Table S6 Outcome of patients treated with radiation therapy as the main treatment

Method	EBRT ($n = 1241$)		BT ($n = 210$)		BT + EBRT ($n = 48$)	
	n	%	*n*	%	*n*	%
Field						
Prostate only	1099	88.56	210	100	43	89.58
Prostate + whole pelvis	137	11.04	–		5	10.42
Dose (Gy)						
<60	22	1.77				
60–64<	118	9.51				
64–68<	143	11.52				
68–72<	572	46.09				
72–76<	137	11.04				
76–80<	142	11.44				
≥80	2	0.16				
Mean/median	69.34/70.0					
Combination						
≤6 m NHT	240	19.34	5	2.38	8	16.67
6–12 m NHT	597	48.11	73	34.76	17	35.42
>12 m	240	19.34	36	17.14	4	8.33
None	240	19.34	90	42.86	17	35.42
Survival status						
NED	720	58.02	162	77.14	24	50.00
Alive with cancer	434	34.97	43	20.48	23	47.92
Stable disease	282	22.72	33	15.71	15	31.25
PSA/clinical failure	130	10.48	10	4.76	8	16.67
Progressive disease	22	1.77	0	0.00	0	0.00
Died of cancer	21	1.69	0	0.00	0	0.00
Died of other causes	45	3.63	0	0.00	0	0.00
Uncertain	21	1.69	5	2.38	0	0.00

$n = 1499$. There were 28 patients who received particle radiotherapy and 27 patients who were treated by uncertain modality that were excluded. BT, brachytherapy; EBRT, external beam radiotherapy; NED, no evidence of disease; NHT, neoadjuvant hormonal therapy; PSA, prostate-specific antigen.

Table S7 Outcome of 485 patients treated with watchful waiting

	n	%
Intended treatment		
RP	47	9.69
Rx	14	2.89
Hx	73	15.05
Maintenance W/W	351	72.37
Survival status		
NED	51	10.52
Alive with disease	417	85.98
Stable disease	394	81.24
PSA/clinical failure	21	4.33
Progressive disease	3	0.62
Died of cancer	3	0.62
Died of other causes	13	2.68
Uncertain	1	0.21

Hx, hormonal ablation therapy; NED, no evidence of disease; RP, radical prostatectomy; Rx, radiation therapy; W/W, watchful waiting.

Appendix I Statistics from various institutions in Japan

Institution	*n*	No. patients
University Hospital	32	2 048
National Hospital	88	4 506
General Hospital	119	4 860
Total	239	11 414

Institution	No. patients
Sapporo Medical University Hospital	55
Sapporo Social Insurance General Hospital	45
Otaru Municipal Hospital	42
Tomakomai City Hospital	25
Hokkaido Social Service Association Social Welfare Service Hakodate Hospital	13
Rumoi City Hospital	14
Ashibetsu Municipal Hospital	9
Kitasaito Hospital	23
Ebetsu City Hospital	16
Kushiro Red Cross Hospital	15
Hokkaido Saiseikai Otaru Hospital	26
Takikawa Municipal Hospital	27
Medical Corporation Bokoi Nikko Memorial Hospital	26
Hakodate Goryoukaku Hospital	85
Fukagawa Municipal Hospital	17
Hokkaido Social Insurance Hospital	19
Muroran City General Hospital	34
Megumino Hospital	23
Social Welfare Corporation Hokkaido Social Work Association Obihiro Hospital	0
Aomori Prefectural Central Hospital	29
Aomori City Hospital	37
Iwate Medical University	67
Iwate Prefectural Oofunato Hospital	11
Kitakami Saiseikai Hospital	30
Japanese Red Cross Sendai Hospital	29
Kesennuma City Hospital	75
Miyagi Cancer Center	165
Akita University Hospital	62
Odate Municipal Hospital	35
Ogachi Chuo Hospital	36
Nihonkai General Hospital	82
Iwaki Urological Hospital	25
Tsukuba University Hospital	30
National Hospital Organization Mito Medical Center	37
Mito Red Cross Hospital	110
Tokyo Medical University Hachioji Medical Center	81
National Hospital Organization Disaster Medical Center	42
Nippon Medical School Tama Nagayama Hospital	0
Tokyo Rinkai Hospital	27
Showakai Hospital	21
Juntendo University Nerima Hospital	0
Hasegawa Hospital	4
Tokai University Hospital	121
Fujisawa City Hospital	72
Chigasaki Municipal Hospital	37

