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Factors Associated With Oncologic Outcomes Following Abdominoperineal or Intersphincteric Resection in Patients Treated With Preoperative Chemoradiotherapy

A Propensity Score Analysis

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Abstract: Due to selection bias, the oncologic outcomes of APR and ISR have not been compared in an interpretable manner, especially in patients treated with preoperative CRT. To assess factors influencing oncologic outcomes in patients with locally advanced low rectal cancer treated with preoperative chemoradiotherapy (CRT) followed by abdominoperineal resection (APR) or intersphincteric resection (ISR).

Between 2006 and 2011, 202 consecutive patients who underwent APR or ISR after preoperative CRT for locally advanced rectal cancer were enrolled in this study. The median follow-up period was 45.3 months (range: 5–85.2 months). Multivariate and propensity score matching (PSM) analyses were performed to reduce selection bias.

Of the 202 patients, 40 patients (19.8%) underwent APR and 162 (80.2%) required ISR. In unadjusted analysis, patients undergoing APR had a higher 5-year local recurrence ($P < 0.001$) and distant metastasis rate ($P = 0.01$), respectively. However, the higher local recurrence rate for APR persisted even after PSM, and these findings were verified in the multivariate analyses. Moreover, patients with advanced tumors, as assessed by restaging magnetic resonance imaging and luminal circumferential involvement, had a significantly higher local recurrence rate after APR compared with ISR.

This is the first PSM based analysis providing evidence of a worse oncologic outcome after APR compared with ISR. In addition, the results of the subgroup analysis suggest that a more radical modification of the current APR is required in cases of advanced cancer.

Abbreviations: APR = abdominoperineal resection, CEA = carcinoembryonic antigen, CRM = circumferential resection margin, CRT = chemoradiotherapy, DMFS = distant metastasis-free survival, ISR = intersphincteric resection, LAR = low anterior resection, LRFS = local recurrence-free survival, MRI = magnetic resonance image, PSM = propensity score matching, TME = total mesorectal excision, TRG = tumor regression grade.

INTRODUCTION

Rectal cancer accounts for approximately 30% of colorectal cancers and is a leading cause of cancer death worldwide.[1] The introduction of total mesorectal excision (TME) and preoperative chemoradiotherapy (CRT) has dramatically decreased the local recurrence rates and improved survival in rectal cancer patients.[2] However, these improvements have been relatively modest for patients with very low rectal cancer, compared with those with mid-to-upper rectal cancer.[3] This poor prognosis of low rectal cancer is mainly ascribed to the insufficient resection plane of the current abdominoperineal resection (ARP) technique, which is still regarded as the standard treatment for low rectal cancer.[4] Indeed, many studies have shown that APR is associated with a high frequency of circumferential resection margin (CRM) involvement and greater tumor perforation.[3–8] However, it is still unknown whether the worse outcome in patients undergoing APR rather than restorative resection is related to tumor biology, surgical, and/or surgeon-specific technique, or patient factors.[5] With these variable confounding factors, the lack of standardization of surgery causes a wide variation in APR rates depending on the geographical area or period over which the study was conducted.[9–11] For example, in the Dutch trial that included 27% of tumors located within 5 cm of the anal verge, APR was performed after preoperative CRT in 28% of cases, suggesting that most low rectal cancers were treated by APR.[11] The heterogeneous surgical treatment of low rectal cancer is also apparent in a United States-based study in which the rate of APR varied between 6% and 100%. Despite these wide variations, the use of APR has been consistently declining worldwide.[9,10,12] This may be accounted for in part by the growing use of intersphincteric resection (ISR) as an alternative to APR. ISR is usually combined with preoperative CRT and is used in cases where a stapling technique cannot be applied.[13,14]

The invasion to the external sphincter is currently considered an absolute oncological indication for APR. In this regard, the assessment of tumor depth is very important and influences the selection of the surgical method in low rectal cancer.[15] Although magnetic resonance imaging (MRI) has shown the best accuracy for preoperative staging,[16,17] restaging MRI (postchemoradiation MRI) is not as accurate as preoperative MRI due to the difficulty in assessing diffuse fibrotic changes in the initial tumor area.[18,19] In this clinical setting, an important, but unanswered, question is whether APR of a low rectal cancer after CRT has different oncological outcomes to

TABLE 1. Comparison of Patients Characteristics Before and After Propensity Score Matching

