrotic mass; near-total regression with microscopic residual tumor (i.e., difficult to find) in the fibrotic tissue; moderate regression, dominant irradiation-related changes with residual tumor (i.e., easy to find); minimal regression, dominant tumor mass with obvious irradiation-related changes; and no regression and no evidence of irradiation-related changes (fibrosis, necrosis, and vascular change).

2.2. Study endpoints during the follow-up

The follow-up period ended when the subjects developed new onset recurrence, death, or lived beyond January 31, 2017. The primary endpoints were the time to the development of new onset recurrence and the time to death. Death was confirmed by referencing the Korea's National Death Registry. The type (local or systemic) of recurrence was investigated as a second endpoint.

2.3. Statistical analysis

Clinicopathological variables were compared using a cross-table analysis, a Fisher exact test with 2-sided verification, or Pearson Chi-square test and an unpaired *t* test, as appropriate. The influence of each variable on the survival time of the patient was calculated using the Kaplan–Meier method, and significant differences between survival times were evaluated using the log-rank test. The prognostic relevance of a single factor was determined using univariate Cox regression analysis, and

selected clinicopathological factors from univariate regression analysis were subjected to multivariate Cox regression analysis. Statistical and clinical importance were both considered for selecting variables of multivariate analysis. Statistical significance was defined as a *P*-value < 0.05. All calculations were performed using the SPSS software (version 21, SPSS, Inc., Chicago, IL).

3. Results

3.1. Patient characteristics

We included 409 patients who received treatment for very low rectal cancer involving a tumor located within 3 cm of the anal verge. The patients underwent either SSR or APR. For SSR, 60 underwent ultra-low anterior resection (uLAR) and 14 patients underwent uLAR with ISR, respectively.

The mean follow-up durations for patients who underwent SSR and APR were 55.7 ± 33.09 months and 75.52 ± 42.93 months, respectively ($P < .001$). The APR group comprised of a higher proportion of men than the SSR group; however, more patients in the SSR group received PCRT, and had earlier yp stages than those of the APR group. There were no differences in patient age, preoperative carcinoembryonic antigen (CEA) level, LVI, perineural invasion (PNI), or CRM involvement (Table 1).

After PCRT, APR group had more ycT3/4 [APR; 139 (78.6%) vs SSR; 43 (69.3%), $P = .004$] and there was no difference in ycN + patients [APR; 130 (73.4%) vs SSR; 45 (72.6%), $P = .761$]. Among patients treated with PCRT, age and sex were similar between the SSR and APR groups; furthermore, the tumor heights were 2.77 ± 0.39 cm and 2.13 ± 0.71 cm, respectively. The SSR group had significantly more patients with early yp stage ($P = .001$). The number of harvested lymph nodes, LVI, PNI, and CRM involvement were not significantly different between the SSR- and APR-treated groups (Supplemental Table 1, <http://links.lww.com/MD/B921>).

Among patients who did not undergo PCRT, the SSR group comprised a greater proportion of women, while the APR group comprised more men. The mean tumor heights for both the SSR and APR groups were within 3 cm from the anal verge; however, the mean tumor height in the APR group was significantly shorter

Table 1
Clinicopathological characteristics of the patients (n=409) (%).

Variables	SSR (n=74)	APR (n=335)	P
Age, mean \pm SD	57 \pm 10.6	55.6 \pm 10.7	.322
Gender			.049
Male	41 (55.4)	226 (67.5)	
Female	33 (44.6)	109 (32.5)	
PCRT	62 (83.8)	177 (52.8)	<.001
Location of tumor, cm from AV, mean \pm SD	2.79 \pm 0.37	2.24 \pm 0.69	<.001
Preoperative CEA	3.69 \pm 8.81	5.95 \pm 12.74	.146
(y)p Stage			<.001
I	33 (44.6)	51 (15.2)	
II	15 (20.3)	125 (37.3)	
III	26 (35.1)	159 (47.5)	
Lymphovascular invasion	8 (10.8)	59 (17.6)	.169
Perineural invasion	6 (8.1)	45 (13.4)	.247
CRM involvement	1 (1.4)	16 (4.8)	.330
Follow-up duration	55.7 \pm 33.09	75.52 \pm 42.93	<.001

APR=abdominoperineal resection, AV=anal verge, CEA=carcinoembryonic antigen, CRM=circumferential resection margin, PCRT=preoperative chemoradiotherapy, SD=standard deviation, SSR=sphincter saving resection.

Table 2
Type of recurrences according to sphincter preservation and PCRT (%).