Appendix I *Continued*

Institution	No. patients
Yokosuka Kyosai Hospital	40
Nippon Kokan Hospital	10
Saiseikai Yokohamashi Tobu Hospital	0
Isehara Kyodo Hospital	15
Odawara Municipal Hospital	57
International Goodwill Hospital	79
Atsugi City Hospital	75
Yokohama City University Medical Center	96
Niigata Cancer Center Hospital	187
Niigata Prefectural Central Hospital	112
Saiseikai Niigata Daini Hospital	4
Kariwagun General Hospital	40
Toyama Red Cross Hospital	40
Kouseiren Takaoka Hospital	60
Saiseikai Toyama Hospital	18
Kanazawa University Hospital	51
Kanazawa Medical University Hospital	41
National Hospital Organization Kanazawa Medical Center	36
Noto General Hospital	29
Fukuiken Saiseikai Hospital	66
Fujita Memorial Hospital	11
Tsuruga Municipal Hospital	21
Yamanashi Prefectural Central Hospital	84
Kanoiwa General Hospital	11
Fujiyoshida Municipal Hospital	31
Ina Central Hospital	72
Japanese Red Cross Society Suwa Hospital	14
Aizawa Hospital	87
Gifu Prefectural General Medical Center	62
Ibi Kosei Hospital	12
Chuno Kousei Hospital	46
Japanese Red Cross Shizuoka Hospital	11
Shimizu Welfare Hospital	32
Hoshigaoka Koseinenkin Hospital	46
Rinku General Medical Center Izumisano Municipal Hospital	32
PL General Hospital	19
Tane General Hospital	29
Kansai Medical University Takii Hospital	75
Saiseikai Suita Hospital	34
Saiseikai Tondabayashi Hospital	15
Aijinkai Chibune General Hospital	4
Bellland General Hospital	29
Hyogo Prefectural Kakogawa Medical Hospital	99
Itami City Hospital	27
Nishikobe Medical Center	37
Saiseikai Hyogoken Hospital	15
Nara Medical University	81
Nara City Hospital	10
Yamato Takada Municipal Hospital	27
Nara Prefectural Mimuro Hospital	48
Hidaka General Hospital	20

Appendix I *Continued*

Institution	No. patients
Naga Municipal Hospital	26
Tottori Red Cross Hospital	55
Tottori Prefectural Kousei Hospital	0
Matsue City Hospital	40
National Hospital Organization Okayama Medical Center	58
Okayama Rosai Hospital	15
Okayama Central Hospital	82
Kurashiki Central Hospital	192
Matsuda Hospital	17
Mizushima Kyodo Hospital	13
Hiroshima University Hospital	56
JA Onomichi General Hospital	23
Onomichi Municipal Hospital	33
Mihara Red Cross Hospital	46
Fukuyama City Hospital	35
Hiroshima-Nishi Medical Center	6
Harada Hospital	6
Yamaguchi University Graduate School of Medicine	13
Shimonoseki City Central Hospital	28
Ube Industries Central Hospital	8
Konan Saint Hill Hospital	3
Shimonoseki Kosei Hospital	19
Shunan City Shinnanyo Hospital	25
Tokushima Municipal Hospital	44
Hitachi General Hospital	59
Ibaraki Prefectural Center Hospital and Cancer Center	46
Mito Saiseikai General Hospital	48
Tochigi National Hospital	50
Tochigi Cancer Center	118
Gunma Cancer Center	112
Tatebayashi Kosei Hospital	109
Saitama Cancer Center	75
Saitama Red Cross Hospital	63
Saitama Medical Center, Saitama Medical University	48
Kuki General Hospital	31
Asakadai Central Hospital	15
Social Insurance Omiya General Hospital	38
Kawaguchi Municipal Medical Center	44
Saitama Medical Center Jichi Medical University	85
Chichibu City Hospital	62
Soka Municipal Hospital	23
Chiba Cancer Center	264
Kameda Medical Center	103
Shinmatsudo Central General Hospital	12
Chiba Aoba Municipal Hospital	38
Gyoutoku Sougou Hospital	0
Keio University School of Medicine	210
Tokyo Women's Medical University	99
Kyorin University Hospital	53
National Center for Global Health and Medicine	77
National Cancer Center Hospital	273