Characteristics	Before Matching			After matching		
	ISR (n = 162)	APR (n = 40)	P	ISR (n = 40)	APR (n = 40)	P
Age (yr)	64.8 ± 9.9	69.5 ± 12.1	0.01	67.3 ± 11.2	69.5 ± 12.1	0.38
Sex (male/female)	122/40 (75.3/24.7%)	29/11 (72.5/27.5%)	0.71	27/13 (67.5/32.5%)	29/11 (72.5/27.5%)	0.62
Body mass index (kg/m^2)	23.4 ± 3.2	22.8 ± 3.4	0.29	22.9 ± 3.1	22.8 ± 3.4	0.86
ASA class (1−2/3)	154/8 (95.1/4.9%)	36/4 (90.0/10.0%)	0.23	37/3 (92.5/7.5%)	36/4 (90.0/10.0%)	0.69
ymrT category			0.09			0.46
0−1	26 (16.0%)	4 (10.0%)		5 (12.5%)	4 (10.0%)	
2	36 (22.2%)	6 (15.0%)		11 (27.5%)	6 (15.0%)	
3	96 (59.3%)	26 (65.0%)		23 (57.5%)	26 (65.0%)	
4	4 (2.5%)	4 (10.0%)		1 (2.5%)	4 (10.0%)	
ymrN category (negative/positive)	120/42 (74.1/25.9%)	22/18 (55.0/45.0%)	0.01	31/9 (77.5/22.5%)	22/18 (55.0/45.0%)	0.03
Distance from anal verge (cm)	4.1 ± 1.4	2.9 ± 1.3	<0.001	3.0 ± 1.0	2.9 ± 1.3	0.61
CEA before neoadjuvant treatment (ng/mL)	9.5 ± 27.8	11.1 ± 24.0	0.74	14.2 ± 49.5	11.1 ± 24.0	0.71
CEA after neoadjuvant treatment (ng/mL)	3.8 ± 11.9	4.1 ± 4.9	0.88	6.4 ± 22.3	4.1 ± 4.9	0.55
Tumor size (cm)	2.7 ± 1.4	3.9 ± 1.8	<0.001	2.7 ± 1.4	3.9 ± 1.8	0.01
CRM (negative/positive)	152/10 (93.8/6.2%)	33/7 (82.5/17.5%)	0.17	35/5 (87.5/12.5%)	33/7 (82.5/17.5%)	0.53
Distal margin (cm)	1.7 ± 1.7	3.7 ± 3.3	0.01	1.2 ± 0.8	3.7 ± 3.3	<0.001
Pathologic T category			0.55			0.68
0	30 (18.5%)	5 (12.5%)		4 (10.0%)	5 (12.5%)	
1	13 (8.0%)	1 (2.5%)		4 (10.0%)	1 (2.5%)	
2	44 (27.2%)	11 (27.5%)		11 (27.5%)	11 (27.5%)	
3	70 (43.2%)	21 (52.5%)		20 (50.0%)	21 (52.5%)	
4	5 (3.1%)	2 (5.0%)		1 (2.5%)	2 (5.0%)	
Pathologic N category (negative/positive)	128/34 (79.0/21.0%)	29/11 (72.5/27.5%)	0.37	30/10 (75.0/25.0%)	29/11 (72.5/27.5%)	0.79
TRG			0.56			0.78
0−1	33 (20.4%)	11 (27.5%)		9 (22.5%)	11 (27.5%)	
2−3	102 (63.0%)	24 (60.0%)		27 (67.5%)	24 (60.0%)	
4	27 (16.7%)	5 (12.5%)		4 (10.0%)	5 (12.5%)	
T-category downstaging (yes/no)	57/105 (35.2/64.8%)	9/31 (22.5/77.5%)	0.12	15/25 (37.5/62.5%)	9/31 (22.5/77.5%)	0.14
N-category downstaging (yes/no)	87/75 (53.7/46.3%)	17/23 (42.5/57.5%)	0.20	20/20 (50.0/50.0%)	17/23 (42.5/57.5%)	0.50
Luminal circumference involved (%)			<0.001			0.11
<25%	89 (54.9%)	10 (25.0%)		18 (45.0%)	10 (25.0%)	
25−50%	40 (24.7%)	12 (30.0%)		9 (22.5%)	12 (30.0%)	
50−75%	19 (11.7%)	6 (15.0%)		8 (20.0%)	6 (15.0%)	
≥75%	14 (8.6%)	12 (30.0%)		5 (12.5%)	12 (30.0%)	
Histologic differentiation			0.01			.08
Well/moderate differentiated	150 (92.6%)	32 (80.0%)		38 (95.0%)	32 (80.0%)	
Poor/undifferentiated	12 (7.4%)	8 (20.0%)		2 (5.0%)	8 (20.0%)	
Lymphovascular invasion (negative/positive)	152/10 (93.8/6.2%)	34/6 (85.0/15.0%)	0.06	38/2 (95.0/5.0%)	34/6 (85.0/15.0%)	0.13
Perineural invasion (negative/positive)	135/27 (83.3/16.7%)	25/15 (62.5/37.5%)	0.01	27/13 (67.5/32.5%)	25/15 (62.5/37.5%)	0.63
Number of lymph nodes retrieved	16.4 ± 9.7	13.4 ± 6.9	0.06	14.3 ± 8.7	13.4 ± 6.8	0.62

