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ORIGINAL ARTICLE

Colorectal surgery in octogenarian patients—outcomes and predictors of morbidity

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Abstract

Introduction Surgery for elderly patients pose a constant challenge. This study aims to review the outcome and find predictors of adverse outcome in octogenarians undergoing major colorectal resection for cancer.

Methods A review of 121 octogenarians who underwent colorectal cancer surgery between September 1992 and May 2008 was performed. Comorbidities were quantified using the weighted Charlson Comorbidity Index and ASA classification. CR-POSSUM scores and ACPGBI scores and the predicted mortality rates were calculated. Outcome measures were morbidity rates and 30-day mortality rates.

Results The patients had a mean age of 83.5 years (range, 80–99). The mean index of comorbidity was 3.1 (2–7) and 12.5% of patients were classified ASA III and above. The mean predicted mortality rate based on CR-POSSUM and ACPGBI scoring models were 11.2% and 5.4% respectively. The overall observed morbidity rate was 30.7% and 30-day mortality was 1.6. Factors found on bivariate analysis to be significantly associated with an increased risk of morbidity were tumor presenting with complication, comorbid coronary heart disease, serum urea levels, ASA classification ≥3 and comorbidity index 3 of 5 ≥ 5. Multivariate analysis revealed the latter two factors to be independent predictors of morbidity.

Conclusion Octogenarians undergoing major colorectal resection have an acceptable perioperative morbidity and mortality rate and survival rate and should not be denied surgery based on age alone. Comorbidity index scores and ASA scores are useful tools to identify poor risk patients.

Keywords Colorectal cancer · Surgery · Geriatric · Morbidity · Mortality

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Introduction

The number of elderly in Japan hit a record of more than 27 million in 2007. Japanese aged 75 or older accounted for nearly 10% of the population. Similar trends are now being seen in other countries in the world. Surgery for these patients poses a constant challenge. The high incidence of comorbidities and limited functional reserve in these patients make surgical management of these patients complex [1, 2]. Although good results in colorectal surgery has been reported [3, 4], there is a pressing need for identification of those patients who will do poorly so that results can be further improved. The aims of this study are to review the outcome of octogenarians undergoing major colorectal surgery and more importantly to identify the predictors of poor outcome in this complex group of patients.

Materials and methods

Patients who underwent operations for colorectal cancer between September 1992 and May 2008 at our department

Table 1 Patient demographics

	Number	
Mean age in years		83.5
Male	57	47.1%
ADL dependent	3	2.9%
Diabetes mellitus	14	13.3%
Coronary artery disease	17	16.2%
Heart failure	3	2.9%
Chronic lung disease	8	7.6%
BMI of 25 and above	11	16.2%
Mean Charlson weighted comorbidity score		3.1 (range 2–7)
ASA 1	51	48.6%
ASA 2	41	39.0%
ASA 3	13	12.4%

were reviewed. There were 2,771 cases during this period of which 175 cases were octogenarians. Of these, 54 were excluded as they underwent non-resection surgery only (11 underwent endoscopic resection, 11 underwent bypass surgery for recurrent or locally advanced disease) or there was insufficient data. There were 121 octogenarians that underwent major colorectal resection during this period that were analyzed. Data from our prospectively collected computer database were extracted and further clinical information was extracted from review of clinical notes. Individual comorbidities were recorded. Quantification of comorbidities was performed using the weighted Charlson comorbidity index [5] and classification according to the American Society of Anesthesiologists (ASA). Colorectal physiologic and operative severity score for the enumeration of mortality and morbidity (CR-POSSUM) score [6] and the Association of Coloproctology of Great Britain and Ireland scores (ACPGBI) and their predicted mortality rates

Table 2 Operations performed

	Frequency	Percent
Segmental colon resection	40	33.1
Laparoscopic segmental colon resection	15	12.4
Right hemicolectomy and sigmoid colectomy synchronous resection	2	1.7
High anterior resection/sigmoid colectomy	20	16.5
Laparoscopic high anterior resection/sigmoid colectomy	11	9.0
Low anterior resection	17	14.0
Laparoscopic low anterior resection	4	3.3
Abdomino-perineal resection	8	6.6
Hartmann's	2	1.7
Transverse colon segmental resection, partial gastrectomy	1	0.8
Sigmoid colectomy and distal pancreatectomy	1	0.8
Total	121	100.0

Table 3 Tumor characteristics

Stage	Number	Percent
I	21	17.5
II	51	42.5
III	39	32.5
IV	9	7.5
Complicated by obstruction	8	6.6
Complicated by perforation	2	1.7

were calculated. Outcome measures were morbidity rates and 30-day mortality rates. Morbidity was defined as any occurrence of major or minor complication.

Analysis for factors correlating to the development of postoperative complications and mortality were performed using factors that were identified by previous studies to be useful predictors [7, 8].

Bivariate analysis was performed using Chi^2 test using SPSS for Windows (SPSS, Chicago, USA), version 15.0 on an IBM personal computer. 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 or nearly significant ($p<0.06$) were used in multivariate analysis.

Results

The patients had a mean age of 83.5 years (range, 80–99). The demographics and comorbidities of the patients are shown in Table 1. The type of colorectal resection is shown in Table 2. The operation was elective in 97.5% ($n=118$) of cases and laparoscopic resection was performed in 24.8% ($n=30$) of patients. Lower rectal resection was performed in 24.0% ($n=29$) of cases.

The tumor characteristics are shown in Table 3, most patients had stage 2 and 3 disease. Ten patients (8.3%) presented with an acute complication of the tumor. Seven out of these ten patients developed postoperative complications.