Appendix I *Continued*

Institution	No. patients
Self-Defense Forces Central Hospital	22
Musashino Red Cross Hospital	94
Yamato Hospital	47
Kanto Central Hospital(of the Mutual Aid Association of Public School Teachers)	87
Toho University Ohashi Medical Center	56
Kitasato Institute Hospital	46
Tokai University Tokyo Hospital	42
Sempo Tokyo Takanawa Hospital	27
Fujieda Municipal General Hospital	60
Kakegawa Municipal General Hospital	46
Juntendo University Shizuoka Hospital	67
Seirei Numazu Hospital	18
Fuji City General Hospital	73
Shizuoka City Shimizu Hospital	58
Nagoya University Graduate School of Medicine	52
Fujita Health University Hospital	113
National Hospital Organization Nagoya Medical Center	20
Chukyo Hospital	30
Chubu Rosai Hospital	26
Nagoya Ekisaikai Hospital	12
Kariya Toyota General Hospital	96
Toyota Memorial Hospital	56
J.A. Aichi Anjo Kosei Hospital	85
Komaki City Hospital	60
Minami Seikyo General Hospital	8
Shinshiro Municipal Hospital	46
Aichi Saiseikai Hospital	56
Inazawa City Hospital	18
Chunichi Hospital	3
Nagoya Memorial Hospital	49
Takeuchi Hospital	63
Social Insurance Shiga Hospital	10
Omihachiman Community Medical Center	34
Kohka Public Hospital	36
Nagahama City Hospital	25
Kyoto University Hospital	179
Kyoto Prefectural University of Medicine	30
National Hospital Organization Kyoto Medical Center	82
Kyoto Second Red Cross Hospital	51
Rakuwakai Otowa Hospital	15
Osaka Medical College	20
Kinki University School of Medicine	41
National Hospital Organization Osaka Medical Center	61
Osaka General Medical Center	77
Minoh City Hospital	71
Izumi City Hospital	18
Federation of National Public Service and Affiliated Personnel Mutual Aid Association Otemae Hospital	20
NTT West Osaka Hospital	39
Yao Municipal Hospital	38
Suita Municipal Hospital	36
Osaka Red Cross Hospital	92

Appendix I *Continued*

Institution	No. patients
Tokushima Red Cross Hospital	43
Health Insurance Naruto Hospital	50
Oe Kyodou Hospital	35
Tsurugi Municipal Handa Hospital	17
National Hospital Organization Zentsuji Hospital	37
Uchinomi Hospital	14
Ehime University Hospital	37
National Hospital Organization Shikoku Cancer Center	186
Matsuyama Red Cross Hospital	88
Kochi Health Sciences Center	0
National Hospital Organization Kochi National Hospital	12
Harasanshin Hospital	216
Kitakyushu City Yahata Hospital	1
Tobata Kyoritsu Hospital	7
Shin Yukuhashi Hospital	4
Takayama hospital	40
Moji Medical Center	20
Saga University	41
Fujisaki Hospital	83
Nagasaki Municipal Hospital	48
Isahaya Health Insurance General Hospital	64
Kouseikai Hospital	32
Kumamoto Chuo Hospital	89
Saiseikai Kumamoto Hospital	53
Kumamoto Urological Hospital	49
Saiseikai Misumi Hospital	6
National Hospital Organization Oita Medical Center	45
Almeida Memorial Hospital	18
Medical Foundation Tenshindo Hetsugi Hospital	0
Koga General Hospital	78
Fujimotohayasuzu Hospital	16
National Hospital Organization Ibusuki National Hospital	14
Kagoshima Prefectural Ohshima Hospital	11
Kagoshima City Hospital	88
Kimotsuki-gun Medical Associated Hospital	5
Izumi General Medical Center	21
Tarumizu Chuo Hospital	7
Akune Citizen Hospital	18
Niimura Hospital	303
Nakagami Hospital	28
Nanbu Tokushukai Hospital	5

Cancer Chemother Pharmacol (2011) 67:587–596
DOI 10.1007/s00280-010-1358-1

ORIGINAL ARTICLE

Final results of randomized trials by the National Surgical Adjuvant Study of Colorectal Cancer (NSAS-CC)

Tetsuya Hamaguchi · Kuniaki Shirao · Yoshihiro Moriya · Shigeaki Yoshida · Susumu Kodaira · Yasuo Ohashi · The NSAS-CC Group

Received: 20 October 2009 / Accepted: 1 May 2010 / Published online: 19 May 2010

Abstract
Objective In the latter 1990s, adjuvant chemotherapy for completely resected Stage III colorectal cancer remained controversial in Japan. We conducted two independent randomized controlled trials in patients with Stage III colon and rectal cancer.

Methods Patients were randomly assigned to receive surgery alone or surgery followed by treatment with UFT (400 mg/m^2/day), given for five consecutive days per week for 1 year. The primary endpoint was relapse-free survival (RFS), and the secondary endpoint was overall survival (OS).

Results A total of 334 patients with colon cancer and 276 with rectal cancer were enrolled. The patients' characteristics were similar between the UFT group and the Surgery-alone group. There was no significant difference in RFS or OS in colon cancer. In rectal cancer, however, RFS and OS were significantly better in the UFT group than in the Surgery-alone group. The only grade 4 toxicity in the UFT group was diarrhea, occurring in one patient with colon cancer and one patient with rectal cancer.

Conclusions Postoperative adjuvant chemotherapy with UFT is successfully tolerated and improves RFS and OS in patients with Stage III rectal cancer. In colon cancer, the expected benefits were not obtained (hazard ratio = 0.89).