APR = abdominoperineal resection; CEA = carcinoembryonic antigen; CRM = circumferential resection margin; ISR = intersphincteric resection; TRG = tumor regression grade.

ISR, especially in tumors for which it is virtually impossible to define a safe resection plane. Hence, we conducted this study to compare the clinicopathologic factors and oncologic outcome in patients with locally advanced low rectal cancers who were treated using preoperative CRT, followed by either APR or ISR. In addition, in order to minimize the selection bias described above, the propensity score matching (PSM) was used.

METHODS

Between 2006 and 2011, 202 consecutive patients who underwent APR or ISR after receiving neoadjuvant CRT for locally advanced (radiological T3-4 and/or N+) rectal cancer were enrolled in this study. Patients who had distant metastases at presentation or recurrent disease were excluded. This study was approved by the scientific review and ethics committee of our institution. Cancer was staged using pelvic MRI (n = 144) and ERUS (n = 58) to determine the extent of local disease at presentation. The median time between the end of neoadjuvant CRT and the restaging MRI was 32 days (range, 22–37 days) and was performed in 198 patients. Abdominopelvic computed tomography (CT), chest CT or X-ray imaging, and positron emission tomography (PET)-CT were used to determine the extent of extrapelvic disease. The location of the tumor was defined as the distance from its lowest margin to the anal verge as measured by rigid sigmoidoscopy.

Details of the preoperative chemoradiation have been published previously.[20,21] Briefly, a total dose of 5040 Gy in 25 fractions of 180 cGy/d over 5 weeks was delivered. Chemotherapy consisted of continuous intravenous infusion of 5-fluorouracil (5-FU; 425 mg/m^2/d) and leucovorin (20 mg/m^2/d) during the first and fifth weeks of radiotherapy. One hundred ninety-three patients (95.5%) received postoperative chemotherapy, the majority (81.8%) of whom were administered 5-FU/leucovorin, while the others (18.2%) received 5-FU/leucovorin with either oxaliplatin or irinotecan, or oral capecitabine.

Experienced surgeons performed radical oncological surgery, including total mesorectal excision, high vascular ligation (inferior mesenteric artery and vein), and en bloc resection of adjacent involved organs, 6 to 8 weeks following the completion of CRT.[20,22,23] Although the decision to perform sphincter-preserving surgery was based on a variety of clinical factors (distance from the anal verge, response to neoadjuvant treatment, preoperative anal sphincter function, and the patient's preference), this procedure was not used when the tumor had invaded the external sphincter. For APR, transabdominalmesorectal excision was performed in the same manner as ISR down to the pelvic floor, and the perineal resection was then started with dissection in the ischiorectal space, and completed with en bloc resection of the internal and external sphincter complex and rectum altogether.

Rectal tumors were staged by 2 gastrointestinal pathologists on the basis of the final pathological features, and in accordance with the seventh UICC tumor-node-metastasis (TNM) staging system.[24] The circumferential resection margin (CRM) was considered positive if microscopic tumor was identified within 1 mm of the surgical resection margin. Tumor regression grade (TRG) was defined on the basis of the ratio of fibrosis to residual cancer and was scored as follows; grade 0, no regression; grade 1, minor regression (dominant tumor mass with obvious fibrosis in 25% or less of the tumor mass); grade 2, moderate regression (26% ≤ fibrosis <50%); grade 3 (fibrosis ≥50%); and grade 4, total regression (no viable tumor cells, fibrotic mass only).[25]