Variables	PCRT			No PCRT		
	SSR	APR	P	SSR	APR	P
Stage I						
Recurrences	5/33 (15.2)	7/50 (14)	.884	0/0	0/1	—
Local	2/5 (40)	0	.152	—	—	—
Systemic	3/5 (60)	7/7 (100)		—	—	
Stage II						
Recurrences	0/10	20/59 (33.9)	.053	1/5 (20)	16/66 (24.2)	.83
Local	—	3/20 (15)	—	—	4/16 (25)	1.00
Systemic	—	17/20 (75)		1/1 (100)	12/16 (75)	
Stage III						
Recurrences	11/19 (57.9)	40/68 (58.8)	.942	3/7 (42.9)	41/91 (45.1)	.91
Local	2/11 (18.2)	10/40 (25)	.637	2/3 (66.7)	2/41 (4.9)	.018
Systemic	9/11 (81.8)	30/40 (75)		1/3 (33.3)	39/41 (95.1)	

APR=abdominoperineal resection, PCRT=preoperative chemoradiotherapy, SSR=sphincter saving resection.

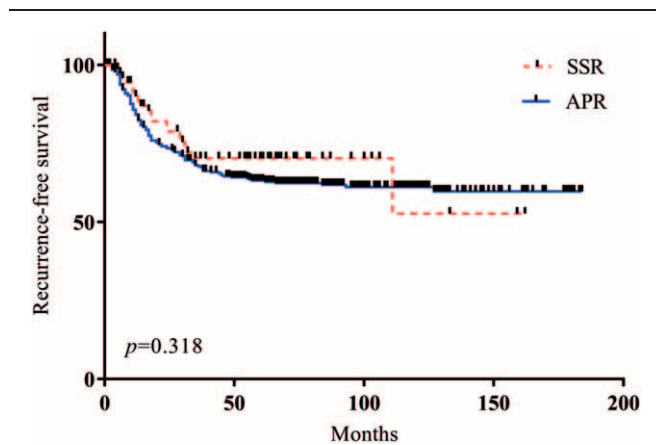


Figure 1. Recurrence-free survival (RFS). No significant difference in RFS was observed between sphincter-saving resection (SSR) and abdominoperineal resection (APR).

than in the SSR group. The pT stages were more advanced in the APR group, while there were no significant differences in pN stage, LVI, PNI, and CRM involvement between the SSR and APR groups. Adjuvant chemoradiation therapy were performed

to most of patients except 5 patients in APR group, but there were no significant difference between 2 groups ($P = .532$; Supplemental Table 2, <http://links.lww.com/MD/B921>).

3.2. Recurrence patterns and recurrence-free survival rates

The overall recurrence rates were 27% (20/74) versus 37% (124/335) in the SSR and APR groups, respectively ($P = .109$). Systemic recurrence was more prevalent than local recurrence in both groups, although not significantly ($P = .119$). The local recurrence rates were 8.1% ($n = 6$) in the SSR group and 5.7% ($n = 19$) in the APR group; on the other hand, the systemic recurrence rates were 18.9% ($n = 14$) versus 31.3% ($n = 105$) in the same groups, respectively. When the patients were stratified by PCRT and pathological stage, the recurrence rates were similar between the 2 surgical treatment groups. In contrast, APR-treated patients who did not receive PCRT had more systemic recurrences at pStage III compared to their SSR-treated counterparts ($P = .018$; Table 2).

The 5-year recurrence-free survival (RFS) rates for the SSR- and APR-treated groups were 70.2% and 84.2%, respectively ($P = .318$; Fig. 1). When the patients were stratified according to PCRT and yp stage (I, II, or III), the 5-year RFS rates were not significantly different (Figs. 2 and 3).