Keywords Stage III colon cancer · Stage III rectal cancer · UFT · Surgery alone · Randomized controlled trial

The Members of the National Surgical Adjuvant Study of Colorectal Cancer are listed in "Appendix".

T. Hamaguchi (✉)
Department of Gastrointestinal Oncology,
National Cancer Center Hospital, 5-1-1 Tsukiji,
Chuo-ku, Tokyo 104-0045, Japan
e-mail: thamaguc@ncc.go.jp

K. Shirao
Department of Medical Oncology, Faculty of Medicine,
Oita University, 1-1 Idaigaoka, Hasama, Yufu,
Oita 879-5593, Japan

Y. Moriya
Department of Surgical Oncology,
National Cancer Center Hospital, 5-1-1 Tsukiji,
Chuo-ku, Tokyo 104-0045, Japan

S. Yoshida
Aomori Prefectural Central Hospital,
2-1-1 Higashitsukurimichi, Aomori,
Aomori 030-8553, Japan

S. Kodaira
Department of Surgery, Nerima General Hospital,
1-24-1 Asahigaoka, Nerima-ku, Tokyo 176-8530, Japan

Y. Ohashi
Department of Biostatistics, School of Public Health,
University of Tokyo, 7-3-1 Hongo, Bunkyo-ku,
Tokyo 113-0033, Japan

Introduction

In Japan, the westernization of lifestyles has become associated with an annual increase in the incidence of colorectal cancer. In 2006, a total of 41,097 persons died of colorectal cancer, accounting for 12.6% of all deaths from malignant tumors. In 2004, 100,137 patients were diagnosed with colorectal cancer (17.6% of all patients with cancer). Colorectal cancer is forecast to become the most prevalent type by 2015, surpassing gastric cancer and lung

cancer [1]. In Europe and North America, colorectal cancer is the second leading cause of death from cancer [2]. Globally, the prevention, early diagnosis, and development of improved treatments for colorectal cancer are thus very important tasks.

In Europe and North America, 40–50% of patients with colorectal cancer who undergo surgery alone die of metastasis or recurrence. In patients with Stage III colon cancer, postoperative adjuvant chemotherapy with fluorouracil (FU) and levamisole (LEV) can cut mortality by 33% [3]. The 1990 National Institutes of Health Consensus Conference thus recommended a combination of FU and LEV (FULEV) as standard adjuvant therapy for Stage III colon cancer. In addition, radiotherapy combined with chemotherapy was recommended as a standard adjuvant therapy for rectal cancer [4]. Subsequent studies reported that FU plus leucovorin (LV) is superior to FU plus LEV for the adjuvant therapy of colon cancer [5]. In the late 1990s, FU plus LV (FULV) was positioned as standard adjuvant therapy for Stage III colon cancer.

In Japan, clinical trials of postoperative adjuvant chemotherapy have focused mainly on oral fluoropyrimidine-based regimens in both colon and rectal cancer. Although meta-analyses suggest that oral FU derivatives were effective [6, 7], standard adjuvant regimens were not established for either colon or rectal cancer until the early 2000s. Preoperative or postoperative radiation was considered unnecessary, since lateral nodal dissection is the standard procedure in Japan. Furthermore, FULV, regarded as more effective than FU alone in Western countries, was not available in Japan until 1999; however, in one comparative study of FU alone and FULV in advanced cancer, there was a difference in overall response rate, but the difference in overall survival was not significant [8]. This prompted us to perform a randomized, controlled study, the National Surgical Adjuvant Study of Colorectal Cancer (NSAS-CC), to examine whether postoperative adjuvant chemotherapy with uracil–tegafur (UFT) alone is useful for the treatment of Stage III colon and rectal cancer. Phase II studies found that UFT, which is widely used in Japan, is effective for the management of advanced cancers of the stomach, colon, rectum, breast, and other organs [9]. UFT monotherapy was used because LV was not available in Japan at the time of planning this study.

Methods

The present study was designed to examine the usefulness of postoperative adjuvant chemotherapy with UFT in patients with curatively resected Stage III colon or rectal cancer. The protocol was approved by the institutional review board at each participating center.

Patients and study design

The eligibility criteria in the study were as follows: (1) histologically confirmed adenocarcinoma; (2) curatively resected (R0 surgery) Stage III (any T, n1 or n2, M0) colon cancer and rectal cancer; (3) a performance status of 0–2 on the Eastern Cooperative Oncology Group scale; (4) an age of 20–75 years; (5) adequate function of main organs (white-cell count $\geq$ 4,000/mm^3, platelet count $\geq$ 100,000/mm^3, aspartate aminotransferase and alanine aminotransferase levels within twice the normal upper limit, serum total bilirubin level $\leq$ 1.2 mg/dL, blood urea nitrogen level $\leq$ 25 mg/dL, serum creatinine concentration $\leq$ 1.5 mg/dL, normal electrocardiogram), and (6) written informed consent obtained from the patient.