Patients were followed up at 3-month intervals for 2 years, then at 6-month intervals for the next 3 years, and once annually thereafter. Follow-up examinations were conducted on a semiannual basis or when disease recurrence was suspected, and included physical examination, serum carcinoembryonic antigen (CEA) assay, chest X-ray or CT, abdomino-pelvic CT or MRI, and colonoscopy. PET-CT was selectively used when recurrence was strongly suspected based on CT or MRI findings. Recurrence was determined by clinical and radiological examinations and/or pathological confirmation. Local recurrence was defined as recurrent disease in the pelvis, including the anastomosis. Distant metastasis was defined as recurrent disease outside the pelvis. The main pattern of recurrence was recorded as the first site of detectable lesion during the follow-up period.[20,22]

Statistical Analyses

To identify the factors associated with each surgical method in the entire cohort, univariate analysis was performed, consisting of the χ^2 test for comparing proportions and the *t* test for comparing continuous variables. After comparing the demographic data between theses 2 groups, we performed propensity analysis using logistic regression analysis to compensate for potential baseline confounding variables. Subsequently, these groups were matched on a 1:1 basis using the "nearest neighbor" matching method.[26] The Kaplan–Meier method was used to calculate cumulative recurrence rates and the log-rank test was used to compare survival between groups. Variables with statistical significance ($P < 0.1$) in univariate analysis were further analyzed using the multivariate Cox forward stepwise logistic regression model. A 2-sided $P \leq 0.5$ was considered to be statistically significant. Statistical analyses were carried out using the SPSS statistical package (version 21.0; SPSS Inc, Chicago, IL) and R 2.14.1. The matching procedure was performed using Propensity Score Matching for SPSS.[27,28]

RESULTS

Patient Characteristics

A total of 202 patients who were followed up for a median period of 45.3 months (range, 5–85.2 months) were eligible for the present analysis, and of these, 40 (19.8%) underwent APR and 162 (80.2%) required ISR. Before PSM, there were considerable

TABLE 2. Logistic Regression of Treatment Selection (Propensity) for APR as Opposed to ISR

Factors	OR (95% CI)	*P* Value
Age (yr)	1.045 (1.004–1.089)	0.33
Distance from anal verge (cm)	0.394 (0.267–0.583)	<0.001
Luminal circumference involved (%)		0.01
<25%	Reference	
25–50%	2.240 (0.813–6.173)	
50–75%	3.547 (0.913–13.778)	
≥75%	14.084 (3.812–52.031)	

CI = confidential interval.

imbalances in the patients' demographical characteristics between the APR and ISR groups: patients selected for APR tended to be older than those in the ISR group, and patients in the APR group had tumors that were closer to the anal verge and larger than those in the ISR group, which was reflected in more extensive circumferential lumen involvement. In addition to these clinical parameters, patients undergoing APR tended to have significantly more adverse pathologic predictors, such as poorly differentiated tumor and perineural involvement. Positive CRMs were also more frequently identified in patients undergoing APR compared with ISR, although this difference was not significant (17.5% vs 6.2%, $P = 0.172$) (Table 1). Tumor perforation was observed in a total of 8 patients: 5 (3.1%) in the ISR group and 3 (7.5%) in the APR group. Multivariate logistic regression analysis of the preoperatively determined variables (age, sex, ASA score, ycT and N stage, distance from the anal

TABLE 3. Impact of Different Clinical and Pathologic Factors on Oncologic Outcome Before and After Propensity Score Matching