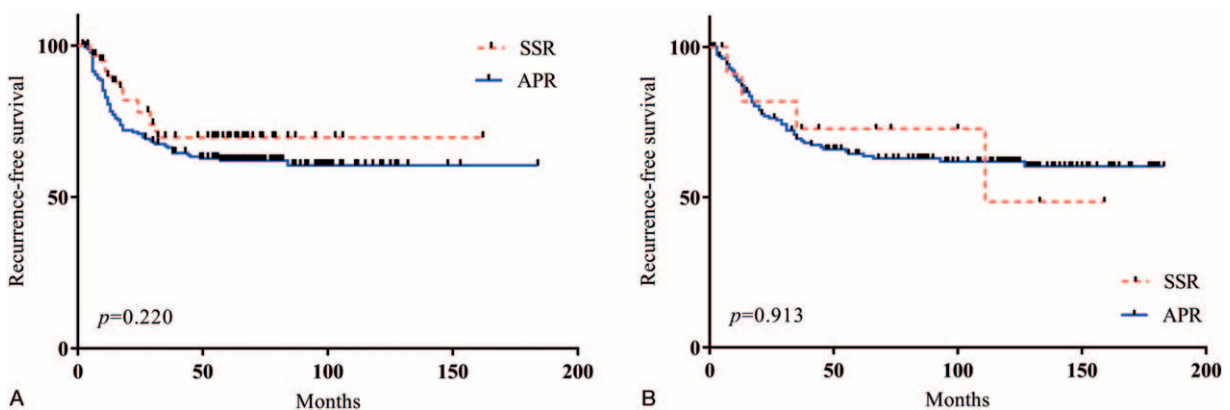


Figure 2. Recurrence-free survival (RFS) according to receipt of preoperative chemoradiotherapy (PCRT). RFS was similar in patients who underwent sphincter-saving resection (SSR) and abdominoperineal resection (APR) regardless of PCRT. (A) Comparison of RFS among patients who received PCRT. (B) Comparison of RFS among patients who did not receive PCRT.

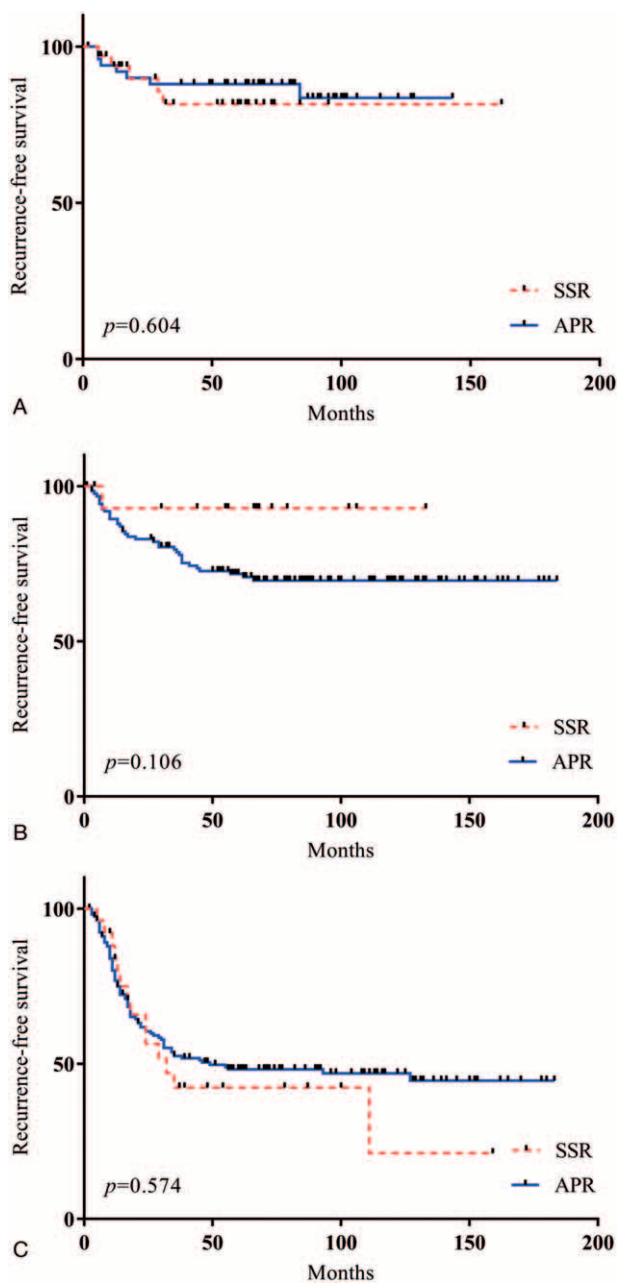


Figure 3. Recurrence-free survival (RFS) according to pathologic stages. RFS was similar in patients who underwent sphincter-saving resection (SSR) and abdominoperineal resection (APR) regardless of tumor stages. (A) (y)p Stage I. (B) (y)p Stage II. (C) (y)p Stage III.

3.3. Risk factors associated with recurrence free survival among patients according to treatment with preoperative chemoradiotherapy

For patients who received PCRT, sex, ypT and ypN stages, and LVI were associated with RFS on univariate analysis. On multivariate analysis, ypT and ypN stages were significantly associated with RFS, while the surgical mode was not (Table 3).