Table 4 Perioperative details

Median CR-POSSUM physiology score	14	Range 13–17
Median CR-POSSUM operative score	7	Range 6–16
Mean predicted mortality based on CR-POSSUM	11.2%	Range 5%–76.8%
Mean ACPGBI patient score	1.8	Range 1.1–4.0
Mean predicted mortality rate based on ACPGBI	5.4%	Range 2.3%–29.8%
Median length of stay in days	11	

Table 5 Outcomes

	Number	Percent
Early postoperative complications	37	30.6
Late complications	7	5.7
30-day mortality	2	1.6

Table 7 Late complications (occurring more than 30 days after surgery)

	Frequency	Percent
Adhesions requiring reoperation	3	2.5
Incisional hernia	4	3.3

Other perioperative details are shown in Table 4. The mean predicted mortality rate based on CR-POSSUM and ACPGBI scoring was 11.2% and 5.4%, respectively. Table 5 shows the overall outcomes. Early postoperative complications and late complications (defined as complications occurring more than 30 days after the initial surgery) are listed in Tables 6 and 7. The overall morbidity rate was 30.6%. The observed 30-day mortality was 1.6% which was substantially lower than the predicted rates mentioned above.

Factors found on bivariate analysis to be significantly associated with an increased risk of morbidity were tumor presenting with complication, coronary heart disease, serum urea level, ASA classification ≥3, and comorbidity index ≥5 (Table 8). It should be noted here that in this analysis, laparoscopic surgery and lower rectal surgery were not found to significantly correlate with increased morbidity.

Multivariate analysis revealed ASA classification ≥3 and comorbidity index ≥5 to be independent predictors of morbidity (Table 9).

The mortality rate was too low in this cohort (inadequate events) to allow a similar analysis for its predictors in this study.

At the mean follow-up of 22.7 months, the overall survival was 94.9%.

Discussion

In our experience, octogenarians represented more than 5% of our patients. As the problem of the aging population continues to deepen, we will see more and more octogenarians. It is therefore not surprising that most of the patients in these series were patients that presented in the recent years (>90% of this cohort was performed during the last 10 years of the study period).

Our results concur with some recent studies published on colorectal surgery in elderly patients [3, 9] and confirm the fact that there is acceptable outcome when major colorectal resections are performed on the elderly. These more recent results have been somewhat improved from data that were published more than a decade ago [10–12], suggesting that results have been improved with increased experience in managing this difficult cohort of patients. Geriatric patients in our institution are thoroughly worked-up prior to surgery

Table 6 Postoperative complications

	Frequency	Valid percentage
Major complications		
Acute coronary syndrome	1	0.8
Heart failure	1	0.8
Anastomotic leak	1	0.8
Chest infection/pneumonia	8	6.6
Post-operative delirium	3	2.5
Intestinal obstruction	1	0.8
Prolonged ileus	5	4.1
Lower GI bleeding	2	1.7
Multiorgan failure	2	1.7
PUO	1	0.8
Acute renal failure	1	0.8
SIADH	1	0.8
Wound dehiscence	5	4.1
Minor complications		
Urinary tract infection	2	1.7
Drain site herniation	1	0.8
Line infection	1	0.8
Wound infection	10	8.3

Table 8 Bivariate analysis correlating with postoperative morbidity

Factor	Odds ratio	95% C.I.	p value
Chi^2 test			
Sex	1.09	0.50–2.37	0.82
Laparoscopic surgery	0.96	0.39–2.37	0.93
Low rectal surgery	0.68	0.25–1.71	0.38
Comorbid ADL dependence	0.96	0.08–10.92	0.97
Comorbid diabetes mellitus	3.00	0.95–9.46	0.05
Comorbid coronary artery disease	*3.41*	*1.17–9.92*	*0.02*
Comorbid lung disease	2.03	0.48–8.65	0.33
Tumor presenting with complication	*6.30*	*1.53–25.96*	*0.01*
BMI of above 25	1.46	0.38–5.69	0.58
Tumor above stage 3	1.03	0.47–2.28	0.94
Blood loss more >1,000 ml	4.71	0.41–54.02	0.17
ASA ≥3	*44.96*	*5.59–361.33*	*<0.01*
Comorbidity Index ≥5	*7.91*	*2.73–22.91*	*<0.01*
Student t test			
Preoperative serum albumin			0.18
Preoperative serum urea			*0.01*

Significant parameters in italics

Table 9 Multivariate analysis correlating to postoperative morbidity

Factor	Odds ratio	95% C.I.	*p* value
Tumor presenting with complication	5.36	0.96–29.94	0.06
Cormorbid diabetes mellitus	1.95	0.40–9.41	0.40
Comorbid coronary artery disease	2.04	0.32–12.	0.45
ASA score ≥3	*24.86*	*2.00–308.54*	*0.01*
Comorbidity index ≥5	*3.98*	*1.01–15.76*	*0.05*

Significant parameters in italics

and no effort is spared with regards to preoperative investigations and interdisciplinary referrals and multidisciplinary management. We believe these all contributed to the good results in our geriatric patients.

Compared to other contemporary reports overseas and in Japan [13–15], our morbidity and mortality rates are relatively lower. We believe this is to some extent due to the patients being nearly totally operated on an elective basis and that many of the patients had minimal comorbidities falling into the ASA 1 and 2 categories. These two important factors have been emphasized previously [7].

Our observed mortality rate of 1.6% is somewhat lower than those that were predicted using the CR-POSSUM (11.2%) and ACPGBI (5.4%) models. These models have not been so well validated in the Japanese population and further studies are required to elucidate the roles of these scoring systems, however, there is some suggestion that CR-POSSUM may overestimate predicted mortality especially in the extremes of age [16, 17]. The ACPGBI model seemed to have predicted mortality rates closer to what was observed in this study. While these scoring models are useful as a quality indicator for our practice, caution has to be exercised when using these models for predicting outcome and deciding on surgery.

The relatively low mortality rate with a morbidity rate of 30.6% reflect the fact that while a significant number of these octogenarians do suffer from postoperative complications, they are actually more resilient than we think and with optimal management, many of these patients with complications do pull-through. We however believe that this excellent mortality rate would not have been possible without the contribution of interdisciplinary input and support.