Factors	Before Matching (n = 202)					After Matching (n = 80)				
	No. of Patients	5-Year LRFS (%)	P	5-Year DMFS (%)	P	No. of Patients	5-Year LRFS (%)	P	5-Year DMFS (%)	P
All	202	85.3		71.1		80	74.5		63.0	
Age (yr)			0.31		0.68			0.32		0.35
≤61	58	89.5		70.8		14	85.7		55.6	
>61	144	83.5		71.7		66	72.0		64.6	
Sex			0.65		0.18			0.83		0.12
Male	151	84.6		73.1		56	73.7		66.9	
Female	51	87.0		65.4		24	74.1		52.6	
Distance from anal verge			0.57		0.71			0.54		0.16
≤4cm	92	83.6		72.2		59	76.3		66.2	
>4cm	110	86.8		69.4		21	69.8		54.8	
Pathologic T category			0.01		<0.001			0.01		0.01
0–2	104	94.0		87.6		36	91.4		79.1	
3–4	98	75.8		52.7		44	60.0		50.1	
Pathologic N category			0.01		<0.001			0.05		<.001
Negative	157	90.0		81.9		59	80.4		71.7	
Positive	45	68.4		34.4		21	57.4		35.6	
CRM			<0.001		0.62			0.01		0.71
Negative	187	89.0		72.0		68	81.0		68.0	
Positive	15	46.1		52.5		12	34.7		0.0	
Differentiation			0.01		0.34			0.04		0.10
Well/moderate	182	87.3		71.5		70	65.3		68.4	
Poorly	20	65.2		68.2		10	50.0		58.3	
Lymphovascular invasion			<0.001		0.01			0.62		0.54
No	186	88.1		75.1		72	63.6		67.1	
Yes	16	50.9		28.4		8	60.0		61.4	
Perineural invasion			0.01		<0.001			<.001		0.01
No	160	89.6		80.8		52	76.4		76.9	
Yes	42	68.2		32.9		28	39.0		45.0	
Luminal circumference Involved (%)			<0.001		0.08			0.01		0.21
<50%	151	91.8		73.5		49	87.4		67.9	
≥50%	51	64.8		64.7		31	52.2		55.6	
Grouped TRG			0.01		0.02			0.23		0.20
4	32	100.0		93.4		9	88.9		91.7	
2 + 3	126	85.9		67.2		51	60.6		64.6	
0 + 1	44	72.6		62.9		20	52.8		51.2	
Surgical method			<0.001		0.01			0.01		0.24
ISR	162	91.0		74.9		40	71.2		78.2	
APR	40	60.0		52.5		40	52.5		52.5	
Number of lymph nodes retrieved			0.01		0.33			0.01		0.22
<12	71	95.7		75.3		33.0	93.8		69.7	
≥12	131	79.5		68.4		47.0	59.3		58.9	

APR = abdominoperineal resection; CEA = carcinoembryonic antigen; CRM = circumferential resection margin; ISR = intersphincteric resection; TRG = tumor regression grade; LRFS = local recurrence-free survival; DMFS = distant metastasis-free survival.
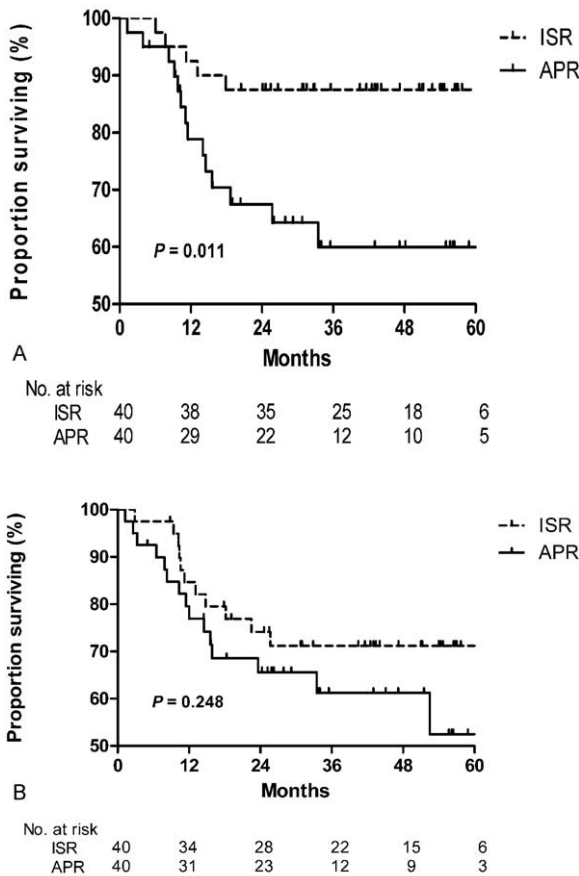
FIGURE 1. Kaplan–Meier curves depicting distant metastasis-free survival and local recurrence-free survival according to the surgery type. APR = abdominoperineal resection; ISR = intersphincteric resection.

verge, tumor size, and circumferential extent) revealed that surgeons more frequently performed APR in patients who were older and had a tumor with extensive luminal involvement and/or was closer to the anal verge (Table 2). In addition to these 3 variables, pathologic T and N categories, CRM, and the number of lymph nodes retrieved were all assessed by constructing 1:1 matched-pairs and, after matching, the 2 groups were balanced with the exception of maximal tumor size ($P = 0.01$).