Patients who met the eligibility criteria were enrolled at the NSAS data center by telephone or fax within 6 weeks of after surgery and were randomly assigned to receive adjuvant chemotherapy with UFT (the UFT group) or surgery alone (Surgery-alone group) according to whether they had been diagnosed with colon cancer or rectal cancer. This was a non-blind study, and treatment was assigned by the minimization technique. Adjustment factors were T stage (T1/T2 vs. T3/T4) and N stage (n1 vs. n2/n3). In rectal cancer, the tumor site (upper vs. lower) was also used as an adjustment factor. Zelen's adjustment [10] was performed to balance the number of patients assigned to each treatment group according to center. Colon cancer, rectal cancer, and N stage were classified according to the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus (5th edition, 1994) [11]. Cancers arising from the rectosigmoid were classified as rectal cancer (see the footnote to Table 1).

The primary endpoint was relapse-free survival (RFS), and the secondary endpoint was overall survival (OS). Both endpoints were evaluated separately for colon cancer and rectal cancer.

Treatment plan

In advanced recurrent colorectal cancer, UFT 400 mg/m^2/day in two divided doses is the recommended dosage according to Japanese Phase I/II study [12]. Therefore, we judged that UFT at 400 mg/m^2/day would be an optimum dosage for postoperative chemotherapy for colorectal cancer. UFT at 600 mg/day has been approved as the upper daily dosage limit in Japan, so we did not wish to use dosages at or above this limit. Although UFT has been given two or three times daily, we considered that the twice-daily dosage would be superior in terms of compliance. A 1-year treatment was chosen in reference to previous Japanese studies of oral FU [6, 7, 13]. In the UFT group, UFT (tegafur, 400 mg/m^2/day; 600 mg/day in patients with a body surface area of $\geq$1.25 m^2

In the Surgery-alone group, anticancer therapy was withheld until the confirmation of recurrence during follow-up.

Follow-up

All patients underwent blood cell count, serum chemical tests, urinalysis, CEA and CA 19-9 as tumor marker tests, chest radiography, and abdominal ultrasonography or computed tomography at 4-month intervals during the first 2 years and at 6-month intervals thereafter. Patients with rectal cancer additionally underwent computed tomography of the pelvis at 6-month intervals. In the UFT group, blood cell count, serum chemical tests, and urinalysis were performed every month during treatment.

Diagnosis of recurrence was based on the results of imaging studies. Cytologic or histologic examinations were performed if necessary. Elevated levels of CEA alone were not regarded as adequate evidence of recurrence. If the CEA was elevated, we checked for signs or symptoms suggestive of tumor recurrence and considered using further imaging studies (i.e., CT scan, MRI, and/or bone scintigram) as needed.

Case report forms for individual patients were submitted to the independent NSAS data center at 6-month intervals during the first 5 years and at yearly intervals thereafter. All events related to the study endpoints, such as recurrence, were evaluated by the Evaluation Committee; treatment assignments were masked at the time of evaluation.

Statistical analysis

There was a wide range in the results that were used as the basis for calculating the target number of subjects; therefore, it was difficult to identify the exact number of cases needed. We set the number in consideration of feasibility. We chose a sample size that would ensure at least 70% detection power even in the most disadvantageous case.

The method of Schoenfeld and Richer was used to estimate sample size. It was assumed that the RFS at 5 years in the Surgery-alone group would be 60–75% for colon cancer and 50–65% for rectal cancer, the enrollment period 2 years, and follow-up period after enrollment 5 years. We then estimated that samples of 390–624 patients with colon cancer and of 312–446 patients with rectal cancer would be required to show a significant difference in endpoints between the groups with an alpha level of 0.05 (one-sided), a statistical power of 80% ($\beta = 0.2$), and a hazard ratio of 0.67 (hazard decreased to 2/3 after treatment with UFT). In the present study, the target number of patients was, therefore, set at 500 for colon cancer and 400 for rectal cancer.

An interim analysis was planned 2 years after completion of enrollment. Early termination would be considered at the time of the interim analysis if the one-sided P value of log-rank test for primary endpoint fell below 0.005, according to the Lan and DeMets spending function method.

For RFS, either recurrence or death, whichever occurred earlier, was defined as an event. The survival time was defined as the period from the date of surgery until the date of an event. OS was defined as the period from the date of surgery to the date of death. All deaths, including deaths from other causes, were regarded as events. Data on patients showing event-free survival were censored at the time of the last follow-up visit. Survival was estimated using the Kaplan–Meier method. The log-rank test was used to compare differences in survival. Hazard ratios were calculated using Cox proportional hazards models. All P values were two sided.

