pulmonary disease. Therefore, it appears that a colonic J-pouch reconstruction after ISR may confer extra risk on males with intraoperative transfusion and/or pulmonary disease. Since males have a longer anal canal than females, the presence of a bulky J-pouch and anastomosis may increase the sphincteric squeeze pressure and worsen anastomotic blood and oxygen supply, thereby predisposing to leakage. Thus, in the presence of other risk factors, countermeasures including a switch to other reconstruction methods may need to be considered.

There are limitations to the present study. First, the study design is retrospective, and this may cause biases. Especially, because all or nearly all patients had complete bowel preparation, elective surgery by high-volume colorectal specialists, pelvic drainage, and defunctioning stoma and did not have neoadjuvant chemoradiotherapy, the significance of these factors could not be evaluated in this study. Second, because the numbers of events were limited particularly for severe leakage, many other risk factors which were significant in the previous studies on leakage after anterior resection were not significant in this study. Thus, further confirmation with a larger number of patients would be preferable.

In conclusion, the present retrospective exploratory study suggests that intraoperative blood transfusion and pulmonary disease are independently significant risk factors for overall and severe anastomotic leakage after ISR, and a colonic J-pouch was associated with severe leakage. By taking account of these factors, we may be able to stratify high-risk patients and prepare countermeasures. However, because numbers of patients and events in this study were limited, further investigation and validation are warranted with larger datasets or in future prospective trials.

Acknowledgements This study was supported in part by a Grant-in-Aid for Clinical Research for Evidence Based Medicine and a Grant-in-Aid for Cancer Research from the Ministry of Health, Labor and Welfare, and a Grant from the Foundation for Promotion of Cancer Research in Japan.

References

1. Nicholls RJ, Hall C. Treatment of non-disseminated cancer of the lower rectum. Br J Surg 1996;83:15–18.
2. Basso N, Minervini S, Marcelli M. Modified abdominotransanal resection for cancer of the lower third of the rectum. Dis Colon Rectum 1987;30:641–643.
3. Kusunoki M, Shoji Y, Yanagi H, Fujita S, Hatada T, Sakanoue Y, Yamamura T, Utsunomiya J. Modified anoabdominal rectal resection and colonic J-pouch anal anastomosis for lower rectal carcinoma: preliminary report. Surgery 1992;112:876–883.
4. Schiessel R, Karner-Hanusch J, Herbst F, Teleky B, Wunderlich M. Intersphincteric resection for low rectal tumors. Br J Surg 1994;81:1376–1378.
5. Kusunoki M, Yanagi H, Shoji Y, Yamamura T, Utsunomiya J. Anoabdominal rectal resection and colonic J pouch-anal anastomosis: 10 years' experience. Br J Surg 1997;84:1277–1280.
6. Gamagami RA, Liagre A, Chiotasso P, Istvan G, Lazorthes F. Coloanal anastomosis for distal third rectal cancer: prospective study of oncologic results. Dis Colon Rectum 1999;42:1272–1275.
7. Schiessel R, Novi G, Holzer B, Rosen HR, Renner K, Holbling N, Feil W, Urban M. Technique and long-term results of intersphincteric resection for low rectal cancer. Dis Colon Rectum 2005;48:1858–1865.
8. Rullier E, Laurent C, Bretagnol F, Rullier A, Vendrely V, Zerbib F. Sphincter-saving resection for all rectal carcinomas: the end of the 2-cm distal rule. Ann Surg 2005;241:465–469.
9. Saito N, Moriya Y, Shirouzu K, Maeda K, Mochizuki H, Koda K, Hirai T, Sugito M, Ito M, Kobayashi A. Intersphincteric resection in patients with very low rectal cancer: a review of the Japanese experience. Dis Colon Rectum 2006;49(10 Suppl):S13–S22.
10. Chamlou R, Parc Y, Simon T, Bennis M, Dehni N, Parc R, Tiret E. Long-term results of intersphincteric resection for low rectal cancer. Ann Surg 2007;246:916–921.
11. Akasu T, Takawa M, Yamamoto S, Fujita S, Moriya Y. Incidence and patterns of recurrence after intersphincteric resection for very low rectal adenocarcinoma. J Am Coll Surg 2007;205:642–647.
12. Nesbakken A, Nygaard K, Lunde OC. Outcome and late functional results after anastomotic leakage following mesorectal excision for rectal cancer. Br J Surg 2001;88:400–404.
13. Ptok H, Marusch F, Meyer F, Schubert D, Gastinger I, Lippert H. Impact of anastomotic leakage on oncological outcome after rectal cancer resection. Br J Surg 2007;94:1548–1554.
14. Vignali A, Fazio VW, Lavery IC, Milsom JW, Church JM, Hull TL, Strong SA, Oakley JR. Factors associated with the occurrence of leaks in stapled rectal anastomoses: a review of 1,014 patients. J Am Coll Surg 1997;185:105–113.
15. Rullier E, Laurent C, Garrelon JL, Michel P, Saric J, Parneix M. Risk factors for anastomotic leakage after resection of rectal cancer. Br J Surg 1998;85:355–358.
16. Law WI, Chu KW, Ho JW, Chan CW. Risk factors for anastomotic leakage after low anterior resection with total mesorectal excision. Am J Surg 2000;179:92–96.
17. Mäkelä JT, Kiviniemi H, Laitinen S. Risk factors for anastomotic leakage after left-sided colorectal resection with rectal anastomosis. Dis Colon Rectum 2003;46:653–660.
18. Matthiessen P, Hallböök O, Andersson M, Rutegård J, Sjödahl R. Risk factors for anastomotic leakage after anterior resection of the rectum. Colorectal Dis 2004;6:462–469.
19. Yeh CY, Changchien CR, Wang JY, Chen JS, Chen HH, Chiang JM, Tang R. Pelvic drainage and other risk factors for leakage after elective anterior resection in rectal cancer patients: a prospective study of 978 patients. Ann Surg 2005;241:9–13.
20. Gastinger I, Marusch F, Steinert R, Wolff S, Koeckerling F, Lippert H. Protective defunctioning stoma in low anterior resection for rectal carcinoma. Br J Surg 2005;92:1137–1142.
21. Peeters KC, Tollenaar RA, Marijnen CA, Klein Kranenbarg E, Steup WH, Wiggers T, Rutten HJ, van de Velde CJ, Dutch Colorectal Cancer Group. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. Br J Surg 2005;92:211–216.
22. Eriksen MT, Wibe A, Norstein J, Haffner J, Wiig JN. Anastomotic leakage following routine mesorectal excision for rectal cancer in a national cohort of patients. Colorectal Dis 2005;7:51–57.
23. Millan M, García-Granero E, Flor B, García-Botello S, Lledo S. Early prediction of anastomotic leak in colorectal cancer surgery by intramucosal pH. Dis Colon Rectum 2006;49:595–601.
24. Matthiessen P, Hallböök O, Rutegård J, Simert G, Sjödahl R. Defunctioning stoma reduces symptomatic anastomotic leakage

after low anterior resection of the rectum for cancer: a randomized multicenter trial. Ann Surg 2007;246:207–214.
25. Borowski DW, Kelly SB, Bradburn DM, Wilson RG, Gunn A, Ratcliffe AA. Impact of surgeon volume and specialization on short-term outcomes in colorectal cancer surgery. Br J Surg 2007;94:880–889.
26. Kruschewski M, Rieger H, Pohlen U, Hotz HG, Buhr HJ. Risk factors for clinical anastomotic leakage and postoperative mortality in elective surgery for rectal cancer. Int J Colorectal Dis 2007;22: 919–927.
27. Tang R, Chen HH, Wang YL, Changchien CR, Chen JS, Hsu KC, Chiang JM, Wang JY. Risk factors for surgical site infection after elective resection of the colon and rectum: a single-center prospective study of 2,809 consecutive patients. Ann Surg 2001;234:181–189.
28. Jonsson K, Jensen JA, Goodson WH 3rd, Scheuenstuhl H, West J, Hopf HW, Hunt TK. Tissue oxygenation, anemia, and perfusion in relation to wound healing in surgical patients. Ann Surg 1991;214:605–613.
29. Hopf HW, Hunt TK, West JM, Blomquist P, Goodson WH 3rd, Jensen JA, Jonsson K, Paty PB, Rabkin JM, Upton RA, von Smitten K, Whitney JD. Wound tissue oxygen tension predicts the risk of wound infection in surgical patients. Arch Surg 1997;132:997–1004.
30. Whooley BP, Law S, Murthy SC, Alexandrou A, Wong J. Analysis of reduced death and complication rates after esophageal resection. Ann Surg 2001;233:338–344.
31. Hallböök O, Påhlman L, Krog M, Wexner SD, Sjödahl R. Randomized comparison of straight and colonic J pouch anastomosis after low anterior resection. Ann Surg 1996;224:58–65.
32. Ho YH, Brown S, Heah SM, Tsang C, Seow-Choen F, Eu KW, Tang CL. Comparison of J-pouch and coloplasty pouch for low rectal cancers: a randomized, controlled trial investigating functional results and comparative anastomotic leak rates. Ann Surg 2002;236:49–55.