The development of morbidity nonetheless has a major impact on overall outcome. Many elderly who develop postoperative complications have higher mortality rates and do not regain their preoperative functional status [7]. As such, the challenge for geriatric surgeons is to minimize postoperative morbidity as much as possible. The most important ingredient is to effectively identify the patients that have a high risk of developing complications. Perhaps what is important about the findings of this study is the finding that individual factors (eg, presence of diabetes or heart disease, serum albumin) are not significant predictors of morbidity on their own and assessment should be based on tools that are more apt to evaluate the overall well-being of the patient undergoing surgery which include ASA scoring and Charlson comorbidity index. The finding that ASA ≥3 and Charlson comorbidity index ≥5 are independent predictors of morbidity with highly significant odds ratios is not different from the findings in a study on another Asian population [7]. While ASA score is widely used in most surgical papers, the Charlson comorbidity index is somewhat still a geriatrician's tool. From the findings in this paper and an earlier publication, we recommend geriatric surgeons to start using this index in their patient assessment in conjunction with the ASA score. Further prospective study is now being carried out by the author to further validate these tools.

Tumor presenting with complication nearly reached significance in multivariate analysis as an independent predictor of morbidity. This factor may have reached significance if the study population was larger. This is not surprising and is reflected by other studies [7]. It should be emphasized that elderly patients who require surgical resection for colorectal cancer should be performed once optimized and not be postponed until complication of the tumor occurs as this is likely associated with a poorer outcome.

It is interesting to note that laparoscopic surgery and lower rectal resection was not found in this study to be statistically significant predictors of poor outcome. This may suggest that laparoscopic and lower rectal surgery may be safe in this age group. However, at this stage we cannot make such a conclusion as this study was not designed to compare laparoscopy vs. open or lower rectal surgery vs. colonic surgery. There is a definite selection bias in this study and these conclusions should be made rather with another prospective study that is not within the scope of this discussion.

The good short-term survival and minimal late complications accompanied by low mortality rates in our series show that it is worthwhile to perform colorectal resections even in octogenarians. The challenge now is not to decide whether to operate but how to achieve excellent outcomes.

Conclusion

Octogenarians undergoing major colorectal resection have an acceptable perioperative morbidity and mortality rate and survival rate and should not be denied surgery based on age alone. Comorbidity index scores and ASA scores are useful tools to identify poor risk patients.

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ORIGINAL CONTRIBUTION

Outcomes of Surgery Alone for Lower Rectal Cancer With and Without Pelvic Sidewall Dissection

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PURPOSE: The goal of this retrospective multicenter study was to investigate the efficacy of pelvic sidewall dissection for lower rectal cancer.

METHODS: Data from 1,272 consecutive patients who underwent total mesorectal excision for lower rectal cancer in 12 institutions from 1991 through 1998 were reviewed. The rates of local recurrence and survival in patients with pelvic sidewall dissection were compared with those without pelvic sidewall dissection. Logistic regression analysis was used to determine independent risk factors for lymph node metastasis and local recurrence, and the Cox proportional hazards model was used to determine independent prognostic factors.

RESULTS: Of the 1,272 patients, 784 underwent pelvic sidewall dissection. Among them, 117 patients (14.9 percent) had lateral pelvic lymph node metastasis. Risk factors for lateral pelvic lymph node metastasis included female gender, tumor not well-differentiated adenocarcinoma, and perirectal lymph node metastasis. Lateral pelvic and perirectal lymph node metastases were independent risk factors for local recurrence. The Cox proportional hazard model showed age, grade of histology, invasion depth of the tumor, perirectal lymph node metastasis, and lateral pelvic lymph node metastasis to be independent prognostic factors. No significant differences between patients with and those without pelvic sidewall dissection were seen regarding rates of local recurrence (10.5 percent *vs.* 7.4 percent) or five-year overall survival (75.8 percent *vs.* 79.5 percent). Although the proportion of patients with advanced stages of disease was greater in patients who had pelvic sidewall dissection, no differences between the two groups were seen in local recurrence even when tumor category was taken into account. However, lack of pelvic sidewall dissection was a predictor of poor prognosis.

CONCLUSIONS: Although pelvic sidewall dissection does not appear to confer overall benefits regarding local recurrence or survival, the effectiveness of pelvic sidewall dissection in specific patient groups remains uncertain. A randomized controlled study is necessary to clarify this issue.

KEY WORDS: Rectal cancer; Lateral pelvic lymph node; Pelvic sidewall dissection; Local recurrence; Prognosis.

Colorectal cancer is the third most common cause of cancer-related death in the United States and Japan.[1] It is well known that, because of its high rate of local recurrence, rectal cancer is associated with a worse prognosis than colon cancer. Various therapies for rectal cancer have been developed since Miles described a method for systematic resection in 1908.[2] In the United States, aortopelvic lymphadenectomy was performed as extended lymph node dissection in the 1950s.[3] However, the effectiveness of lateral pelvic lymph node dissection was not accepted in Western countries. Stearns and Deddish[4] reported that extended lymphadenectomy

Study Group for Rectal Cancer Surgery of the Japanese Society for Cancer of the Colon and Rectum.

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in rectal cancer led to an increase of blood loss and urinary and sexual dysfunction without any survival benefit. Since then, pelvic sidewall dissection has rarely been performed in Western countries. In addition, lateral pelvic lymph node metastasis was considered part of the systemic disease.

In 1982, Heald[5] proposed a new concept for resection of rectal cancer, total mesorectal excision. This technique decreased the rate of local recurrence in patients with rectal cancer. Total mesorectal excision with chemoradiotherapy has now become the standard treatment for advanced rectal cancer in Western countries. In Japan, pelvic sidewall dissection has been actively performed along with total mesorectal excision for rectal cancer since the late 1970s, pelvic sidewall dissection has been reported to be useful in advanced lower rectal cancer.[6] In past studies, the rates of positive lateral nodes have ranged from 10.6 percent to 25.5 percent.[7–13] However, there has been no randomized controlled study on the usefulness of pelvic sidewall dissection in patients with rectal cancer. Therefore, the definitive efficacy of pelvic sidewall dissection is still unclear.