PROGNOSIS

The actuarial 5-year local recurrence-free survival and distant metastases-free survival rates for the whole cohort were 85.3% and 71.1%, respectively (Table 3). Patients undergoing APR had a higher 5-year local recurrence ($P < 0.001$) and distant metastasis rate ($P = 0.01$) (Figure 1). It was particularly noteworthy that the higher local recurrence rate for APR persisted even after PSM (Table 3), and these findings were verified in the multivariate analyses not only for the entire cohort but also after PSM (Table 4). In addition, patients with advanced tumors, as assessed by restaging MRI and luminal circumferential involvement, suffered local recurrence significantly more frequently if they had been treated using APR rather than ISR (Figure 2).

DISCUSSION

This study in patients with low rectal cancer treated with either APR or ISR after preoperative CRT shows that local failure is more common among the former, even after correcting for significant biases between these 2 groups. Furthermore, this difference in local recurrence was more pronounced among patients with advanced rectal cancers, as assessed preoperatively by their depth and degree of luminal invasion. As a result, in this subgroup, a more radical operation rather than conventional APR should be considered, if it is not possible to preserve the sphincter.

Our findings generally agree with previous studies, in which patients undergoing APR more frequently suffered local recurrence compared with patients undergoing restorative surgery.[3–7] It has also been suggested that inadequate excision, resulting in a greater CRM involvement and a less intact TME plane, is a major determinate of outcome. Nagtegaal et al [4] reported that local recurrence rates were higher among patients with positive CRMs, regardless of the surgical technique used, and a more positive margin was present in patients undergoing APR (30.4%) compared with anterior resection (AR) (10.7%, $P = 0.01$). On the basis of these findings, they attributed the poor oncologic outcome of the patients who underwent APR to an insufficient resection plane, and concluded that the current form of APR is a nonradical surgery. However, patients who had a positive CRM had a 5-year local recurrence rate of 30.4% after APR and 17.1% after AR. It is possible, therefore, that other factors may lead surgeons to select APR and are responsible to some extent for the higher local recurrence rates. In a similar setting, Reshef et al[5] demonstrated that patients had a worse outcome after APR rather than AR even in the absence of CRM. Taken together, although technical factors such as CRM involvement are important and obtaining a clear CRM is critical in reducing the risk of local recurrence, these findings suggest that there are also other factors influencing local control. Indeed, Reshef et al[5] expressed their opinion that matching the APR and restorative surgery groups for tumor-specific factors, patient factors, and technical factors would be necessary, and other previous studies were also not free from this type of selection bias.[5,6,8] Patients undergoing APR were on average older, had a higher ASA score, and a lower mean tumor distance from the anal verge. In addition, even adverse histologic features such as worse tumor differentiation, higher pathologic T stage, and a greater frequency of lymph node involvement were more common in patients undergoing APR. This is supported by a study comparing the use of APR and ISR following preoperative CRT, in which the former was performed more frequently for patients showing a lesser degree of tumor regression ($P = 0.01$).[6]

To our knowledge, our study is the first report applying PSM to assess the oncologic outcome of APR compared with ISR following the neoadjuvant CRT. We selected variables that were considered to be important factors based on the findings of previous studies, or our own multivariate analysis for this matching. Patients factors (age and sex), technical factors (CRM and the number of lymph nodes retrieved), and tumor factors (pathologic T and N categories, distance from anal verge, extent of luminal circumference, tumor differentiation, and perineural invasion) were selected and optimally adjusted. After compensating for bias in this way, patients who underwent APR still had significantly worse local control. We therefore suggest that the current APR method is insufficient to achieve local disease eradication when compared with ISR that does

TABLE 4. Multivariate Analysis for Metastases-Free and Local Recurrence-Free Survival After Chemoradiotherapy and Rectal Cancer Resection

Factors	Before Matching (n = 202)		After Matching (n = 80)	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Local recurrence-free survival				
CRM		0.20		0.29
Negative	Reference		Reference	
Positive	3.056 (1.192−7.833)		3.012 (1.122−8.084)	
Number of lymph nodes retrieved		0.01		0.01
<12	Reference		Reference	
≥12	5.047 (1.506−16.914)		7.171 (1.626−31.626)	
Pathologic T stage		0.04		not applicable
0−2	Reference		not applicable	
3−4	2.618 (1.004−6.830)		not applicable	
Surgical method		0.01		0.04
ISR	Reference		Reference	
APR	3.056 (1.192−7.833)		2.945 (1.013−8.564)	
Metastases-free survival				
Pathologic N staging		0.01		0.01
Negative	Reference		Reference	
Positive	2.589 (1.388−4.827)		2.786 (1.247−6.227)	
Pathologic T stage		0.03		not applicable
0−2	Reference		not applicable	
3−4	2.356 (1.086−5.112)		not applicable	
Perineural involvement		0.01		0.01
Negative	Reference		Reference	
Positive	2.628 (1.421−4.858)		3.668 (1.604−8.388)	