J Gastrointest Surg (2010) 14:500–505
DOI 10.1007/s11605-009-1105-2

ORIGINAL ARTICLE

Long-Term Outcome of Metachronous Rectal Cancer Following Ileorectal Anastomosis for Familial Adenomatous Polyposis

Tomohiro Yamaguchi · Seiichiro Yamamoto · Shin Fujita · Takayuki Akasu · Yoshihiro Moriya

Received: 19 July 2009 / Accepted: 9 November 2009 / Published online: 25 November 2009

Abstract
Background Total colectomy with ileorectal anastomosis (IRA) for familial adenomatous polyposis (FAP) carries a potential risk of metachronous cancer in the residual rectum. This study evaluated the risk of cancer development in the residual rectum.
Methods Ninety-six patients who underwent initial surgery for prevention and cure of FAP were studied, and a clinicopathologic comparison was conducted between 59 patients who underwent IRA and 24 who underwent total proctocolectomy.
Results The 5-year overall survival rates were 94% after IRA and 95% after total proctocolectomy with no significant difference. The incidence of dense-type rectal polyps (4/17, 24%) was significantly higher in patients who developed metachronous rectal cancer following IRA compared to that in patients who did not (1/39, 3%). Moreover, 60% of patients with dense-type colon polyps developed metachronous rectal cancer compared to 24% in patients without and 80% of those with dense type rectal polyps developed metachronous rectal cancer compared to 25% without. Endoscopic surveillance of the eight Tis or T1 patients was performed at intervals of 6 months to 1 year after IRA but was not performed in three T3 patients for more than 2 years.
Conclusions Effective IRA requires selection of patients without invasive rectal cancer and without dense rectal polyps in whom long-term postoperative follow-up of the residual rectum is possible.

Keywords Ileorectal anastomosis · Familial adenomatous polyposis · Metachronous rectal cancer

Introduction

The prevention of advanced colorectal cancer requires colectomy or proctocolectomy in patients with familial adenomatous polyposis (FAP) at a premalignant stage.[1] In Western countries, total proctocolectomy with ileal-pouch anal anastomosis (IPAA) is often indicated for preventive and curative resection, whereas total colectomy with ileorectal anastomosis (IRA) is more common in Japan. IPAA is an ideal strategy to reduce the risk of postoperative cancer in the residual rectum but often causes postoperative dyschezia[2,3] and deteriorated quality-of-life (QOL).[2–4] IRA provides superior postoperative bowel function compared to IPAA and is sometimes indicated in selected patients in Japan on this basis; however, the risk of cancer in the residual rectum is unavoidable after IRA, and prevention requires long-term endoscopic surveillance.

It has been suggested that IRA should be limited to patients with non-dense colorectal polyps;[5–8] patients with

A part of this paper was presented at the 2nd Biennial Scientific Meeting of International Society for Gastrointestinal Hereditary Tumors held between March 27 and 30, 2007 in Yokohama, Tokyo.

T. Yamaguchi · S. Yamamoto (✉) · S. Fujita · T. Akasu · Y. Moriya
Colorectal Surgery Division, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: seyamamo@ncc.go.jp

T. Yamaguchi
Department of Surgery, Shiga University of Medical Science, Seta Tsukinowa-cho, Otsu, Shiga 520-2192, Japan

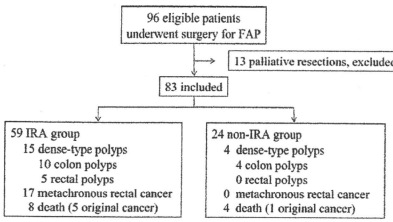

Figure 1 Study profile.

attenuated familial adenomatous polyposis;[9] young females who desire future pregnancy;[10] and patients for whom long-term follow-up can be conducted;[8] however, only a few studies have compared cancer recurrence and prognosis between IRA and IPAA. In this study, we examined these issues and identified risk factors for the development of metachronous cancer in the residual rectum following IRA.

Material and Methods

Ninety-six patients (male 62, female 34) who underwent initial surgery for prevention and cure of FAP at the National Cancer Center Hospital (Tokyo, Japan) between 1962 and 2007 were studied retrospectively. Patients who underwent palliative resections (partial colectomy, abdominoperineal resection, or ileostomy) were excluded. A clinicopathologic comparison was conducted between 59 patients who underwent IRA (IRA group) and 24 (non-IRA group) who underwent total proctocolectomy with ileoanal anastomosis (IAA) or IPAA, or total proctocolectomy with ileostomy. Age at the first operation, sex, surveillance period, density of polyps, presence of coexisting cancer, recurrence, overall survival, and relapse-free survival were examined in the two groups. More than 2,000 polyps in colon tissue samples were defined as dense-type polyposis and less than 2,000 polyps were defined as non-dense type. The number of polyps was counted roughly by the pathologist in charge. Rectal polyposis with more than 20 polyps on endoscopy was defined as a dense type, and less than 20 polyps were defined as a non-dense type. Clinicopathological factors were also compared between subgroups of patients who did and did not develop cancer in the residual rectum following IRA. Patients with intramucosal carcinoma were included in the subgroup who developed cancer in the residual rectum. Background and surgical data were obtained from a retrospective study of medical records. Since the study was a single-center observational design, approval by the institutional review board was not required in the present study.

Fisher's exact test and chi-square test were used for comparison between groups. Continuous nonparametric data were analyzed by the Mann–Whitney *U* test. Recurrence and survival rates were analyzed by the Kaplan–Meier method, and comparison of outcomes was conducted by log-rank test. A significant difference was assumed at $P<0.05$. Analyses were performed by using software (JMP, Version 7. SAS Institute Inc., Cary, NC).

Results

Figure 1 shows the study profile. Chronological changes in the operative procedure are shown in Table 1. IRA was performed in 42% patients (18/43) from 1962 to 1990 and in 77% (41/53) from 1991 to 2007.

The patient demographics are summarized in Table 2. Significantly more patients had coexisting rectal cancer in the non-IRA group; however, no significant differences were observed regarding the rate of patients with dense-type colorectal polyps between the two groups.

Prognosis was examined in all patients except for three Stage IV patients in the IRA group. The 5- and 10-year overall survival rates were 94% and 94%, respectively, in the IRA group, and 95% and 90%, respectively, in the non-IRA group, with no significant difference between groups (Fig. 2). There was also no significant difference in relapse-free survival rates between groups ($p=0.7111$; Fig. 3). There were eight deaths in the IRA group (five due to the original cancer and three of unknown cause) and four in the non-IRA group (one due to the original cancer, two due to other diseases, and one of unknown cause).

The patterns of cancer recurrence and metachronous cancer development in each group are shown in Table 3. Metachronous rectal cancer was detected in 17 patients in the IRA group.

A comparison of the 17 patients (30%) with metachronous cancer in the residual rectum and 39 patients (70%)

Table 1 Surgery for Familial Adenomatous Polyposis between 1962 and 2007

	1962–1990	1991–2007
IRA	18 (42)	41 (77)
IPAA	15 (35)	9 (17)
APR	5 (12)	1 (2)
Others	5 (12)	2 (4)
Total	43	53

Values in parentheses are percentages

IRA total colectomy with ileorectal anastomosis; *IPAA* total proctocolectomy with ileal-pouch anal anastomosis; *APR* abdominoperineal resection

Table 2 Patient Characteristics between IRA Group and Non-IRA Group

		IRA group (n=59)	Non-IRA group (n=24)	P value
Median age at operation (range)		30 (13–65)	31 (20–51)	0.9651
Sex	Male	35	19	0.1272
	Female	24	5	
Median follow-up (years)		8.9	16.1	0.1624
Colon polyps	Dense-type	10	4	1.0000
	Not dense-type	49	20	
Rectal polyps	Dense-type	5	0	0.3148
	Not dense-type	54	24	
Colon cancer	Present	30	7	0.0906
	Absent	29	17	
Rectal cancer	Present	5	7	0.0334
	Absent	54	17	
Pathological TNM stage for patients with cancer		31	11	
	0	12	2	0.5974
	I	5	2	
	IIA	1	0	
	IIB	0	0	
	IIIA	2	1	
	IIIB	5	4	
	IIIC	3	2	
	IV	3	0	

without cancer following IRA showed that cancer of the residual rectum occurred more frequently in patients with dense-type rectal polyps (p=0.0259; Table 4), and the incidence of dense-type rectal polyps (4/17, 24%) was significantly higher among those who developed metachronous rectal cancer following IRA compared to that in patients who did not (1/39, 3%). Moreover, 60% of patients with dense-type colon polyps developed metachronous rectal cancer compared to 24% in those without, and 80% of those with dense-type rectal polyps developed compared to 25% without.

Treatment after metachronous rectal cancer is demonstrated in Table 5. Initially, local therapy was performed for 10 of the 17 patients with cancer in the residual rectum, and surgery was performed on seven. Four of the 10 patients who initially received local treatment subsequently underwent radical surgery because of metachronous rectal cancer that could not be managed by endoscopic resection or pathological invasive cancer. Thus, surgery was required in 65% (11/17) of patients who developed cancer in the residual rectum. The surgery was performed at an average of 8.8 years after IRA (range 1.3–23.3 years).

Among the 11 patients who required radical surgery after IRA, eight with Tis-T1 invasion had undergone endoscopic surveillance at intervals of 6 months to 1 year after IRA, but the other three T3 patients did not undergo surveillance for more than 2 years before the second operation because of patient-related circumstances that had interrupted the

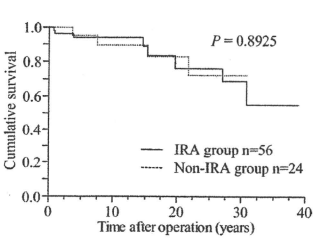

Figure 2 Overall survival rates in IRA and non-IRA groups.

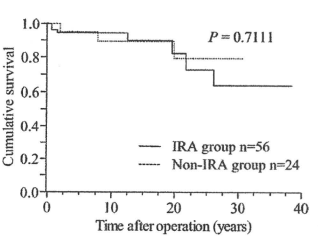

Figure 3 Relapse-free survival rates in IRA and non-IRA groups based on cancer recurrence.