The 6th edition of the AJCC cancer staging manual[14] designated both internal and external iliac lymph nodes as regional nodes in rectal cancer. However, details regarding lateral pelvic lymph nodes were not mentioned.

The aim of this retrospective multicenter study was to clarify the characteristics of lymph node metastasis located in the pelvic sidewall as well as in the mesorectum in patients with lower rectal cancer and to investigate the efficacy of pelvic sidewall dissection performed in addition to total mesorectal excision. We previously reported on the indications for pelvic sidewall dissection both in patients with upper and in those with lower rectal cancer from the database of the 12 member institutes of the Japanese Society for Cancer of the Colon and Rectum.[15] In the present study, we clarified details of the outcomes of surgery alone for lower rectal cancer with and without pelvic sidewall dissection.

PATIENTS AND METHODS

Patients

We reviewed records of 1,272 patients with lower rectal cancer enrolled in a database of patients who underwent curative resection at 12 institutions between 1991 and 1998. None of the patients received radiotherapy in this study. Lower rectal cancer was defined as the distal margin of tumor being located below the peritoneal reflection. All institutions were members of the Japanese Society for Cancer of the Colon and Rectum. This study was approved by the local Ethics Committee of each institution. All patients received total mesorectal excision.

The indications for pelvic sidewall dissection were T2-T4 in five institutions, T3-T4 in two, suspected positive lymph nodes in the mesorectum in one, and T3-T4 or suspected positive lymph nodes in the mesorectum in four. These criteria were determined at each institution based on risk analysis of lateral pelvic lymph node metastasis. Patients who underwent transanal local excision or endoscopic mucosal resection were excluded from this study. Other exclusion criteria were cancers associated with ulcerative colitis, Crohn's disease, or familial adenomatous polyposis.

Preoperative investigations included barium enema examination, colonoscopy, endoscopic ultrasonography, chest x-ray, ultrasonography (US) or computed tomography (CT) of the liver, and blood tests using carcinoembryonic antigen (CEA). Most institutions established a follow-up examination period of 5 to 10 years. The follow-up system consisted of serum tumor marker measurements every three months for the first three years and every six months for the next two years, hepatic imaging (US or CT) and chest x-ray every three to six months, pelvic CT every year, and colonoscopy every one to two years.

Statistical Analysis

We analyzed the risk factors for perirectal lymph node metastasis in all 1,272 patients who underwent total mesorectal excision and those for lateral pelvic lymph node metastasis in the 784 patients who had pelvic sidewall dissection in addition to total mesorectal excision. Prognostic factors were also analyzed.

Statistical analysis was performed using the StatView statistical package (StatView 5.0; Abacus Concepts, Inc., Berkeley, CA). Data are expressed as numbers of patients and percentages or means±standard deviation. The relationships between each parameter and lymph node metastasis or local recurrence were analyzed using the chi-squared test. Logistic regression analysis was used to determine independent risk factors for lymph node metastasis and local recurrence. The Kaplan-Meier method was used to calculate the actuarial survival of patients. Overall survival rates in all groups were compared by log rank test. Cox's proportional hazards model was used to determine independent prognostic factors in patients with lower rectal cancer. Statistical significance was established at $P < 0.05$ for all results.

RESULTS

Pelvic Sidewall Dissection

Of the 1,272 patients, 784 underwent pelvic sidewall dissection in addition to total mesorectal excision. Characteristics of patients with and without pelvic sidewall dissection are shown in Table 1. Pelvic sidewall dissection was more likely to be performed in younger than in older patients. Patients who had pelvic sidewall dissection were significantly more likely to have tumors ≥4 cm in size ($P < 0.0001$), not well differentiated adenocarcinoma ($P = 0.0006$), greater depth of tumor invasion ($P < 0.0001$),

TABLE 1. Characteristics of patients with and without pelvic sidewall dissection

	PSD (n = 784)		No PSD (n = 488)		
	n	(%)	n	(%)	P value
Gender					
Male	507	(64.7)	296	(60.7)	0.15
Female	277	(35.3)	192	(39.3)	
Age (yr)					
≥62	348	(44.4)	252	(51.6)	0.011
<62	436	(55.6)	235	(48.2)	
Unknown			1		
Size (cm)					
<4	246	(31.4)	299	(61.3)	<0.0001
≥4	535	(68.2)	182	(37.3)	
Unknown	3	(0.4)	7		
Histology					
Well or moderately differentiated adenocarcinoma	723	(92.2)	471	(96.5)	0.0006
Others	61	(7.8)	15	(3.1)	
Unknown	0		2	(0.4)	
T category					
T1	37	(4.7)	196	(40.2)	<0.0001
T2	207	(26.4)	127	(26.0)	
T3	497	(63.4)	157	(32.2)	
T4	43	(5.5)	8	(1.6)	
AJCC staging					
I	179	(22.8)	282	(57.8)	<0.0001
II	224	(28.6)	86	(17.6)	
III	381	(48.6)	120	(24.6)	

PSD = pelvic sidewall dissection.

and a more advanced stage of cancer ($P < 0.0001$) than those who did not receive pelvic sidewall dissection. For example, the proportion of patients with category T3 or T4 tumors or cancer stage III was approximately twice as high in patients who received pelvic sidewall dissection as in those who did not.

Lymph Node Metastasis

Perirectal lymph node metastasis was observed in 476 (37.4 percent) of all patients who underwent surgery, and lateral pelvic lymph node metastasis was observed in 117 (14.9 percent) of those who had pelvic sidewall dissection (Table 2). The rates of both types of metastasis increased significantly with depth of tumor invasion ($P <$ 0.0001). Table 3 shows the distribution of patients with each type of node metastasis in relation to tumor category for the 784 patients with pelvic sidewall dissection. A total of 92 patients (11.7 percent) had both types of metastasis, 263 (33.5 percent) had only perirectal, 25 (3.2 percent) had only lateral pelvic, and 404 (51.5 percent) had no neither type of lymph node metastasis.