APR = abdominoperineal resection; CRM = circumferential resection margin; ISR = intersphincteric resection; NS = not statistically significant.

achieve an acceptable local recurrence rate, even for advanced stage disease. APR may thus ultimately be modified to more extensive surgery, especially for advanced disease.

Theoretically, the ISR technique or a modified version of it could allow a sphincter-preserving operation for the majority of patients who underwent APR for low rectal cancer, even if the tumor invades the anal canal.[29,30] In agreement with these reports, 305 (88.4%) patients underwent sphincter preserving surgery (143; LAR, 162; ISR) after preoperative CRT in our study. Furthermore, the local recurrence rate remains within a favorable range regardless of tumor stage in patients who undergo ISR, despite the current lack of consensus on the best type of surgery for patients with very low rectal cancer. Surgeons would prefer a stapled anastomosis if they could avoid dissecting some, or all of the anal sphincter. However, as stated above, it was even more difficult to decide whether to use APR and ISR for patients who have undergone radiotherapy. Currently, the invasion of the sphincter muscle or an undifferentiated tumor with aggressive characteristics is regarded as an absolute indication for APR.[15,29] Base on this guideline, relatively few patients actually undergo APR, especially as sphincter invasion is rare above the anal canal.[15,30] Holzer et al[15] reported that the external anal sphincter was infiltrated by cancer in 2 (5%) of 40 patients with histologically verified adenocarcinoma of the lower rectum but without evidence of distant metastases. Similarly, Shirouzeet al[30] demonstrated that only 2 (2.7%) of 75 patients in whom the lowest edge of the tumor was located more than 2 cm above the dentate line showed external sphincter invasion. In this present study, we also found that only 2 (5%) of 40 patients treated with APR showed pathological sphincter invasion. Therefore, when the tumor is located more than 2 cm from the dentate line, the decision as to which surgical method should be used is based not on the likely oncologic outcomes but is instead a functional problem. As a result, the decision as to which surgical technique will provide the best oncological outcome is difficult when the tumor is located in the anal canal or within 2 cm of the dentate line. In this situation, when the tumor is assessed as ymrT3 or involves a luminal circumference greater than 50%, more radical surgery, such as cylindrical APR[31,32] will be needed. In this present study, we demonstrated that the ymrT category and the extent of luminal circumference could be used to help decide whether more radical surgery is required. MRI has been shown to be the best modality for assessing rectal tumor invasion, and for selecting the optimal surgical method.[15−17] Some authors have drawn attention to the limited accuracy of restaging MRI due to post-therapeutic inflammation and fibrosis.[18,19] In fact, the discrimination is more prominent when analyzed using the ypT rather than the ymrT category; the 5-year local recurrence-free survival rates in patients who underwent APR and ISR, and who were confirmed to have tumor stage ypT3-4, were 81.0% and 39.5%, respectively (*P* = 0.01), but they were 83.3% and 50.2%, respectively, when analyzed in patients with ymrT3-4 tumors (*P* = 0.02). The number of cancer cells in post-therapeutic inflammation and fibrosis is usually overestimated.[18] In a recently published meta-analysis[33] evaluating the accuracy of restaging MRI it was shown that most T0 rectal cancers could not be accurately identified, although only a
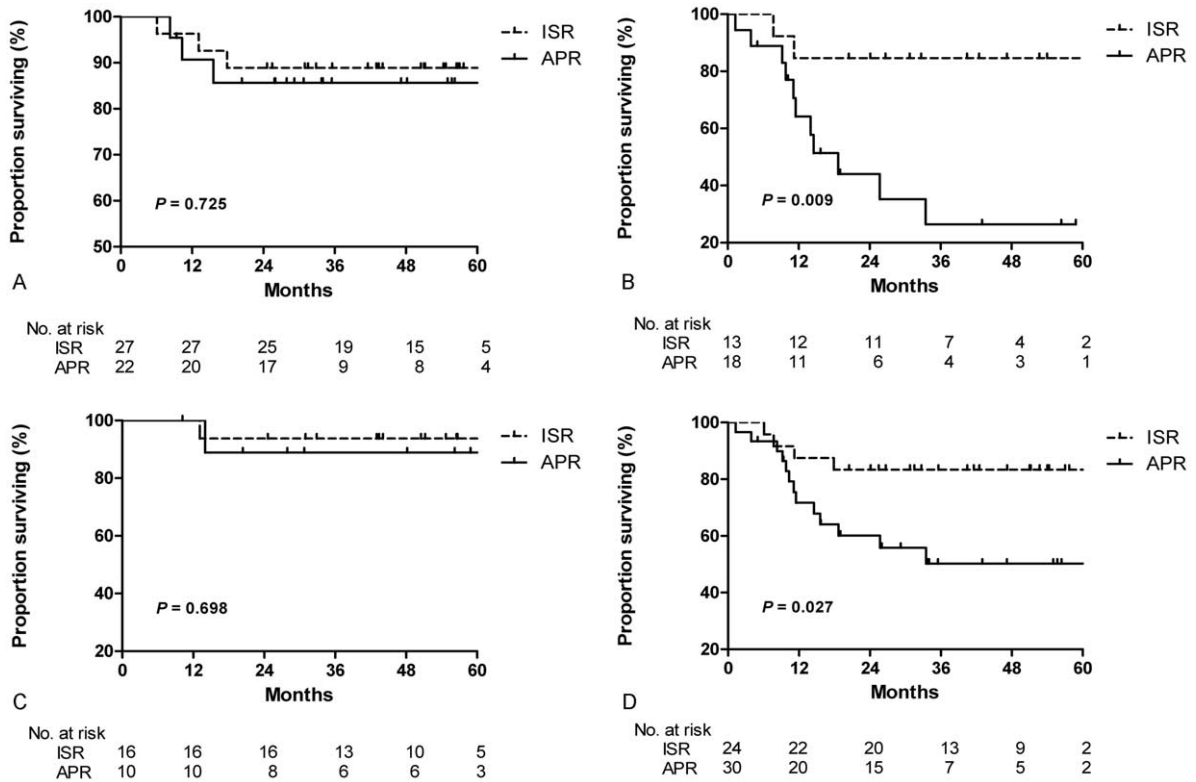
FIGURE 2. Kaplan–Meier curves depicting local recurrence-free survival of patients who underwent abdominoperineal resection (APR) or intersphincteric resection (ISR). Local recurrence rates with respect to luminal circumferential involvement; A <50%, B ≥50%. Local recurrence rates with respect to restaging magnetic resonance image findings; C, ymrT0–2, D, ymrT3–4.