Table 3 Pattern of Recurrence between IRA Group and Non-IRA Group

		IRA group (n=59)	Non-IRA group (n=24)
Metachronous cancer	Rectum	17	–
Recurrence	Liver	2	2
	Lung	0	0
	Small intestine	0	1
Total		19	3

Table 5 Treatment for Metachronous Rectal Cancer

Procedure	Initial treatment	Final treatment
Operation	7	11 (65)
Proctectomy with IAA or IPAA	5	9[a]
APR	2	2
Local resection	10	6 (35)
EMR	9	5
Trans-anal resection	1	1

Values in parentheses are percentages

IAA total proctocolectomy with ileoanal anastomosis; *IPAA* total proctocolectomy with ileal-pouch anal anastomosis; *APR* abdomino-perineal resection; *EMR* endoscopic mucosal resection

[a] One patient required total pelvic exenteration for the pelvic recurrence after IAA

postoperative surveillance. Regarding the surgical procedure of the 11 patients who required radical surgery after IRA, sphincter-preserving operations (IAA or IPAA) were performed in 88% (7/8) of patients with pathological Tis/T1 lesion, while 66.7% (2/3) of patients with pathological T3 lesion.

Discussion

A non-IRA procedure is ideal for preventive resection for patients with FAP to reduce the risk of metachronous cancer in the residual rectum, but IRA provides superior postoperative bowel function through alleviation of post-operative dyschezia and is sometimes indicated in Japan. Our findings demonstrate that IRA has no adverse effect on long-term prognosis, provided that appropriate surveillance is performed, despite the high risk of cancer development in the residual rectum. This suggests that IRA may be an option for selected patients who seem to be appropriately screened after IRA.

There have been several comparisons of IRA and non-IRA procedures, and IRA has been found to be superior to IPAA in that it provides a satisfactory level of postoperative defecation.[2,3] Some studies have reported improved QOL after IRA compared to IPAA,[2,3] but others have found no difference between these procedures based on findings from questionnaire surveys using the Short Form-36 Health Survey and the European Organization for Research and Treatment of Cancer Colorectal QoL Questionnaire.[4] Duijvendijk et al. had found no difference regarding QOL between the IRA and IPAA groups based on the responses to questionnaire surveys. Female fecundity has been found to deteriorate following IPAA compared with IRA,[10] which suggests that IRA might be superior in female patients who desire a future pregnancy, or IPAA should be performed after delivery. Meta-analysis by Aziz et al. of 12 reports published from 1991 to 2003 indicated that the development of adverse effects, such as bowel frequency, night defecation, and use of incontinence pads, was significantly lower after IRA than after IPAA, whereas fecal urgency was lower after IPAA.[11] Sexual dysfunction, dietary restriction, and postoperative complications did not differ between IRA and IPAA; however, the rate of reoperation within 30 days was significantly higher in patients who underwent IPAA than IRA (23.4% vs. 11.6%).[11]

The rate of cancer development in the residual rectum following IRA depends on the surveillance period and the

Table 4 Patients Characteristics with or without Metachronous Rectal Cancer after IRA

		Metachronous rectal cancer		P value
		Present (n=17)	Absent (n=39)	
Colon polyps	Dense-type	6 (60)	4 (40)	0.0520
	Not dense-type	11 (24)	35 (76)	
Rectal polyps	Dense-type	4 (80)	1 (20)	0.0259
	Not dense-type	13 (25)	38 (75)	
Colon cancer	Present	6 (22)	21 (78)	0.2520
	Absent	11 (38)	18 (62)	
Rectal cancer	Present	2 (50)	2 (50)	0.5770
	Absent	15 (29)	37 (71)	
Length of residual rectum	<11 cm	9 (35)	17 (65)	0.5702
	≥11 cm	8 (27)	22 (73)	

Values in parentheses are percentages

age of the patient.[12,13] Studies with follow-up periods of 5 years or longer have reported rates of 7–37%.[6,8,12–20] The risk rate of postoperative rectal cancer in the residual rectum in our study was 30% over a surveillance period of 8.9 years. This relatively high rate may have been due to the inclusion of Tis patients in the analysis. If the six patients with Tis tumors are excluded, the rectal cancer rate in this group would be only 20% (11/59). Although Tis lesions are regarded as adenomas in Western countries, it cannot be rejected that patients with Tis lesion in the residual rectum require resection of the lesion, and if local resection fails, radical surgery is indicated; therefore, patients with Tis lesions were included in the present study. However, most of the noninvasive lesions can be managed by endoscopic resection, thus, not requiring resection of the remnant rectum. Moreover, postoperative rectal cancer developed more often in patients with dense-type colorectal polyps (p=0.0259); therefore, we recommend that IRA is not indicated for patients with many colon polyps or those with 20 or more rectal polyps.

The correlation between the density of polyps and the rate of cancer development has been examined at a genetic level. Nieuwenhuis et al.[21] suggested that the severity of colonic polyposis may depend on the position of a mutation in the APC gene, with mutations between codons 1250 and 1464, and especially those at codon 1309, contributing to the severity of colonic polyposis. Other studies have proposed that mutations localized at the ends of the gene and in the alternatively spliced region of exon 9 cause a mild form of FAP, and it has been recommended that IRA should be limited to patients for whom a genetic diagnosis indicates a mild form of FAP.[6,9] Besides the density of polyps, development of a desmoid tumor should be considered in determining the indication for IRA, since a secondary proctectomy may be difficult to perform if cancer develops in the residual rectum in association with a desmoid tumor. Therefore, it has been proposed that IPAA should be selected for patients with a family history of desmoid tumor and those with a mutation located distal to codon 1444 in the APC gene.[1]

The stage at which cancer develops in the residual rectum clearly has a strong influence on prognosis. Vasen et al.[22] have reported that Dukes B, C, and D colon cancers account for 76% of cancers in the residual rectum, with most being detected at an advanced stage. In the present study, most patients were detected at an early stage, and Dukes B, C, and D colon cancers accounted for 29% (5/17). Detection at an early stage was arguably achieved by performing periodic endoscopic surveillance at intervals of 6 months to 1 year following surgery. Indeed, for the three T3 patients out of 11 patients who required further surgery, no endoscopic surveillance had been performed for 2 years or more before cancer was diagnosed; therefore, there may be no difference in prognosis after IRA and non-IRA procedures provided that appropriate surveillance is performed. Previous studies have shown that the main causes of death following IRA are cancer in the residual rectum, duodenal cancer,[23] and desmoid tumor;[24] however, duodenal and desmoid cancers may develop independently of the type of operative procedure. Therefore, IRA has no effect on overall survival when indicated appropriately in selected patients and with long-term periodic endoscopic surveillance to detect cancer in the residual rectum at an early stage. Vasen et al.[1] recommended intervals of 3 to 6 months for endoscopic follow-up of the rectum after IRA and suggested an indication for proctectomy in patients with multiple large (>5 mm) rectal adenomas with a high degree of dysplasia. Further acquisition of data is required to establish the appropriate interval for surveillance colonoscopy and to determine whether endoscopic resection is applicable following IRA.

Conclusion

Selection of an appropriate operative procedure for FAP requires consideration of a variety of factors, including the density of the colon or rectal polyps, whether future pregnancy is desired, the patient has a high risk of desmoid tumor, and the position of the mutation in an APC gene. Strict screening of patients will result in no difference in prognosis after IRA and non-IRA surgery, and we consider that the results demonstrated in the present study are essential in selecting suitable patients for IRA. Thus, IRA may be indicated for selected patients without invasive rectal cancer and without dense rectal polyps for whom frequent surveillance of the residual rectum can be performed over their lifetime.

References

1. Vasen HF, Moslein G, Alonso A, Aretz S, Bernstein I, Bertario L, Blanco I, Bulow S, Burn J, Capella G, Colas C, Engel C, Frayling I, Friedl W, Hes FJ, Hodgson S, Jarvinen H, Mecklin JP, Moller P, Myrhoi T, Nagengast FM, Parc Y, Phillips R, Clark SK, de Leon MP, Renkonen-Sinisalo L, Sampson JR, Stormorken A, Tejpar S, Thomas HJ, Wijnen J. Guidelines for the clinical management of familial adenomatous polyposis (FAP). Gut 2008;57:704–713.
2. Bjork J, Akerbrant H, Iselius L, Svenberg T, Oresland T, Pahlman L, Hultcrantz R. Outcome of primary and secondary ileal pouch-anal anastomosis and ileorectal anastomosis in patients with familial adenomatous polyposis. Dis Colon Rectum 2001;44:984–992.
3. Gunther K, Braunrieder G, Bittorf BR, Hohenberger W, Matzel KE. Patients with familial adenomatous polyposis experience better bowel function and quality of life after ileorectal anastomosis than after ileoanal pouch. Colorectal Dis 2003;5:38–44.