The lateral pelvic area was classified into 6 parts (Fig. 1): internal iliac areas both distal and proximal to superior vesical artery, obturator area, external iliac area, common iliac area, and aortic bifurcation area. Of the 117 patients with lateral pelvic lymph node metastasis, 55 (47 percent) had lymph node metastasis along the internal iliac artery distal to the superior vesical artery, 45 (38 percent) in the obturator area, and 30 (26 percent) along the internal iliac artery proximal to superior vesical artery. Only 9 patients (7.7 percent) had lateral pelvic lymph node metastasis found in other areas.

TABLE 2. Lymph node metastasis in patients with lower rectal cancer in relation to tumor invasion depth of tumor

	All patients			Patients with PSD		
		Perirectal LNM			Lateral pelvic LNM	
Tumor category	Total	n	(%)	Total	n	(%)
T1	233	19	(8.2)	37	2	(5.4)
T2	334	81	(24.3)	207	17	(8.2)
T3	654	347	(53.1)	497	82	(16.5)
T4	51	29	(56.9)	43	16	(37.2)
Total	1272	476	(37.4)	784	117	(14.9)

PSD = pelvic sidewall dissection; LNM = lymph node metastasis.

TABLE 3. Type of lymph node metastasis in relation to tumor category in 784 patients with pelvic sidewall dissection

	Perirectal + Lateral pelvic +		Perirectal + Lateral pelvic −		Perirectal − Lateral pelvic +		Perirectal − Lateral pelvic −		Total	
Tumor	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
T1	1	(2.7)	5	(13.5)	1	(2.7)	30	(81.1)	37	(100)
T2	11	(5.3)	41	(19.8)	6	(2.9)	149	(72.0)	207	(100)
T3	67	(13.5)	204	(41.0)	15	(3.0)	211	(42.5)	497	(100)
T4	13	(30.2)	13	(30.2)	3	(7.0)	14	(32.6)	43	(100)
Total	92	(11.7)	263	(33.5)	25	(3.2)	404	(51.5)	784	(100)

Risk factors for perirectal lymph node metastasis. Parameters such as gender, age, size of tumor, histology of tumor, T category, lymphatic invasion, and venous invasion were analyzed as potential risk factors for perirectal lymph node metastasis in the 1,272 patients undergoing total mesorectal excision for lower rectal cancer (Table 4). All of the above-mentioned variables had significant effects on perirectal lymph node metastasis in a univariate analysis. Multivariate analysis showed female gender (P = 0.0004), age under 62 years old (P = 0.0073), histology other than well or moderately differentiated adenocarcinoma (P = 0.0008), T category (T3 or T4, P < 0.0001), lymphatic invasion (P < 0.0001), and venous invasion (P = 0.037) to be independent risk factors for perirectal lymph node metastasis.

Risk factors for pelvic lymph node metastasis. In the 784 patients undergoing pelvic sidewall dissection in addition to total mesorectal excision for lower rectal cancer, univariate analysis showed significant effects of female gender, size of tumor, histology, T category, lymphatic invasion, venous invasion, and perirectal lymph node metastasis on lateral pelvic lymph node metastasis (Table 5). Only female gender (P = 0.0037), histology other than well or moderately differentiated adenocarcinoma (P = 0.0047), and the presence of perirectal lymph node metastasis (P < 0.0001) were independent risk factors for lateral pelvic lymph node metastasis on multivariate analysis.

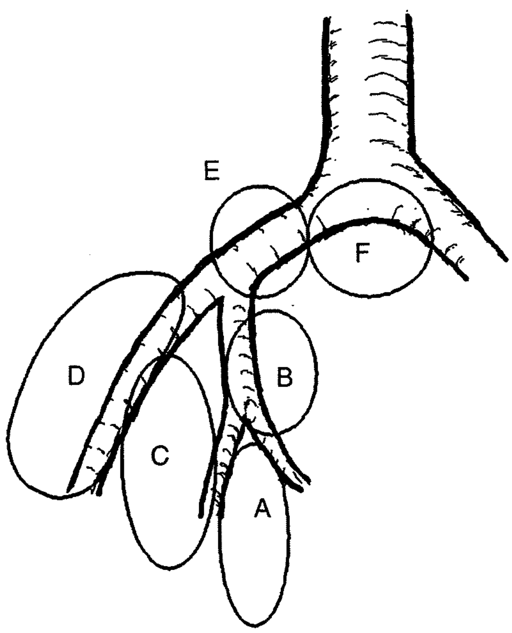

FIGURE 1. A schema of the lateral pelvic area: **(A)** internal iliac area distal to superior vesical artery and **(B)** proximal to superior vesical artery, **(C)** obturator area, **(D)** external iliac area, **(E)** common iliac area, and **(F)** aortic bifurcation area.

Local Recurrence of Cancer

Of all 1272 patients undergoing total mesorectal excision, 118 (9.3 percent) had a local recurrence of cancer. The mean follow-up was 3.3 ± 1.9 years in patients with and 5.1 ± 2.3 years in those without recurrence. As shown in Table 6, the rate of recurrence did not differ between patients who had pelvic sidewall dissection and those who did not (10.5 percent *vs.* 7.4 percent), regardless of the invasion depth of the tumor.

The rate of local recurrence was 4.1 percent in patients with stage I lower rectal cancer, 5.8 percent in those with stage II, and 16.1 percent in those with stage III. Of the 117 patients with lateral pelvic lymph node metastasis, 28 (23.9 percent) experienced local recurrence.