Statistical analysis was performed by statistical analysts and the NSAS data center. All analyses were done using the Statistical Analysis System (SAS, version 8, SAS Institute Inc., Cary, NC, USA).

Results

Accrual and interim analysis

From October 1996 through April 2001, we enrolled 334 patients with colon cancer and 276 with rectal cancer. Although the numbers of enrolled patients fell short of the initially set goals, the enrollment period was not prolonged, since about 5 years has elapsed since the start of the study, and it was judged that the effectiveness of postoperative adjuvant chemotherapy could be evaluated by a meta-analysis with other studies.

An interim analysis was performed in 2003. Data and safety were assessed by an independent data monitoring committee (IDMC). The IDMC recommended publishing the results of the analysis, since the criteria for early termination had been met for rectal cancer and their effectiveness confirmed. On the basis of this recommendation, the results of the interim analysis for rectal cancer were published (median follow-up period, 3.0 years) [15].

The results of the present analysis are based on follow-up data received as of March 2006, 5 years after the completion of enrollment (median follow-up period, 6.2 years).

Patients' characteristics

Four registered patients were confirmed not to meet the eligibility criteria after enrollment (registration before

completion was 72% in patients with colon cancer and 80% in those with rectal cancer. The median initial daily dose of UFT was 397 mg/m^2/day in patients with colon cancer and 395 mg/m^2/day in those with rectal cancer.

Relapse-free survival

At the time of the last follow-up, 49 patients with colon cancer in the UFT group, 51 with colon cancer in the Surgery-alone group, 46 with rectal cancer in the UFT group, and 59 with rectal cancer in the Surgery-alone group suffered recurrence or died. In patients with colon cancer, the 5-year RFS was 71.3% in the UFT group (95% confidence interval, 64.3–78.2%) and 69.6% in the Surgery-alone group (95% confidence interval, 62.4–76.7%). The hazard ratio for the UFT group, when compared with the Surgery-alone group, was 0.89 (95% confidence interval, 0.60–1.32), with no significant differences between the groups ($P = 0.56$). In patients with rectal cancer, the 5-year RFS was 68.9% in the UFT group (95% confidence interval, 61.1–76.8%) and 56.3% in the Surgery-alone group (95% confidence interval, 47.9–64.8%). The hazard ratio for the UFT group when compared with the Surgery-alone group was 0.66 (95% confidence interval, 0.45–0.97). The RFS was significantly better in the UFT group ($P = 0.033$; Fig. 2).

Overall survival

Overall, 36 patients with colon cancer in the UFT group, 42 with colon cancer in the Surgery-alone group, 29 with rectal cancer in the UFT group, and 43 with rectal cancer in the Surgery-alone group died. In patients with colon cancer, the 5-year overall survival (OS) was 81.3% in the UFT group (95% confidence interval, 75.4–87.3%) and 76.7% in the Surgery-alone group (95% confidence interval, 70.2–83.2%). The hazard ratio for the UFT group, when compared with the Surgery-alone group, was 0.82 (95% confidence interval, 0.53–1.29), with no significant difference between the groups ($P = 0.39$). In patients with rectal cancer, the 5-year OS was 85.3% in the UFT group (95% confidence interval, 79.4–91.3%) and 72.1% in the Surgery-alone group (95% confidence interval, 64.4–79.7%). The hazard ratio for the UFT group when compared with the Surgery-alone group was 0.60 (95% confidence interval, 0.38–0.97). OS was significantly better in the UFT group ($P = 0.034$; Fig. 3).

Patterns of relapse

As of the last follow-up, recurrence was diagnosed in 45 (26.8%) patients with colon cancer in the UFT group, 47 (28.7%) with colon cancer in the Surgery-alone group, 41 (29.5%) with rectal cancer in the UFT group, and 57 (42.2%) with rectal cancer in the Surgery-alone group. Analysis of patterns of relapse indicated that the rate of distant metastasis in patients with rectal cancer was lower in the UFT group (Table 3).