4. Van Duijvendijk P, Slors JF, Taat CW, Oosterveld P, Sprangers MA, Obertop H, Vasen HF. Quality of life after total colectomy with ileorectal anastomosis or proctocolectomy and ileal pouch-anal anastomosis for familial adenomatous polyposis. Br J Surg 2000;87:590–596.
5. Tonelli F, Valanzano R, Monaci I, Mazzoni P, Anastasi A, Ficari F. Restorative proctocolectomy or rectum-preserving surgery in patients with familial adenomatous polyposis: results of a prospective study. World J Surg 1997;21:653–658. discussion 9.
6. Bulow C, Vasen H, Jarvinen H, Bjork J, Bisgaard ML, Bulow S. Ileorectal anastomosis is appropriate for a subset of patients with familial adenomatous polyposis. Gastroenterology 2000;119: 1454–1460.
7. Valanzano R, Ficari F, Curia MC, Aceto G, Veschi S, Cama A, Battista P, Tonelli F. Balance between endoscopic and genetic information in the choice of ileorectal anastomosis for familial adenomatous polyposis. J Surg Oncol 2007;95:28–33.
8. Soravia C, Klein L, Berk T, O'Connor BI, Cohen Z, McLeod RS. Comparison of ileal pouch-anal anastomosis and ileorectal anastomosis in patients with familial adenomatous polyposis. Dis Colon Rectum 1999;42:1028–1033. discussion 33–4.
9. Nieuwenhuis MH, Mathus-Vliegen LM, Slors FJ, Griffioen G, Nagengast FM, Schouten WR, Kleibeuker JH, Vasen HF. Genotype-phenotype correlations as a guide in the management of familial adenomatous polyposis. Clin Gastroenterol Hepatol 2007;5:374–378.
10. Olsen KO, Juul S, Bulow S, Jarvinen HJ, Bakka A, Bjork J, Oresland T, Laurberg S. Female fecundity before and after operation for familial adenomatous polyposis. Br J Surg 2003;90:227–231.
11. Aziz O, Athanasiou T, Fazio VW, Nicholls RJ, Darzi AW, Church J, Phillips RK, Tekkis PP. Meta-analysis of observational studies of ileorectal versus ileal pouch-anal anastomosis for familial adenomatous polyposis. Br J Surg 2006;93:407–417.
12. Bjork JA, Akerbrant HI, Iselius LE, Hultcrantz RW. Risk factors for rectal cancer morbidity and mortality in patients with familial adenomatous polyposis after colectomy and ileorectal anastomosis. Dis Colon Rectum 2000;43:1719–1725.
13. Heiskanen I, Jarvinen HJ. Fate of the rectal stump after colectomy and ileorectal anastomosis for familial adenomatous polyposis. Int J Colorectal Dis 1997;12:9–13.
14. Nugent KP, Phillips RK. Rectal cancer risk in older patients with familial adenomatous polyposis and an ileorectal anastomosis: a cause for concern. Br J Surg 1992;79:1204–1206.
15. Bess MA, Adson MA, Elveback LR, Moertel CG. Rectal cancer following colectomy for polyposis. Arch Surg 1980;115:460–467.
16. Heimann TM, Bolnick K, Aufses AH Jr. Results of surgical treatment for familial polyposis coli. Am J Surg 1986;152:276–278.
17. De Cosse JJ, Bulow S, Neale K, Jarvinen H, Alm T, Hultcrantz R, Moesgaard F, Costello C. Rectal cancer risk in patients treated for familial adenomatous polyposis. The Leeds Castle Polyposis Group. Br J Surg 1992;79:1372–1375.
18. Sarre RG, Jagelman DG, Beck GJ, McGannon E, Fazio VW, Weakley FL, Lavery IC. Colectomy with ileorectal anastomosis for familial adenomatous polyposis: the risk of rectal cancer. Surgery 1987;101:20–26.
19. Bulow S. The risk of developing rectal cancer after colectomy and ileorectal anastomosis in Danish patients with polyposis coli. Dis Colon Rectum 1984;27:726–729.
20. Iwama T, Mishima Y, Utsunomiya J. The impact of familial adenomatous polyposis on the tumorigenesis and mortality at the several organs. Its rational treatment. Ann Surg 1993;217:101–108.
21. Nieuwenhuis MH, Vasen HF. Correlations between mutation site in APC and phenotype of familial adenomatous polyposis (FAP): a review of the literature. Crit Rev Oncol Hematol 2007;61:153–161.
22. Vasen HF, van Duijvendijk P, Buskens E, Bulow C, Bjork J, Jarvinen HJ, Bulow S. Decision analysis in the surgical treatment of patients with familial adenomatous polyposis: a Dutch-Scandinavian collaborative study including 659 patients. Gut 2001;49:231–235.
23. Nugent KP, Spigelman AD, Phillips RK. Life expectancy after colectomy and ileorectal anastomosis for familial adenomatous polyposis. Dis Colon Rectum 1993;36:1059–1062.
24. Arvanitis ML, Jagelman DG, Fazio VW, Lavery IC, McGannon E. Mortality in patients with familial adenomatous polyposis. Dis Colon Rectum 1990;33:639–642.

Langenbecks Arch Surg (2010) 395:545–549
DOI 10.1007/s00423-010-0642-1

ORIGINAL ARTICLE

Improving prediction of lateral node spread in low rectal cancers—multivariate analysis of clinicopathological factors in 1,046 cases

Kok-Yang Tan · Seiichiro Yamamoto · Shin Fujita · Takayuki Akasu · Yoshihiro Moriya

Received: 25 January 2010 / Accepted: 22 March 2010 / Published online: 2 April 2010

Abstract
Introduction This study aims to search for independent predictors of lateral node metastasis in low rectal cancers.
Materials and methods We analyzed 1,046 patients who underwent curative resection for lower rectal cancer in our prospectively collected database. All lymph nodes were dissected from the fresh specimen, and their locations were documented prospectively according to the classification by the Japanese Society of Cancer of the Colon and Rectum.
Results More than 35% of the patients had demonstrated upward nodal metastasis in the direction of the inferior mesenteric vessels, while 11% demonstrated lateral node metastasis, which was present in 17.3% of patients with T3 and T4 lesions. Multivariate analysis revealed five factors to be statistically significant independent predictors of lateral node metastasis: female sex, tumors that were not well differentiated, pathological T3 and above, positive microscopic lymphatic invasion, and positive mesorectal nodes. Using the variables sex, differentiation, T stage, and mesorectal nodes as risk factors, because these could be elucidated preoperatively, the presence of lateral node metastasis was then analyzed according to the number of positive risk factors. When there were fewer than three positive factors, the risk of lateral nodal spread was low (4.5%). When three or more risk factors were positive, the odds of lateral node metastasis were more than 7.5 times higher ($p<0.001$).
Conclusion The findings of this study provide a scoring system that can be used to guide the clinician to the presence of lateral node metastasis in low rectal cancers.

Keywords Rectal cancer · Lateral node spread · Lymph nodes · Risk factors

Introduction

Although the management of lateral node metastasis for low rectal cancers below the peritoneal reflection is still controversial [1–5], most authors agree on the importance of lateral lymph node metastasis in low rectal cancer [6], the reported incidence being between 13.8% [7] and 17.3% for pT3 and above lesions [8, 9].

It was previously elegantly demonstrated that it is the lower rectal cancers with deeper invasion that are associated with lateral node metastasis [9, 10]. However, independent risk factors of lateral node metastasis in low rectal cancers alone have yet to be elucidated. Some studies have attempted to identify some of these factors [8, 11], but these studies were relatively small and used a selected cohort. With the advent of better imaging modalities of the rectum and pelvis (transrectal ultrasonography, high-resolution computed to-

All listed authors contributed to the conception of the paper, data collection, and interpretation. All gave input during drafting and revision of the article and its final approval.

This paper is not funded by any source. There are no potential conflicts of interests of any of the authors with regards to the findings in this paper.

K.-Y. Tan · S. Yamamoto (✉) · S. Fujita · T. Akasu · Y. Moriya
Colorectal Surgery Division,
National Cancer Center Hospital, 5-1-1 Tsukiji,
Chuo-ku, Tokyo 104-0045, Japan
e-mail: seyamamo@ncc.go.jp

K.-Y. Tan
e-mail: kokyangtan@gmail.com

K.-Y. Tan
Department of Surgery, Alexandra Health,
Singapore, Singapore

mography (CT), and magnetic resonance imaging (MRI)), accurate preoperative evaluation of the presence of lateral node spread became possible; however, the quality of preoperative imaging differs among institutions, and there is a need to identify low rectal cancer patients at high risk of lateral spread even when imaging studies are negative.

This study aimed to identify independent predictors of lateral node metastasis in low rectal cancers by analyzing a large number of cases. This in turn will then help colorectal surgeons make treatment decisions for their patients preoperatively.

Materials and methods

Patients who underwent curative resection for rectal cancer below the peritoneal reflection between January 1980 and October 2008 at the National Cancer Center, Tokyo were reviewed. The level of the tumor was documented at the time of the resection. Surgery for low rectal cancers was low anterior resection, abdomino-perineal resection, Hartmann's operation, or pelvic exenteration for locally advanced tumors. All patient data were obtained from a prospectively collected database in the department.

The practice of lateral node dissection has evolved over the years. Routine bilateral node dissection for all clinical stage I, II, and II lower rectal cancers in the 1980s and early 1990s. With the advent of better imaging modalities of the rectum and pelvis (transrectal ultrasonography, high-resolution CT, and MRI) in the latter half of the 1990s, a more selective approach to patient selection was undertaken. Lateral node dissection was undertaken for patients with a clinical diagnosis of site in the lower rectum (distal to the middle Houston valve) and depth of invasion that was staged clinically to be T3 and above. Lateral node dissection was also undertaken when preoperative pelvic imaging using high-resolution CT or pelvic MRI revealed a lymph node in the lateral region that was more than 1 cm in size or if the surgeon found a clinically suspicious lateral node intraoperatively. Although, with these selection criteria, some patients with lateral lymph node metastases may have been missed; however, most of the patients who did not undergo lateral node dissection were patients with moderate to high risk for radical surgery, with relatively early stage tumors. We believe that the inclusion of these patients have the increased risk of bias because there are no data regarding lateral node status; therefore, the patients without lateral node dissection were excluded from the present study.

Adjuvant postoperative radiotherapy for low rectal cancers is not performed routinely after lateral node dissection. Preoperative radiotherapy is administered in locally advanced cases (clinical T4) and tumors that are very low (<5 cm from the anal verge) with bilateral lateral node involvement as judged by preoperative imaging [12].