Risk factors for local recurrence. In the 784 patients who underwent pelvic sidewall dissection in addition to total mesorectal excision, univariate analysis showed significant effects of female gender, size of tumor, histology, tumor category, perirectal lymph node metastasis, and lateral pelvic lymph node metastasis local recurrence (Table 7). Multivariate analysis revealed that perirectal lymph node metastasis (P = 0.0016) and lateral pelvic lymph node metastasis (P = 0.0075) were independent risk factors for local recurrence.

Survival

No significant difference in overall five-year survival was seen between patients with pelvic sidewall dissection and those without pelvic sidewall dissection (75.8 percent *vs.* 79.5 percent) (Fig. 2). However, although no differences were seen between the two groups in patients with stage I or stage III cancer, patients with stage II lower rectal cancer who underwent pelvic sidewall dissection had a significantly better prognosis (87.0 percent five-year survival)

TABLE 4. Risk factors for perirectal lymph node metastasis in 1,272 patients with lower rectal cancer

		Perirectal LNM		Univariate analysis			Multivariate analysis		
	Total	n	(%)	OR	95% CI	P value	OR	95% CI	P value
Gender									
Male	803	278	(34.6)	1			1		
Female	469	198	(42.2)	1.38	1.09–1.74	0.007	1.63	1.25–2.13	0.0004
Age (yr)									
≥62	642	221	(46.4)	1			1		
<62	629	255	(53.6)	1.03	1.03–1.63	0.0244	1.43	0.54–0.91	0.0073
Unknown	1								
Size (cm)									
<4	545	136	(25.0)	1			1		
≥4	717	339	(47.3)	2.70	2.12–3.44	<0.0001	1.29	0.95–1.76	NS
Unknown	10								
Histology									
Well or moderately differentiated adenocarcinoma	1194	425	(35.6)	1			1		
Others	76	51	(67.1)	3.69	2.26–6.04	<0.0001	2.48	1.46–4.22	0.0008
Unknown	2								
T category									
T1–2	567	100	(17.6)	1			1		
T3–4	705	376	(53.3)	5.35	4.12–6.94	<0.0001	3.46	2.50–4.78	<0.0001
Lymphatic invasion									
Absent	343	46	(13.4)	1			1		
Present	922	430	(46.6)	5.64	4.03–7.90	<0.0001	3.50	2.42–5.06	<0.0001
Unknown	7								
Venous invasion									
Absent	493	120	(24.3)	1		<0.0001	1		
Present	772	356	(46.1)	2.66	2.07–3.41		1.36	1.02–1.82	0.037
Unknown	7								

OR = odds ratio; CI = confidence interval; LNM = lymph node metastasis.

than those who did not (67.1 percent five-year survival); $P = 0.0026$).

Prognostic factors. In Cox proportional hazard analyses of all 1,272 patients with lower rectal cancer, age ($P = 0.0015$), histology ($P = 0.0002$), T category ($P = 0.0002$), perirectal lymph node metastasis ($P < 0.0001$), and pelvic sidewall dissection ($P = 0.029$) were independent prognostic factors (Table 8). In the 784 patients with pelvic sidewall dissection, age ($P = 0.0017$), histology ($P = 0.0047$), T category ($P = 0.021$), perirectal lymph node metastasis ($P < 0.0001$), and lateral pelvic lymph node metastasis ($P < 0.0001$) were independent prognostic factors (Table 9). In patients with stage III lower rectal cancer, the five-year survival rate of those without lateral pelvic lymph node metastasis was 67.3 percent *vs.* 47.7 percent for patients with lateral pelvic lymph node metastasis.

DISCUSSION

In this study, 37.4 percent of patients with lower rectal cancer had perirectal lymph node metastasis and 14.9 percent of those who underwent pelvic sidewall dissection had lateral pelvic lymph node metastasis. The rates of lateral pelvic lymph node metastasis reported in previous studies vary from 10.6 percent to 25.5 percent, with most reporting rates around 15 percent.[7,8,11–13] Thus, our result was consistent with those of previous studies.

The rates of perirectal lymph node metastasis and lateral pelvic lymph node metastasis increased with the invasion depth of the tumor. A total of 16.5 percent of patients with T3 tumors and 37.2 percent of those with T4 tumors had lateral pelvic lymph node metastasis. Effective treatment of lateral pelvic lymph node metastasis would likely improve the prognosis of patients with T3 and T4 lower rectal cancer.

We investigated the risk factors for both perirectal lymph node metastasis and lateral pelvic lymph node metastasis and found that female gender and histology showing the main tumor to be not well or moderately differentiated were independent risk factors for both types of lymph node metastasis in lower rectal cancer. The reason why female gender was a risk factor was obscure. There is some possibility that a female hormone such as estrogen is associated with lymph node metastasis, as appears to be the case in breast cancer.[16] Further studies will be essential to clarify this issue.

In our study, multivariate analysis revealed that, in addition to perirectal lymph node metastasis, lateral pelvic lymph node metastasis was an independent risk factor for local recurrence. Our patients with lateral pelvic lymph node metastasis had a local recurrence rate of 23.9

TABLE 5. Risk factors for lateral pelvic lymph node metastasis in 784 patients with pelvic sidewall dissection