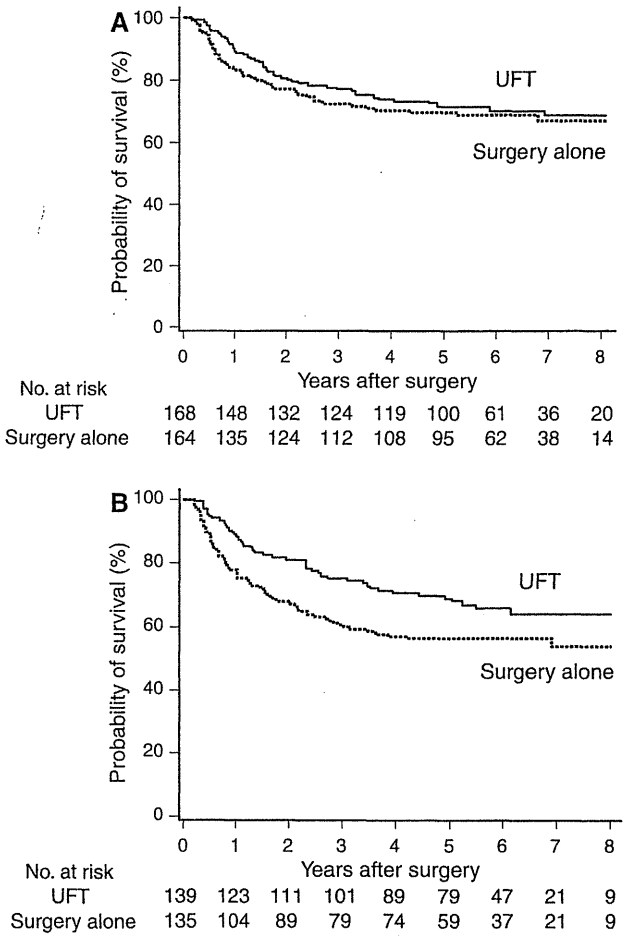

Fig. 2 Kaplan–Meier estimates of relapse-free survival by treatment, **a** colon cancer, **b** rectal cancer

Ancillary analysis

In the present study, we classified patients according to whether they had colon cancer or rectal cancer as defined by the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus (5th edition, 1994) [11]. Cancers developing in the rectosigmoid were classified as rectal cancer. In Europe and North America, cancers arising from the rectosigmoid are usually included in clinical studies of postoperative adjuvant chemotherapy for colon cancer. Some studies have also included tumors with their lower margins located above the peritoneal reflection. To facilitate a comparison of our results with those of Western studies, we calculated RFS and OS for patients with colon cancer plus those with tumors arising

of the initially scheduled 500 patients were enrolled and that the 5-year RFS in the Surgery-alone group was higher in patients with colon cancer (about 70%) than in those with rectal cancer. The study may, therefore, have been not sensitive enough to detect the effect of UFT in patients with colon cancer. Studies performed in Europe and North America in the 1980s have shown that adjuvant chemotherapy with methyl-CCNU, vincristine and FU (MOF), FULEV, or FULV was more effective than surgery alone in patients with colon cancer [3, 18–21]. Subsequent controlled studies comparing MOF with FULV [22] and FULEV with FULV [5] showed that DFS was significantly better with FULV. Combined chemotherapy with FULV was established as standard treatment for Stage III colon cancer in the latter half of the 1990s. More recently, controlled clinical trials comparing FULV with FULV with oxaliplatin (OX) (MOSAIC, NSABP C-07) in patients with Stage II/III colon cancer demonstrated that DFS was significantly better in the FULV plus OX group [23, 24]. At present, regimens combining FULV with OX with molecular targeted agents (bevacizumab, cetuximab) are being evaluated. FULV has also been compared with oral fluoropyrimidines (capecitabine, UFT and LV), and these treatments have been found to be equivalent in terms of efficacy [25, 26]. Oral fluoropyrimidines are now regarded as an alternative treatment to FULV. With respect to survival benefit, the adoption in Japan of FULV with OX regimens confirmed to be effective by clinical trials performed in Europe and North America, appears to be warranted.

Comparison of the results of Japanese clinical studies with those of studies performed in Europe and North America must take into account differences in surgical procedures and outcomes. Although direct comparisons are not feasible, the outcomes (RFS [DFS]) of patients with colon cancer in the Surgery-alone group of our study were superior to those of patients with Stage III colon cancer who received FULV and comparable to those in patients who received FULV with OX in the MOSAIC and NSABP C-07 studies [27]. We considered there seem to be two factors why the difference of the outcome between the western population and our results is [28]. The first is a difference in the standard nodal dissection procedures used in Japan and in the West. In Japan, D2 or D3 nodal dissection is conducted by dividing the dissection procedure into three parts (D1, D2, and D3) along the main surgical trunk artery root. In Western countries, dissection of the main trunk artery root is not performed, and only dissection below the D2 level is implemented. A retrospective multicenter study analysis by the Japanese Society for Cancer of the Colon and Rectum has revealed a 5–10% incidence of nodal metastasis in the region in which the dissection procedure differs between Japan and the West [29]. This difference in the dissection procedure may have caused the difference in surgical results.