Patients enrolled in the JCOG 0212* (https://center.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&recptno=R000000068&type=summary&language=E) study were included in this present study. Patients that were randomized to TME alone in this trial were followed up carefully, and their pattern of recurrence was documented if any. Patients found to have local recurrence in the region of the lateral nodes were classified as having positive lateral nodes at the primary resection.

There were 1,200 resection cases, and patients with no data on lateral node status were excluded. After exclusion, 1,046 patients from our database were analyzed.

All definitions are according to those set by the Japanese Society of Cancer of the Colon and Rectum [13]. Parameters analyzed were patient sex, tumor morphological type, tumor size measured from a freshly pinned out specimen, tumor differentiation, pathological T stage, and microscopic lymphatic and venous invasion in sections of the tumor. All lymph nodes were dissected from the fresh specimen, and their locations according to the classification by the Japanese Society of Cancer of the Colon and Rectum were documented prospectively.

Bivariate analysis was performed using chi [2] test using SPSS for Windows (SPSS Inc., Chicago, USA), version 15.0. Results are expressed as odds ratios with 95% confidence intervals. Stepwise logistic regression analysis was used in multivariate analysis to identify parameters that independently affect outcome. Only factors that were found on bivariate analysis to be statistically significant ($p<0.05$) were used in multivariate analysis.

Results

Patient and tumor characteristics are shown in Table 1. These characteristics are similar to other rectal cancer cohorts described in the literature. The median number of lymph nodes harvested was 30±19.8. Upward nodal metastasis in the direction of the inferior mesenteric vessels were present in 35.9% (n=377) of patients, while 11% (n=116) had demonstrated lateral node metastasis. Bivariate analysis revealed that female sex, size more than 3 cm, tumors that were not well differentiated, pathological T3 and above, positive microscopic lymphatic, and venous invasion in the tumor and positive mesorectal nodes were all statistically significant risk factors of lateral node metastasis (Table 1). Only 3.5% of patients with T1 and T2 lesions had lateral node metastasis, while the value was 17.3% for patients with T3 and T4 lesions.

Upon multivariate analysis of these factors, five factors were found to be statistically significant independent predictors of lateral node metastasis. These were female sex, tumors that were not well differentiated, pathological T3 and

Table 1 Patient and tumor characteristics

	Lateral lymph node status		*p* Value
	Positive (n=113)	Negative (n=933)	
Sex ratio (male/female)	60:53	646:287	0.001
Mean age (year)	58.60±10.99	59.48±11.28	0.433
Pathological T stage[a]			
T1 (n=189)	1	188	<0.001
T2 (n=301)	16	285	
T3 (n=516)	81	435	
T4 (n=32)	14	18	
Ratio of T1+T2/T3+T4	17:95	473:453	<0.001
Differentiation			
Well (n=525)	27	498	<0.001
Moderately (n=463)	66	397	
Poorly (n=25)	7	18	
Mucinous or signet ring cell (n=33)	13	20	
Ratio of well differentiated/not well differentiated	27:86	498:435	<0.001
Microscopic tumor lymphovascular invasion			
Lymphatic invasion (positive/negative)	78:35	358:575	<0.001
Venous invasion (positive/negative)	65:48	366:567	<0.001
Mean tumor size in cm (range)			
<3 cm:>3 cm	3:102	151:660	<0.001
Mesorectal nodes status (positive/negative)	84:29	293:640	<0.001

[a] Data missing for eight patients

above, positive microscopic lymphatic invasion, and positive mesorectal nodes (Table 2). Of these five, microscopic lymphatic invasion cannot be elucidated preoperatively.

Using sex, differentiation, T stage and mesorectal nodes as risk factors, the presence of lateral node metastasis was then analyzed according to the number of positive risk factors (Table 3). When there were fewer than three positive factors, the risk of lateral nodal spread was low (4.7%). When three or more risk factors were positive, the odds of lateral node metastasis were more than 7.5 times higher (hazard ratio 7.567, 95% CI 4.941–11.587, p<0.001).

When subgroup analysis was performed for T1 and T2 lesions only, 17 of 490 patients (3.5%) had lateral node metastasis. This became 36.4% (8 of 22) when the remaining three risk factors were present (hazard ratio 29.143, 95% CI 9.791–86.745).

Discussion

While the practice of lateral node dissection has been abandoned by most Western centers, in Japan, this procedure has remained part of the surgical treatment of rectal cancers with many important refinements since the 1970s [14, 15]. As such, it is not surprising that most of the data on lateral node metastasis in rectal cancers are from Japan [6]. Important data on the risk factors of lateral node metastasis were reported by Sugihara et al. [9] who performed multivariate analysis on 930 patients from 12 centers in Japan with upper and lower rectal cancers. The patients were treated between 1991 and 1998. After multivariate analysis of all pathological factors, only three were found to be independent risk factors: female sex, low rectal lesions, and tumors more than 4 cm in size; however, when only factors that can be

Table 2 Multivariate analysis for independent risk factors for lateral nodal spread

	Hazard ratio	95% CI	*p*
Male sex	*0.441*	*0.280–0.696*	*<0.001*
Size 3 cm and above	2.829	0.806–9.932	0.105
Not well differentiated	*2.251*	*1.354–3.744*	*0.002*
pT3 and above	*2.775*	*1.425–5.404*	*0.003*
Positive lymphatic invasion	*1.935*	*1.176–3.183*	*0.009*
Positive vascular invasion	1.298	0.822–2.051	0.263
Mesorectal nodes positive	*3.101*	*1.829–5.256*	*<0.001*

Significant factors in italics

Table 3 Risk of lateral node spread based on number of positive risk factors

Number of factors positive	*N*	Lateral node spread	Percentage
0	173	1	0.6
1	297	8	2.7
2	290	27	9.3
3	217	50	23.0
4	61	26	42.6

assessed preoperatively were analyzed, T stage of T3 and above and non-well differentiation became independent predictors as well. Of these factors, location in the lower rectum had the highest hazard ratio of 6.4 (95% CI 3.5–11.8). For this reason, we chose to only concentrate on tumors below the peritoneal reflection for this study.

For tumors of the lower rectum only, several studies have reported the risk factors for lateral spread. Ueno et al. [8] found low placement of the tumor, differentiation, and mesenteric nodes as independent risk factors in 237 patients, while in a smaller study on 96 patients, multivariate analysis was not performed likely due to inadequate numbers. The aim of this study was to analyze risk factors in a large number of patients so as to reduce random sampling error, thus giving the most accurate representation of patients with low rectal cancers. In order to obtain a large sample size, operations dating back to 1980 were included; as such, some factors including preoperative CT could not be included in this analysis. However, this study is very likely able to give the most accurate correlation of clinicopathological factors with lateral node spread to date.

In this study on a large number of patients, the most important risk factors found to have independently the highest hazard ratios are not dissimilar to those elucidated previously [8, 9]. In recent years, priority for lateral node dissection has been given to patients with low rectal lesions, T3 and above lesions, and when mesorectal nodes are detected, and this study confirms that this is a sound approach.

The findings from this study and the utility of a risk factor scoring system may further help surgeons to select patients for the management of lateral node metastasis. This may further be augmented by preoperative imaging modalities for lateral nodes. Female sex and cell differentiation can be easily determined preoperatively. A slightly bigger challenge is the clinical diagnosis of the T stage and the presence of mesorectal or lateral nodes using imaging modalities. Transrectal ultrasonography and pelvic MRI have been found to be very good modalities for determining the T stage and the presence of mesorectal nodes [16, 17]. An institution should choose the modality based on its own expertise and review their results, correlating preoperative diagnosis to pathological diagnosis. We feel that it will not be difficult for institutions to use this scoring system to predict the risk of lateral spread.

There has been much less experience on imaging involving lateral nodes, but increasing numbers of studies have emerged showing some efficacy using CT or MRI [18–20]. However, the problem of overstaging based on a single preoperative imaging modality is very real [6]. As such, single modality imaging can only be used as an adjuvant and not as sole assessment for the presence of positive lateral nodes. It is very likely that combined imaging and correlation with clinicopathological factors will provide the best accuracy. In another study by our center, focusing on patients with only advanced upper and lower rectal cancers with preoperative CT, it was demonstrated that similar risk factors used in combination with preoperative CT was most accurate in predicting lateral node spread [21].

One interesting finding from this study is that of patients with T1 or T2 lesions with lateral node metastasis. While the overall rate of lateral node metastasis was low, 3.5% of patients in this group had all three risk factors, and in this group of patients, more than one third had lateral node spread. We feel that for this small group of patients with three positive risk factors, imaging for lateral nodes should be performed with a view of managing the lateral nodes.

A recent study found that the approach to the management of cancers of the lower rectum by our center (described earlier) yielded a 5-year local recurrence rate of only 6.6% [22]. In an earlier study, we found that in patients with pathological N1 lymph node metastasis, the 5-year disease-free survival rate was 73.3% in patients who underwent lateral pelvic node dissection compared to 35.3% among those who did not [2]. These results suggest that it is important to address lateral node metastasis.

The treatment approach for patients with a high risk of lateral node metastasis is still very controversial and not within the scope of this discussion. It should be noted, however, that the survival rates of patients with lateral nodes do not suggest that it is a systemic disease [6, 9]. Most Western surgeons will employ radiotherapy, but there are now emerging reports of long-term adverse effects and functional problems from radiotherapy for rectal cancers [23–25]. On the other hand, the Japanese have been developing and refining lateral node dissection and have been achieving improved functional results over the recent years [15]. In Japan, the JCOG 0212 trial was started from June 2003. This is a multicenter trial randomizing patients to total mesorectal excision (TME) or TME plus lateral node dissection. The main aim of this trial was to answer the question of efficacy of lateral node dissection when there is no clinical imaging diagnosis of lateral node metastasis. The results of JCOG 0212 will only be available around 2016.