For patients who did not receive PCRT, pN stage, LVI, PNI, and CRM involvement were factors that were significantly associated with RFS. Among these, pN stage, CRM status, and LVI were independent risk factors for RFS on multivariate analysis; however, the mode of surgery was not (Table 4).

4. Discussion

In this study, SSR did not impair oncologic outcomes in patients with very low rectal tumors when stratified according to pathologic stage or PCRT administration.

Because of the diversity of surgical methods, it is important to take into account differences between indications. Hence, we classified patients according to their pathologic stage or whether they underwent PCRT. Furthermore, we excluded patients with pStage IV cancers and investigated only those with tumor heights within 3 cm of the anal verge to minimize any bias that may result from the heterogeneous characteristics of patients in each group.

However, the proportion patients in both group was very different. Sphincter preservation in low rectal cancer would be affected by surgeon's experience and philosophy. Six surgeons participated in the present study had a more than 300 cases of rectal cancer surgery. Therefore, the surgeon's experience would not affect sphincter preservation as technical aspect.

In addition to pathologic and therapeutic factors, the height of a low rectal tumor is a known key factor for local recurrence.^[13–17] The risk of local recurrence has been shown to be higher for tumors in the lower third of the rectum than for those in the upper third.^[13–16] In cases of very low rectal tumors that are adjacent to the anal sphincter complex, positive circumferential margins and tumor perforations can influence local recurrence and survival rates after surgery. To compare the oncological outcomes between SSR and APR, therefore, it is necessary to limit investigations to very low rectal cancers. Although several studies compared outcomes between SSR and APR, most included patients with higher tumors (i.e., 5–6 cm from the anal verge) that were relatively distant from the anal sphincter.^[18–20]

In this study, there was a higher proportion of men in the APR group, and PCRT was performed more frequently in the SSR group. Although most studies did not show differences according to sex, some showed that more men undergo APR compared to SSR.^[20,21]

The patients' ages in both groups in our study were not significantly different; however, aging is known to be associated with atrophy of the anal sphincter, and the incidence of fecal incontinence ranges from 2% to 17% in the population at large.^[22] Moreover, old age is a contributing factor to postoperative incontinence after low anterior resection.^[23] Even though age was not associated with oncologic outcomes after surgery for very low rectal cancer, we should note that age is an important consideration when determining the treatment options for patients with low rectal cancer.

ISR was reported to show oncological outcomes that were comparable to conventional low anterior resection of very low rectal cancers.^[24,25] Most related studies reported favorable oncologic outcomes following ISR; however, patients in these studies also exhibited heterogeneity of tumor heights, local recurrence rates, and 5-year survival rates.

A Japanese study of patients who underwent SSR and APR, which is the largest of its kind to date, found that SSR produced higher overall survival (OS) rates than APR, although disease-free survival (DFS) rates were similar.^[12] However, the positions of the tumors in their study were relatively high (up to 5 cm from the anal verge), and some of their patients who underwent SSR experienced extensive surgeries. Moreover, the number of patients who had received PCRT was different in each subgroup (36% in the SSR subgroup vs none in the APR group). Klose et al^[19] also reported comparable DFS rates with SSR and APR for patients with rectal tumors within 5 cm from the anal verge;

Table 3**Multivariate analysis of the factors associated with 5-year recurrence-free survival among patients treated with PCRT.**

Variables	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
Gender						
Male	1		.015			
Female	1.406	0.884–2.238				
SSR						
SSR	1		.227	1		.794
APR	1.400	0.811–2.417		1.078	0.613–1.896	
ypT stage						
ypT0–2	1		<.001	1		.009
ypT3–4	2.522	1.559–4.079		2.007	1.194–3.376	
ypN stage						
0	1		<.001	1		<.001
1	3.649	2.297–5.795		3.222	1.995–5.203	
2	3.268	1.557–6.858		2.371	1.093–5.145	
Location of tumor, cm from AV	0.856	0.635–1.154	.309			
CRM involvement	1.103	0.404–3.012	.848			
Lymphovascular invasion	2.082	1.101–3.938	.024	1.160	0.596–2.260	.662
Perineural invasion	1.665	0.952–2.913	.074	1.044	0.581–1.876	.885

APR = abdominoperineal resection, AV = anal verge, CEA = carcinoembryonic antigen, CI = confidence interval, CRM = circumferential resection margin, PCRT = preoperative chemoradiotherapy, SD = standard deviation, SSR = sphincter-saving resection.

their study included similar numbers of patients who received PCRT in each surgery subgroup. However, they performed no additional analyses of factors associated with oncologic outcomes.