The other factor was a substantial difference in the handling of surgical specimens. In Japan, the median number of lymph nodes examined was 17, and the number examined was less than 12 in 32% of surgical cases. According to the American SEER report, the median number of lymph nodes examined was nine, and the number examined was less than 12 in 63% of surgical cases [30]. Thus, a substantial difference in treatment results was likely to have been caused by "stage migration".

The Japanese Clinical Oncology Group (JCOG) is conducting a comparative study of the safety and efficacy of adjuvant oral fluoropyrimidines (UFT and LV) with FULV in patients with Stage III colon cancer (including tumors located in the upper rectum) [31]. Recruitment of 1,101 patients is complete. An interim analysis has demonstrated a 3-year DFS (FU+LV or UFT+LV) of about 75% [32]. Combination therapy of FULV with OX should also be critically evaluated, not only for survival benefit but also for adverse effects and economic factors.

Acknowledgments We thank the patients and investigators who participated in these two trials. We also thank Mr. Takayuki Aki for his assistance and advice on this paper. This study was supported by the Japan Health Sciences Foundation and by Taiho Pharmaceutical Company, Tokyo, Japan.

Conflict of interest statement None declared.

Appendix

Members of the National Surgical Adjuvant Study of Colorectal Cancer

Study Chairpersons—S. Yoshida; S. Kodaira;

Study Coordinators—K. Shirao; Y. Shimada;

Statistical Analyst—Y. Ohashi;

Evaluation Committee—Y. Moriya; S. Imaoka; T. Kato; S. Kodaira; E. Ikeda; T. Takahashi;

Independent Data and Safety Monitoring Committee—N. Saijo; Y. Ariyoshi; S. Ebihara; H. Origasa; M. Fukuoka; T. Mitsuishi; T. Tsuruo;

Participating Centers—Keiyukai Sapporo Hospital, Hokkaido; Sapporo Kosei General Hospital, Hokkaido; National Hospital Organization Hirosaki National Hospital, Aomori; National Hospital Organization Sendai Medical Center, Miyagi; Miyagi Cancer Center, Miyagi; Yamagata Prefectural Central Hospital, Yamagata; Ibaraki Prefectural Central Hospital, Ibaraki; Tochigi Cancer Center, Tochigi; Gunma Prefectural Cancer Center, Gunma; National Cancer Center Hospital East, Chiba; Cancer Institute Hospital, Tokyo; National Cancer Center Hospital, Tokyo;

24. Kuebler JP, Wieand HS, O'Connell MJ, Smith RE, Colangelo LH, Yothers G, Petrelli NJ, Findlay MP, Seay TE, Atkins JN, Zapas JL, Goodwin JW, Fehrenbacher L, Ramanathan RK, Conley BA, Flynn PJ, Soori G, Colman LK, Levine EA, Lanier KS, Wolmark N (2007) Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol 25:2198–2204
25. Twelves C, Wong A, Nowacki MP, Abt M, Burris H III, Carrato A, Cassidy J, Cervantes A, Fagerberg J, Georgoulias V, Husseini F, Jodrell D, Koralewski P, Kroning H, Maroun J, Marschner N, McKendrick J, Pawlicki M, Rosso R, Schuller J, Seitz J-F, Stabuc B, Tujakowski J, Van Hazel G, Zaluski J, Scheithauer W (2005) Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 352:2696–2704
26. Lembersky BC, Wieand HS, Petrelli NJ, O'Connell MJ, Colangelo LH, Smith RE, Seay TE, Giguere JK, Marshall ME, Jacobs AD, Colman LK, Soran A, Yothers G, Wolmark N (2006) Oral uracil and tegafur plus leucovorin compared with intravenous fluorouracil and leucovorin in stage II and III carcinoma of the colon: results from national surgical adjuvant breast and bowel project protocol C-06. J Clin Oncol 24:2059–2064
27. Allegra C, Sargent DJ (2005) Adjuvant therapy for colon cancer—the pace quickens. N Engl J Med 352:2746–2748
28. Ishiguro M, Sugihara K (2010) Difference in treatment and outcome of colorectal cancer between japan and western countries. Frontiers in colorectal cancer. Medical Review Co., Ltd, Japan, pp 14–19
29. Japanese Society for Cancer of the Colon and Rectum (ed) (2009) JSCCR guidelines 2009 for the treatment of colorectal cancer. Kanehara & Co., Ltd
30. Baxter NN, Virnig DJ, Rothenberger DA, Morris AM, Jessurun J, Virnig BA (2005) Lymph node evaluation in colorectal cancer patients: a population-based study. J Natl Cancer Inst 97:219–225
31. A Trial Comparing Adjuvant Oral UFT/LV to 5-FU/l-LV in Stage III Colorectal Cancer (JCOG-0205-MF)
32. http://www.jcancer.jp/ronbun_db/pdf/40.pdf (in Japanese)

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 non-randomized 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