It cannot be denied that lateral node metastasis exists and should not just be passed off as systemic disease, and it is important to identify patients with a high-risk of lateral spread. These high-risk patients should be counseled carefully about these risks, implications, and treatment modalities. There are advantages and disadvantages to both radiotherapy and lateral node dissection, and it is important for patients to make a well-informed decision regarding the treatment of their cancer.

Conclusion

The findings of this study provide a scoring system that can be used to guide the clinician to the presence of lateral node metastasis in low rectal cancers. When there were fewer than three positive factors, the risk of lateral nodal spread was low (4.7%). When three or more risk factors were positive, the odds of lateral node metastasis were more than 7.5 times higher. Considering the outcome of the present study together with the analysis of JCOG 0212 trial, we believe that selection for lateral lymph node dissection can be improved.

References

1. Moriya Y, Hojo K, Sawada T, Koyama Y (1989) Significance of lateral node dissection for advanced rectal carcinoma at or below the peritoneal reflection. Dis Colon Rectum 32(4):307–315
2. Fujita S, Yamamoto S, Akasu T, Moriya Y (2003) Lateral pelvic lymph node dissection for advanced lower rectal cancer. Br J Surg 90(12):1580–1585
3. Kim TH, Jeong SY, Choi DH et al (2008) Lateral lymph node metastasis is a major cause of locoregional recurrence in rectal cancer treated with preoperative chemoradiotherapy and curative resection. Ann Surg Oncol 15(3):729–737
4. Mortenson MM, Khatri VP, Bennett JJ, Petrelli NJ (2007) Total mesorectal excision and pelvic node dissection for rectal cancer: an appraisal. Surg Oncol Clin N Am 16(1):177–197
5. Koch M, Kienle P, Antolovic D et al (2005) Is the lateral lymph node compartment relevant? Recent Results Cancer Res 165:40–45
6. Yano H, Moran BJ (2008) The incidence of lateral pelvic side-wall nodal involvement in low rectal cancer may be similar in Japan and the West. Br J Surg 95(1):33–49
7. Moriya Y, Sugihara K, Akasu T, Fujita S (1997) Importance of extended lymphadenectomy with lateral node dissection for advanced lower rectal cancer. World J Surg 21(7):728–732
8. Ueno M, Oya M, Azekura K et al (2005) Incidence and prognostic significance of lateral lymph node metastasis in patients with advanced low rectal cancer. Br J Surg 92(6):756–763
9. Sugihara K, Kobayashi H, Kato T et al (2006) Indication and benefit of pelvic sidewall dissection for rectal cancer. Dis Colon Rectum 49(11):1663–1672
10. Steup WH, Moriya Y, van de Velde CJ (2002) Patterns of lymphatic spread in rectal cancer. A topographical analysis on lymph node metastases. Eur J Cancer 38(7):911–918
11. Wu ZY, Wan J, Li JH et al (2007) Prognostic value of lateral lymph node metastasis for advanced low rectal cancer. World J Gastroenterol 13(45):6048–6052
12. Fujita S, Yamamoto S, Akasu T, Moriya Y (2008) Outcome of patients with clinical stage II or III rectal cancer treated without adjuvant radiotherapy. Int J Colorectal Dis 23(11):1073–1079
13. Japanese Research Society for Cancer of the Colon and Rectum (1983) General rules for clinical and pathological studies on cancer of the colon, rectum and anus. Part II. Histopathological classification. Jpn J Surg 13(6):574–598
14. Moriya Y, Sugihara K, Akasu T, Fujita S (1995) Nerve-sparing surgery with lateral node dissection for advanced lower rectal cancer. Eur J Cancer 31A(7–8):1229–1232
15. Moriya Y (2006) Function preservation in rectal cancer surgery. Int J Clin Oncol 11(5):339–343
16. Rovera F, Dionigi G, Boni L et al (2007) The role of EUS and MRI in rectal cancer staging. Surg Oncol 16(Suppl 1):S51–S52
17. Nicholls RJ, Tekkis PP (2008) Multidisciplinary treatment of cancer of the rectum: a European approach. Surg Oncol Clin N Am 17(3):533–551, viii
18. Matsuoka H, Nakamura A, Masaki T et al (2007) Optimal diagnostic criteria for lateral pelvic lymph node metastasis in rectal carcinoma. Anticancer Res 27(5B):3529–3533
19. Arii K, Takifuji K, Yokoyama S et al (2006) Preoperative evaluation of pelvic lateral lymph node of patients with lower rectal cancer: comparison study of MR imaging and CT in 53 patients. Langenbecks Arch Surg 391(5):449–454
20. Yano H, Saito Y, Takeshita E et al (2007) Prediction of lateral pelvic node involvement in low rectal cancer by conventional computed tomography. Br J Surg 94(8):1014–1019
21. Fujita S, Yamamoto S, Akasu T, Moriya Y (2009) Risk factors of lateral pelvic lymph node metastasis in advanced rectal cancer. Int J Colorectal Dis 24:1085–1090
22. Kusters M, van de Velde CJ, Beets-Tan RG et al (2009) Patterns of local recurrence in rectal cancer: a single-center experience. Ann Surg Oncol 16(2):289–296
23. Birgisson H, Pahlman L, Gunnarsson U, Glimelius B (2008) Late gastrointestinal disorders after rectal cancer surgery with and without preoperative radiation therapy. Br J Surg 95(2):206–213
24. Birgisson H, Pahlman L, Gunnarsson U, Glimelius B (2007) Late adverse effects of radiation therapy for rectal cancer—a systematic overview. Acta Oncol 46(4):504–516
25. Birgisson H, Pahlman L, Gunnarsson U, Glimelius B (2005) Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish Rectal Cancer Trial. J Clin Oncol 23(34):8697–8705

Int J Colorectal Dis (2011) 26:79–87
DOI 10.1007/s00384-010-1036-0

ORIGINAL ARTICLE

Diverting stoma in rectal cancer surgery. A retrospective study of 329 patients from Japanese cancer centers

Akio Shiomi · Masaaki Ito · Norio Saito · Masayuki Ohue · Takashi Hirai · Yoshiro Kubo · Yoshihiro Moriya

Accepted: 22 July 2010 / Published online: 5 August 2010

Abstract
Background A diverting stoma (DS) has been constructed for many patients with low anterior resection (LAR), but it is still controversial whether DS can prevent anastomotic leakages. The aim of this study was to investigate the risk factors of anastomotic leakage including DS construction, and to evaluate the clinical course affected by DS according to the necessity of urgent abdominal reoperation for anastomotic leakage.

Patients and methods This was a retrospective analysis of 329 middle or lower rectal cancer patients who underwent LAR with mechanical reconstruction using circular staplers. Clinical data were collected from five cancer centers in Japan.

Results The overall anastomotic leakage rate was 10.0% (33 of 329). We experienced one mortality in this series (0.3%; 1/329). Clinical factors associated with DS construction included tumor location, operation time, intraoperative bleeding, lateral lymph node dissection, simultaneous resection of other organs, and the level of anastomosis, respectively.

On univariate analysis, high ligation of the inferior mesenteric artery had a significantly high leakage rate, but not on multivariate analysis. DS construction had no connection with the overall leakage rate. Concerning the clinical course affected by DS, the frequency of urgent reoperation was significantly increased in patients without DS compared with those with DS, 11.1% and 54.2%, respectively ($p=0.04$).

Conclusions LAR was the safe and preferred option for rectal cancer patients with very low mortality and an acceptable leakage rate. DS did not have a relationship with overall anastomotic leakage, but did seem to mitigate its consequences and reduce the requirement for urgent abdominal reoperation.

Keywords Rectal cancer · Anastomotic leakage · Diverting stoma · Defunctioning stoma · Low anterior resection

A. Shiomi (✉)
Department of Colorectal Surgery,
Shizuoka Cancer Center Hospital,
1007 Shimonagakubo, Nagaizumi-cho,
Sunto-gun, Shizuoka 411-8777, Japan
e-mail: a.shiomi@scchr.jp

M. Ito · N. Saito
Department of Colorectal Surgery,
National Cancer Center Hospital East,
Kashiwa, Chiba, Japan

Y. Moriya
Department of Colorectal Surgery,
National Cancer Center Hospital,
Tokyo, Japan

M. Ohue
Department of Surgical Oncology,
Osaka Medical Center for Cancer and Cardiovascular Diseases,
Osaka, Japan

T. Hirai
Department of Gastroenterological Surgery,
Aichi Cancer Center Hospital,
Nagoya, Japan

Y. Kubo
Department of Surgical Oncology,
Shikoku Cancer Center Hospital,
Matsuyama, Japan

Introduction

Anastomotic leakage is a major problem in rectal cancer surgery, because a sphincter-preserving operation has become standard for many rectal cancer patients. A

temporary diverting stoma (DS) has been constructed for many patients in low anterior resection (LAR). But the indication of DS construction for patients without intraoperative adverse events has not been clarified for a long time. Theoretically, DS was constructed to divert the fecal stream from anastomotic sites, and to protect fragile anastomotic sites. But it remains unproven whether diverting the fecal stream in itself directly prevents leakage. Several retrospective studies showed that the absence of DS was a risk factor for leakage in LAR, whereas others did not. Therefore, it is controversial whether DS can prevent anastomotic leakage. Although recent randomized studies [1, 2] and meta-analyses [3, 4] have shown that DS reduced the incidence of symptomatic leakage in LAR for rectal cancer, there is still limited evidence as to the impact of DS on leakage. Moreover, there have been few analyses about this issue in multicenter studies with a large number of patients from Japan.