		Lateral pelvic LNM		Univariate analysis			Multivariate analysis		
	Total	n	(%)	OR	95% CI	P value	OR	95% CI	P value
Gender									
Male	507	60	(11.8)	1			1		
Female	277	57	(20.6)	1.93	1.30–2.87	0.001	1.88	1.23–2.87	0.0037
Age (yr)									
≥62	398	54	(13.6)	1					
<62	386	63	(16.3)	1.24	0.84–1.84	0.279	...	...	...
Size (cm)									
<4	246	22	(8.9)	1			1		
≥4	535	95	(17.8)	2.20	1.35–3.59	0.0013	1.67	0.92–3.01	0.085
Unknown	3								
Histology									
Well or moderately differentiated adenocarcinoma	723	96	(13.3)	1			1		
Others	61	21	(34.4)	3.43	1.94–6.06	<0.0001	2.48	1.35–4.55	0.0047
T category									
T1–2	244	19	(7.8)	1			1		
T3–4	540	98	(18.1)	2.63	1.57–4.40	0.0002	1.18	0.63–2.24	0.60
Lymphatic invasion									
Absent	134	9	(6.7)	1			1		
Present	648	108	(16.7)	2.78	1.37–5.63	0.0033	1.42	0.66–3.05	0.36
Unknown	2								
Venous invasion									
Absent	232	22	(9.5)	1			1		
Present	551	95	(17.2)	1.99	1.22–3.25	0.0054	1.67	0.97–2.85	0.056
Unknown	1								
Perirectal LNM									
Absent	429	25	(5.8)	1			1		
Present	355	92	(25.9)	5.65	3.54–9.03	<0.0001	4.22	2.58–6.90	<0.0001

OR = odds ratio; CI = confidence interval; LNM = lymph node metastasis.

percent, compared with the overall rate of 9.3 percent in our series. In patients undergoing curative resection for T3 or T4 rectal tumors, Ueno *et al.*[13] found a local recurrence rate of 44.0 percent in patients with lateral pelvic lymph node metastasis and 11.7 percent in those without ($P < 0.001$).

Lateral pelvic lymph node metastasis was also an independent predictor of poor prognosis in our patients with pelvic sidewall dissection, as were age, histology, T category, and perirectal lymph node metastasis. In patients with stage III lower rectal cancer, the five-year survival rate of those without lateral pelvic lymph node metastasis was approximately 20 percentage points higher than that of patients with lateral pelvic lymph node metastasis. Therefore, adjuvant therapy for patients with lateral pelvic lymph node metastasis is important. Patients with stage III colorectal cancer usually receive adjuvant chemotherapy. However, more intensive chemotherapy might be recommended for those with lateral pelvic lymph node metastasis.

The definition of the lateral pelvic area in the 6th edition of AJCC cancer staging manual seems rather unclear. The present study showed that lymph node metastasis along the external iliac artery was very rare. More than 90 percent of metastatic lymph nodes were located in the obturator area and along the internal iliac

TABLE 6. Local recurrence of cancer in patients with and without pelvic sidewall dissection

	PSD			Non-PSD				All		
		Recurrence			Recurrence				Recurrence	
	Total	n	(%)	Total	n	(%)	P value	Total	n	(%)
T1	37	1	(2.7)	196	4	(2.0)	NS	233	5	(2.1)
T2	207	10	(4.8)	127	10	(7.9)	NS	334	20	(6.0)
T3	497	61	(12.3)	157	21	(13.4)	NS	654	82	(12.5)
T4	43	10	(23.1)	8	1	(12.5)	NS	51	11	(21.6)
Total	784	82	(10.5)	488	36	(7.4)	NS	1272	118	(9.3)

PSD = pelvic sidewall dissection; NS = not significant.

TABLE 7. Risk factors for local recurrence of cancer in 784 patients with pelvic sidewall dissection

		Local recurrence		Univariate analysis			Multivariate analysis		
	Total	n	(%)	OR	95% CI	P value	OR	95% CI	P value
Gender									
Male	507	43	(8.5)	1			1		
Female	277	39	(14.1)	1.77	1.12–2.80	0.01	1.56	0.96–2.53	0.073
Age (yr)									
<62	436	45	(10.3)	1					
≥62	348	37	(10.6)	1.03	0.65–1.64	0.89	...	...	...
Size (cm)									
<4	246	16	(6.5)	1			1		
≥4	535	66	(12.3)	2.02	1.15–3.57	0.01	1.21	0.63–2.35	0.57
Unknown	3								
Histology									
Well or moderately differentiated adenocarcinoma	723	68	(9.4)	1			1		
Others	61	14	(23.0)	2.87	1.50–5.48	0.0009	1.78	0.89–3.55	0.10
T category									
T1–2	244	11	(4.5)	1			1		
T3–4	540	71	(13.1)	3.21	1.67–6.17	0.0003	1.99	0.93–4.25	0.077
Lymphatic invasion									
Absent	134	11	(8.2)	1					
Present	648	71	(11.0)	1.38	0.71–2.67	0.34	...	...	...
Unknown	2								
Venous invasion									
Absent	232	20	(8.6)	1					
Present	551	62	(11.3)	1.34	0.79–2.28	0.27	...	...	...
Unknown	1								
Perirectal LNM									
Absent	429	22	(5.1)	1			1		
Present	355	60	(16.9)	3.76	2.26–6.27	<0.0001	2.43	1.40–5.89	0.0016
Lateral pelvic LMN									
Absent	667	54	(8.1)	1			1		
Present	117	28	(23.9)	3.57	2.15–5.93	<0.0001	2.11	1.22–3.65	0.0075

OR = odds ratio; CI = confidence interval; LNM = lymph node metastasis.

artery. The lymph nodes in the internal iliac area distal to the superior vesical artery were most frequently involved. Almost half of the lateral pelvic lymph node metastases were located in this area. The next most frequent site of

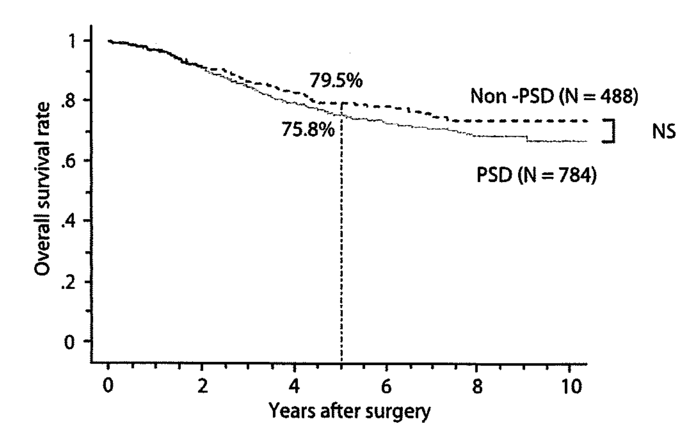

FIGURE 2. The overall survival curve of patients with and without pelvic sidewall dissection. The 5-year overall survival rates in patients with and without pelvic sidewall dissection were 75.8 percent and 79.5 percent, respectively.

lateral pelvic lymph node metastasis was the obturator area. Canessa *et al.*[17] reported an anatomic study using cadaveric dissection, in which most of the metastatic lymph nodes found in the lateral pelvic area were located in the obturator area. Therefore, we believe that the next AJCC cancer staging manual should mention not the external iliac area but the obturator area as a site of regional lymph node metastasis in lower rectal cancer.