In our study, the incidence and type of recurrence were not statistically different between the SSR and APR groups. Although there have been many controversial reports regarding influence of PCRT on OS, it generally known to improve local control.^[17,26] The pathologic stage is also an independent predictive factor for oncologic outcome after treatment according to most previous studies. When patients were stratified according to PCRT use and pathologic stage in our study, the incidences and patterns of recurrence did not differ among patients with different cancer stages. However, in patients with Stage III disease who

underwent SSR but did not receive PCRT, the local recurrence rate was higher than that of the APR group even though CRM involvement was similar between the 2 groups. However, the number of patients in that group was too small (n=3); thus, a reliable analysis was not possible. Adjuvant chemoradiotherapy was also potential associated factors with oncologic outcomes. In the present study, patients who received adjuvant treatment were not different between 2 groups. Although completion of adjuvant treatment was not reported because of limitation of medical record, the compliance rate in our institution was high based on the previous reports^[27] and it might not be a major detrimental factor for oncologic outcomes.

CRM involvement is a well-known risk factor for RFS after rectal cancer surgery^[28]; however, we found no association

Table 4**Multivariate analysis of the factors associated with 5-year recurrence-free survival among patients treated without PCRT.**

Variables	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
Gender						
Male	1		.401			
Female	1.240	0.750–2.048				
SSR						
SSR	1		.914	1		.706
APR	1.058	0.384–2.915		0.821	0.295–2.286	
pT stage						
pT1–2	1		.690	1		.776
pT3–4	1.182	0.509–2.746		1.138	0.467–2.773	
pN stage						
0	1		<.001	1		.001
1	1.607	0.847–3.046	.146	1.626	0.855–3.092	.138
2	4.122	2.191–7.754	<.001	3.273	1.709–6.270	<.001
Location of tumor, cm from AV	0.919	0.631–1.338	.662			
CRM involvement	8.850	3.589–21.823	<.001	5.374	2.142–13.481	<.001
Lymphovascular invasion	3.353	2.017–5.574	<.001	2.618	1.524–4.497	<.001
Perineural invasion	2.205	1.171–4.152	.014	1.443	0.731–2.851	.291

APR = abdominoperineal resection, AV = anal verge, CEA = carcinoembryonic antigen, CI = confidence interval, CRM = circumferential resection margin, PCRT = preoperative chemoradiotherapy, SD = standard deviation, SSR = sphincter-saving resection.

between CRM involvement and RFS in patients who received PCRT. Of note, our patients underwent long-course PCRT; however, there are insufficient studies of the effect of long-course PCRT on positive CRM status. Additionally, only one trial investigated CRM after short-course PCRT, and found that PCRT lowered the local recurrence rate in the intermediate margin but not in the positive margin.^[29] Furthermore, LVI was not investigated as a variable in most studies.^[11,19,30] In our previous study of outcomes following ISR, PNI was an influencing factor for DFS and OS, while LVI was not; however, we did not perform stratification according to PCRT.^[3]

This study had some limitations. First, it was retrospective and included analyses of relatively small patient subgroups. Even though we strove to minimize differences between the subgroups of patients who underwent SSR and those who underwent APR, differences in clinicopathological and treatment profiles remained. Indeed, when we do categorization of patients according to pathologic stage and PCRT treatment, the number of patients in each cohort is even more decreased. Therefore, statistical significance of surgery type for oncologic outcome has limitation for analysis in this subgroup. Second, adjuvant chemoradiotherapy is an important treatment for oncologic outcome. Even though, there was no statistical difference between SSR and APR group, but we cannot verify whether adjuvant treatments were completed in patients who were underwent the treatment in other institutions. Third, we did not elucidate the functional outcomes and postoperative complications of SSR and APR, which are also important considerations when deciding on the treatments for low rectal cancer. Nevertheless, this study is valuable in that it focused on rectal cancer that is near the anal sphincter, which is an actual concurrent indication for SSR and APR, and analyzed different prognostic factors according to whether PCRT was performed.

5. Conclusion

SSR was the preferred treatment option for patients with very low rectal cancer. We show that the oncological outcome of SSR was comparable to that of APR in a highly selected group of patients, regardless of PCRT administration. Pathologic nodal stage was a common independent risk factor for RFS, again, regardless of the use of PCRT. On the other hand, CRM was significantly associated with RFS in patients who did not receive PCRT, but not in those who did. Additional well-designed, large-scale studies should be performed to investigate the oncological and functional outcomes of SSR. We plan to perform prospective study to evaluate influence of surgery type on oncologic outcome and functional outcome for patients who treated with chemoradiotherapy.

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