The aim of this study was to investigate the risk factors of anastomotic leakage including DS construction, and to evaluate the clinical course affected by DS according to the necessity of urgent abdominal reoperation for such leakage using data collected from five cancer centers in Japan.

Patients and method

Patients

We reviewed the clinical data from five cancer centers in Japan which participated in the "Studies on the standardization for diagnosis, treatment, and follow-up of colorectal cancer patients", sponsored by Grant-in-Aid 18-2 for Cancer Research from the Ministry of Health, Welfare and Labor of Japan. All data on patient demographics, comorbidities, and the histological results were investigated retrospectively from the clinical records of each hospital.

From 2002 to 2004, a total of 329 consecutive patients with primary rectal cancer underwent LAR, and were investigated in this series. LAR was performed on patients with middle or lower rectal cancer, and reconstructions were done using circular staplers. Coloanal anastomosis using the hand-sewn technique was excluded from this study. Patients with subtotal colectomy, total proctocolectomy, abdominoperineal resection, Hartmann's procedure, or with pull-through procedures were also excluded.

Surgical procedure

The inferior mesenteric artery (IMA) was divided either at its origin or below the origin of the left colic artery (LCA). High ligation of IMA was defined as dividing IMA at its origin, while low ligation was defined as dividing IMA below the origin of LCA. For oncological lymph node dissection, we classify regional lymph nodes into three groups: perirectal, intermediate, and main lymph nodes. Perirectal nodes are lymph nodes in the mesorectum along the superior rectal artery. Intermediate nodes are lymph nodes along IMA between the origin of the left colic artery and the origin of the terminal sigmoid artery. Main nodes mean the lymph nodes along the IMA proximal to the origin of the LCA [5]. Lymph node dissection for UICC stage I is complete dissection of perirectal and intermediate lymph nodes, that is, low ligation without lymph node dissection around the root of IMA. Lymph node dissection for stage II, III, and IV is complete dissection of all regional lymph nodes, that is, high or low ligation with lymph node dissection around the root of IMA [6].

After total mesorectal excision or tumor-specific mesorectal excision [7], we performed rectal irrigation, while clamping the anal side of the tumor. The rectum was then divided transversely or vertically [8]. After that, we usually added lateral lymph node dissection for patients diagnosed with stage II, III, and IV [9]. Although the extent of lymphadenectomy for stage IV is still debatable, in the case that every distant metastasis (stage IV) was resectable, we perform full lymph node dissection.

Reconstruction was done using a circular stapler. Most anastomoses were straight, and colonic J pouch or transverse coloplasty pouch was sometimes used at the discretion of the operating surgeon. Intraoperative leakage test by transanal instillation of fluid or air was performed depending on the surgeon. Pelvic drain was used routinely.

Indication of DS construction

No clear applicable criteria for DS construction were stipulated in the present study. The DS construction decision was made by the individual surgeon in each case.

Definition of anastomotic leakage

Anastomotic leakage was defined clinically by the presence of the following: discharge of gas, pus, or feces from the drain or wound; discharge of pus per rectum; or rectovaginal fistula. All clinically suspicious anastomotic leakages were confirmed by one or more of the following image diagnoses: contrast study; CT scan; rectoscopy. If these cases were proven not to show anastomotic insufficiency by these imaging studies, they were defined as pelvic abscess

and not as anastomotic leakage. We did not perform routine diagnostic imaging after LAR to detect anastomotic dehiscence in clinically stable patients.

Variables analyzed

Variables included in this analysis were age, gender, body mass index (BMI), bowel obstruction, tumor location, tumor invasion, adjuvant therapy, level of IMA ligation, lateral lymph node dissection, type of anastomosis (single stapling technique, SST; or double stapling technique, DST), pouch surgery, intraoperative blood loss, operating time, DS construction, synchronous resections of other organs (hepatectomies for simultaneous liver metastasis or extended surgery to adherent organs, or additional cancer resections for double cancers), tumor size, and distal resection margin of specimen.

Bowel obstruction was defined as stenosis preventing the passage of a colon fiberscope. Tumor location was classified into middle or lower rectum according to the main part of the tumor. Tumors in the lower rectum were defined as those in which the main part was located below the peritoneal reflection. Tumor location in relation to the anal verge was preoperatively measured using rigid scope or digital examination. Tumor invasion was classified according to the UICC-TNM classification (6th edition [10]) preoperatively. Tumor size and distal resection margin were measured on the specimen before fixation with formalin. The level of anastomosis from the anal verge was measured with a digital examination. But due to the retrospective nature of this study, when the data were not available, the distance was calculated from the tumor location and distal resection margin.

Statistical analysis

In the univariate analysis, the chi-squared test and Mann–Whitney test were used. After univariate analysis, variables with a p value$\leq$0.1 were selected for multivariate analysis. A multivariate analysis was performed using a binary logistic regression model. All p values <0.05 were considered statistically significant.

Table 1 Patient characteristics

Gender	
Male	215
Female	114
Age(years)	59.0±10.5 (23–87)
Tumor location (cm)	6.1±1.7 (4.0–12.0)
Bowel obstruction	
No	305
Yes	18
Missing	6
Tumor invasion	
T1,T2	108
T3,T4	215
Missing	6
Neoadjuvant chemo Tx	
No	324
Yes	5
Anastomosis	
SST	15
DST	314
High ligation	
No	142
Yes	183
Missing	4
LLND	
No	197
Yes	132
Level of anastomosis (cm)	4.1±1.4 (1.0–9.5)
Intraoperative bleeding (ml)	598±590 (10–3723)
Operating time (min)	240±104.1 (90–620)
BMI (k/m^2)	22.6±3.1 (14.1–31.2)
Tumor size (cm)	4.4±2.3 (0–12.0)
Simultaneous resection	
No	292
Yes	37
DS construction	
No	209
Yes	120

Values are number or mean±standard deviation (ranges)

DS diverting stoma, *BMI* body mass index, *SST* single stapling technique, *DST* double stapling technique, *LLND* lateral lymph node dissection

Results

Patient characteristics

From 2002 to 2004, a total of 329 consecutive patients underwent LAR. Patient characteristics were shown in Table 1. One hundred and eighteen middle rectal cancer patients and 211 low rectal cancer patients were investigated in this series. Average distance from the lower edge of the tumor to the anal verge was 6.1 cm (4.0–12.0 cm). Average distance from anastomosis to the anal verge was 4.1 cm (1.0–9.5 cm).

Neoadjuvant chemotherapy was performed for five patients, but others were treated by surgery alone. Neo-

adjuvant radiotherapy or chemoradiotherapy was not performed in this series, because preoperative therapy for resectable rectal cancer was not standard in Japan.

Synchronous resections included 20 extended resections for direct invasion of adjacent organs, 13 hepatectomies for liver metastasis, and five resections of double primary cancers.

Morbidity and mortality

The overall rate of anastomotic leakage was 10.0% (33 of 329). We experienced only one mortality in this series (0.3%; 1/329). This patient died from a septic complication caused by anastomotic leakage in the case of LAR with DS 6 days after initial surgery.

Diverting stoma

A DS was constructed in 120 patients (36.5%; 120 of 329) in initial LAR, respectively. Among the colorectal surgeons participating in this study, ileostomy was major and chosen for 92 (76.7%) patients, while transverse colostomy was done for 28 (23.3%) patients.

The DS construction rate had a significant association with tumor location. DS was constructed in only 12.7% of middle rectal cancer patients, but in 48.3% of low rectal cancer patients who experienced temporary stoma at initial LAR, respectively.

Other factors found to be significantly associated with DS construction included tumor location, operation time, intraoperative bleeding, lateral lymph node dissection,

Table 2 Univariate analysis of factors related with DS construction

	Diverting stoma		Rate	*p*-value
	DS(−)	DS(+)		
Gender				
Male	130	85	39.5	0.11
Female	79	35	30.7	
Age (years)	58.8±10.7 (23–87)	59.4±10.2 (29–75)		0.42
Tumor location (cm)	6.4±1.6 (4.0–12.0)	5.9±1.7 (4.0–12.0)		0.001
Bowel obstruction				
No	195	110	36.1	0.76
Yes	11	7	38.9	
Tumor invasion				
T1,T2	71	37	34.6	0.50
T3,T4	133	82	38.1	
Neoadjuvant chemo Tx				
No	204	120	37.0	0.10
Yes	5	0	0.0	
Anastomosis				
SST	8	7	46.7	0.40
DST	201	113	36.0	
High ligation				
No	125	58	31.7	0.12
Yes	82	60	42.3	
LLND				
No	146	51	25.9	<0.0001
Yes	63	69	52.3	
Level of anastomosis (cm)	4.2±1.4 (1.0–9.0)	3.8±1.4 (1.0–9.5)		0.002
Intraoperative bleeding (ml)	505±524 (10–2985)	760±662 (17–3723)		<0.0001
Operating time (min)	231±90.6 (90–559)	318±102.7 (130–620)		<0.0001
BMI (k/m^2)	22.9±3.0 (14.1–31.2)	22.3±3.2 (15.8–30.8)		0.07
Tumor size (cm)	4.4±2. (0–12.0)	4.4±2.3 (1.0–10.0)		0.97
Simultaneous resection				
No	192	100	34.2	0.02
Yes	17	20	54.1	

Values are number or mean± standard deviation (ranges)

BMI body mass index, *SST* single stapling technique, *DST* double stapling technique, *LLND* lateral lymph node dissection

simultaneous resection of other organs, and level of anastomosis (Table 2).

Risk factors of anastomotic leakage

Clinical variables were analyzed to investigate the risk factors for anastomotic leakage (Table 3). On univariate analysis, LAR with high ligation of IMA had a significantly high leakage rate ($p<0.05$). There were increased but statistically insignificant impacts on leakage in males, bowel obstruction, massive intraoperative bleeding, and simultaneous resection of other organs.