few were misdiagnosed (sensitivity; 15.3%, specificity; 94.6%). In contrast, T3-4 lesions were correctly diagnosed, although T2 lesions were apt to be over-staged to the T3-4 category. However, it is still a valuable diagnostic method as it can prevent under-treatment. Moreover, MR sensitivity and specificity for CRM involvement were 85.4% and 80.0%, respectively. This means that restaging MRI is a critical tool for the treatment of locally advanced rectal cancer. Finally, as pointed out by Rullier et al,[34] careful digital rectal examination when the anal sphincter is fully relaxed would be more helpful than any other preoperative diagnostic tool. Our findings suggest that this selection method worked well in patients treated with ISR. We demonstrated that the local recurrence rate in patients with a ypT3-4 tumor was similar to that of the whole patient population (86.1% vs 91.0%).

This study has a number of limitations. First, the exact indication of APR is not included. As discussed above, invasion of the external sphincter was rare, and some of the factors that may have influenced the choice of surgical method could not always be determined. Second, it can be argued this study includes too few patients, and in fact, although tumor perforation is regarded as an important predictive factor for local recurrence following resection of low rectal cancer, we could not fully assess its impact in our study due to its rarity. Finally, more refined MRI predictors, such as CRM involvement, were not used.[7] In a future study, a more detailed and informative analysis based on preoperative MRI may provide more individualized treatment guidelines.

In conclusion, APR is still essential for the treatment of low rectal cancer following preoperative CRT. However, we found that there was a significantly worse outcome after APR compared with ISR in terms of local disease eradication, even after risk adjustment in propensity score analyses. This suggests that the current APR method needs to be modified in advanced disease. A more detailed preoperative diagnostic guideline is needed for the individualized treatment of patients with very low rectal cancer after preoperative CRT.

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