Nine (7.5%) of 120 patients with DS had leakage, compared with 24 (11.5%) of 209 patients without DS ($p=0.25$). DS construction also had no relevance to the overall anastomotic leakage.

Risk factors of leakage limited to the LAR without DS were also investigated. As shown in Table 4, no obvious statistical significance was found with any clinical factor.

A multivariate analysis of risk factors for anastomotic leakage showed every factor including high ligation of IMA construction as not statistically significant (Table 5).

Table 3 Univariate analysis of leakage risk factors

	Leakage		Rate	*p*-value
	No leakage	Leakage		
Gender				
Male	190	25	11.6	0.19
Female	106	8	0.7	
Age(years)	58.8±10.6 (23–87)	61.1±10.0 (40–76)		0.20
Tumor location (cm)	6.2±1.7 (4.0–12.0)	6.5±1.7 (4.0–10.0)		0.31
Bowel obstruction				
No	276	29	9.5	0.16
Yes	14	4	22.2	
Tumor invasion				
T1,T2	101	7	6.5	0.12
T3,T4	189	26	12.1	
Neoadjuvant chemo Tx				
No	291	33	10.2	0.59
Yes	5	0	0.0	
Anastomosis				
SST	13	2	13.3	0.66
DST	283	31	9.9	
High ligation				
No	135	7	4.9	0.02
Yes	157	26	14.2	
LLND				
No	177	20	10.1	0.93
Yes	119	13	9.8	
Level of anastomosis (cm)	4.1±1.4 (1.0–9.5)	4.4±1.3 (1.9–7.0)		0.13
Intraoperative bleeding (ml)	573±559 (10–3365)	817±791 (40–3723)		0.06
Operating time (min)	261±102 (90–616)	273±118 (113–620)		0.70
BMI (k/m^2)	22.7±3.1 (14.1–31.2)	22.5±3.2 (16.1–27.0)		0.87
Tumor size (cm)	4.4±2.3 (0–12.0)	5.0±2.3 (2.0–11.0)		0.18
Simultaneous resection				
No	266	26	8.9	0.06
Yes	30	7	18.9	
DS construction				
No	185	24	11.5	0.25
Yes	111	9	7.5	

Values are number or mean± standard deviation (ranges)

BMI body mass index, *SST* single stapling technique, *DST* double stapling technique, *LLND* lateral lymph node dissection

Table 4 Univariate analysis of leakage risk factors (without DS patients)

	Leakage		Rate	*p*-value
	No leakage	Leakage		
Gender				
Male	114	16	12.3	0.63
Female	71	8	10.1	
Age(years)	58.7±10.8 (23–87)	59.7±10.1 (40–76)		0.65
Tumor location (cm)	6.4±1.6(4.0–12.0)	6.3±1.6 (4.0–10.0)		0.61
Bowel obstruction				
No	173	22	11.3	0.64
Yes	9	2	18.2	
Tumor invasion				
T1,T2	65	6	8.5	0.28
T3,T4	115	18	13.5	
Neoadjuvant chemo Tx				
No	180	24	11.8	0.54
Yes	5	0	0.0	
Anastomosis				
SST	7	1	12.5	0.63
DST	178	23	11.4	
High ligation				
No	108	17	13.6	0.47
Yes	75	7	8.5	
LLND				
No	130	16	11.0	0.72
Yes	55	8	12.7	
Level of anastomosis (cm)	4.2±1.4 (1.0–9.0)	4.2±1.1(2.2–7.0)		0.89
Intraoperative bleeding (cm)	480±502 (10–2985)	703±650 (40–2720)		0.07
Operating time (cm)	228±88 (90–552)	248±108(113–559)		0.60
BMI (k/m^2)	22.9±3.0 (14.1–31.2)	22.7±3.1 (16.1–27.0)		0.82
Tumor size (cm)	4.3±2.3 (0–12.0)	5.0±2.4 (2.0–11.0)		0.26
Simultaneous resection				
No	171	21	10.9	0.31
Yes	14	3	17.6	

Values are number or mean± standard deviation (ranges)

BMI body mass index, *SST* single stapling technique, *DST* double stapling technique, *LLND* lateral lymph node dissection

Clinical course affected by DS construction

The clinical course affected by DS was also investigated, focusing on the necessity of urgent abdominal reoperation for anastomotic leakage. Nine of 120 (7.5%) patients who underwent LAR with DS experienced leakage. Of these nine, only one patient (11.1%) needed urgent reoperation for peritonitis, and eight patients were treated conservatively. Twenty-four of 209 (11.5%) patients who underwent LAR without DS experienced leakage, and 13 (54.2%) of them needed urgent reoperation, while 11 patients were treated conservatively (Table 6). The need for reoperation was significantly increased in patients without DS compared to those with DS, 54.2% and 11.1%, respectively (p=0.04).

Table 5 Multivariate analysis of leakage risk factors

	p-value	Odds ratio (95% CI)
High ligation	0.17	1.9 (0.77–4.54)
Intraoperative bleeding	0.78	1.0 (0.99–1.00)
Simultaneous resection	0.12	2.2 (0.82–6.09)

Discussion

LAR was the safe and preferred option for middle or low rectal cancer patients with very low mortality and an acceptable leakage rate among the institutes participating in this study. DS did not have a statistically significant

Table 6 Clinical course affected by diverting stoma

DS in initial LAR		Leakage		Conservative therapy	Urgent operation	Rate of urgent operation	
			%			%	
DS(+)	120	9	7.5	8	1	11.1	p=0.04
DS(−)	209	24	11.5	11	13	54.2	

relationship with the overall leakage rate. Although we cannot conclude the value of DS in terms of leakage prevention from this retrospective study, DS did seem to mitigate the consequences of leakage and reduce the need for urgent abdominal reoperation for leakage. There have been few reports about this issue in multicenter studies with a large number of patients from Japan.

With the advances in surgical procedures and devices in recent decades, sphincter-preserving surgery has become the treatment of choice for rectal cancer patients. In addition, simple and easy reconstruction has become possible thanks to circular stapling devices, even in low-level anastomosis within a narrow pelvis.

However, anastomotic leakage is still a major problem in rectal cancer surgery, sometimes resulting in severe morbidity or mortality. Since stapled anastomosis developed in the 1970s, the mortality of sphincter-preserving operations has decreased. In 1975, Fain et al. [11] reported their experience of mechanical suturing in 165 rectal cancer patients with a mortality of 2.4%. Now, symptomatic anastomotic leakage has been reported to occur in 5% to 20% of cases [12–20], and when present, the associated risk of postoperative mortality is increased to between 6% and 22% [15]. The present study encountered very low mortality (1/329; 0.3%), which is not inferior to the 0.8% recently described [2]. Our result shows the obviously improved safety of LAR using mechanical anastomosis in the Japanese cancer centers participating in this study.

Several risk factors for anastomotic leakage have been reported [12–20], and the relationship between DS and leakage was discussed in many retrospective or nonrandomized prospective studies. Wong et al. [21] reported no statistical difference between patients who were defunctioned (3.8%; 28/742) and those who were not (4%; 13/324). So, they concluded that DS did not reduce the postoperative leak rate. They also concluded that a stoma carried a certain morbidity and also added to the cost of the entire operation, so it should not be performed routinely. On the other hand, Peeters et al. [18] reported that the absence of DS was significantly associated with a higher leakage rate: 43 (8.2%) of 523 patients with DS had leakage, compared with 64 (16.0%) of 401 patients without DS (p<0.001). In the present study, DS construction had no association with the overall anastomotic leakage rate. This reflects our low leakage rate in cases without DS (11.5%; 24 of 209). This rate is comparable to the leakage rate in cases with DS in a randomized controlled trial by Matthiessen et al. (10.3%; 12 of 116) [1].

Although absence of DS was not a risk factor of leakage in this study, because of a general selection bias of nonrandomized study including ours, we cannot conclude whether or not DS can prevent the leakage. This bias results from the selective creation of DS for the patients anticipated to undergo "risky" anastomosis by each surgeon as shown in this investigation. We can also point out another bias, namely that clinically unapparent leakages might have been missed in either group because no systematic assessment of the anastomosis for clinically stable patients was performed in the present study.

Only four randomized control studies sought to investigate the association between DS and leakage [1, 2, 22, 23]. Matthiessen et al. [1] reported the result of intraoperative randomization of a patient undergoing LAR for rectal cancer within 15 cm from the anal verge, and anastomosed within 7 cm. 10.3% (12 of 116) of patients with defunctioning stoma (n=116) had symptomatic leakage, against 28.8% (33 of 118) of those without stoma (n=118). They concluded that defunctioning stoma significantly decreased the rate of symptomatic leakage and was therefore recommended in LAR for rectal cancer. Pakkastie et al. [22] and Graffner et al. [23], on the other hand, could not find any statistical difference between the two groups in their randomized studies comprising 50 and 38 patients, respectively. But due to the small sample, no firm conclusion could be made. So, it is still controversial whether DS can prevent anastomotic leakage. The problem is the limited evidence about this issue. The value of DS in preventing leakage should be evaluated by more prospective studies in the future. And prospective, randomized studies are also warranted to address this issue.

Other reported risk factors include male gender [13–16], level of anastomosis [12–15], previous radiation therapy [13, 14], absence of pelvic drainage [18], poor bowel preparation [12], blood transfusion [12], immunosuppression, and underlying vascular insufficiency. Among these risk factors, male gender and level of anastomosis were widely accepted as significant for leakage. In the present study, there were increased impacts on leakage in male gender, bowel obstruction, massive intraoperative bleeding, and simultaneous resection of other organs. Although statistical significance was not reached, these factors were