In many Western countries, the standard therapy for lower rectal cancer is total mesorectal excision with chemoradiotherapy.[18,19] In Japan, total mesorectal excision with pelvic sidewall dissection is accepted as a standard treatment, but the effectiveness of pelvic sidewall dissection has been controversial. We observed no differences in the rates of local recurrence between patients with and those without pelvic sidewall dissection. Because patients undergoing pelvic sidewall dissection tended to have more advanced disease, this finding may not be surprising. However, we found no difference in recurrence rates for any invasion depth of the tumor.

A recent study in patients with stage II or stage III rectal cancer reported a higher rate of local recurrence

TABLE 8. Prognostic factors for overall survival in 1272 patients with lower rectal cancer

	Patients	Cox proportional hazard model		
	n	HR	95% CI	P value
Gender				
Male	803	1		
Female	469	0.88	0.69–1.13	0.32
Age (yr)				
≥62	642	1		
<62	629	1.47	1.16–1.87	0.0015
Size (cm)				
<4	545	1		
≥4	717	1.13	0.84–1.54	0.42
Unknown	10			
Histology				
Well or moderately differentiated adenocarcinoma	1194	1		
Others	76	2.01	1.39–2.90	0.0002
Unknown	2			
T category				
T1–2	567	1		
T3–4	705	1.90	1.35–2.67	0.0002
Lymphatic invasion				
Absent	343	1		
Present	922	1.33	0.94–1.88	0.11
Unknown	7			
Venous invasion				
Absent	493	1		
Present	772	1.18	0.90–1.56	0.23
Unknown	7			
Perirectal LNM				
Absent	796	1		
Present	476	2.26	1.75–2.93	<0.0001
Pelvic sidewall dissection				
Performed	784	1		
Not performed	488	1.36	1.03–1.78	0.029

HR = hazard ratio; CI = confidence interval; LNM = lymph node metastasis.

rate with pelvic sidewall dissection than with chemoradiotherapy.[20] However, that study was neither randomized nor case-matched. Watanabe *et al.*[21] found no differences in recurrence in patients with T3 or T4 rectal tumors who underwent radiation with or without pelvic sidewall dissection, but the number of subjects in that study was small. A randomized controlled study is essential to clarify the effect of pelvic sidewall dissection on local recurrence in patients with advanced lower rectal cancer.

We also found no difference in overall survival between patients with and those without pelvic sidewall dissection. Again, this may not be surprising because of the more advanced state of disease in the group receiving pelvic sidewall dissection. However, the Cox proportional hazards model showed that lack of pelvic sidewall dissection was a significant predictor of poor prognosis. In addition, patients with stage II lower rectal cancer who had pelvic sidewall dissection appeared to have a significantly better prognosis than those without pelvic sidewall dissection, although patients with stage I or III lower rectal cancer did not receive the same survival benefit. Thus, the indication for pelvic sidewall dissection may be potentially limited to those with stage II. However, the possibility exists that the better prognosis in patients with stage II cancer with pelvic sidewall dissection was a result of stage migration. Namely, patients with a diagnosis of stage II who did not undergo pelvic sidewall dissection may have actually had stage III disease that went undiagnosed because the nodes were not identified.

Fujita *et al.*[22] reported that pelvic sidewall dissection improved the prognosis of rectal cancer patients with a small number of lymph node metastases. In their study, the five-year disease-free survival rate was 73.3 percent in patients with N1 lymph node metastasis who underwent pelvic sidewall dissection, and 35.3 percent in those without pelvic sidewall dissection ($P = 0.013$). In contrast, Nagawa *et al.*[23] demonstrated that pelvic sidewall dissection was not necessary in patients with advanced lower rectal cancer who underwent preoperative radiotherapy. In their study, no difference was observed in either overall survival or disease-free survival between patients with and those without pelvic sidewall dissection in addition to preoperative radiotherapy. Their study was a randomized controlled trial, but the number of recruited patients was only 51. A large-scale randomized controlled study on the efficacy of pelvic sidewall dissection has not yet been

TABLE 9. Prognostic factors for overall survival in 784 patients with pelvic sidewall dissection

	Patients	Cox proportional hazard model		
	n	HR	95% CI	P value
Gender				
Male	507	1		
Female	277	0.80	0.59–1.08	0.15
Age (yr)				
<62	436	1		
≥62	348	1.59	1.19–2.11	0.0017
Size (cm)				
<4	246	1		
≥4	535	0.97	0.66–1.43	0.87
Unknown	3			
Histology				
Well or moderately differentiated adenocarcinoma	723	1		
Others	61	1.83	1.20–2.79	0.0047
T category				
T1–2	244	1		
T3–4	540	1.68	1.08–2.62	0.021
Lymphatic invasion				
Absent	134	1		
Present	648	1.50	0.90–2.51	0.11
Unknown	2			
Venous invasion				
Absent	232	1		
Present	551	1.25	0.88–1.78	0.22
Unknown	1			
Perirectal LNM				
Absent	429	1		
Present	355	2.47	1.78–3.45	<0.0001
Lateral pelvic LNM				
Absent	667	1		
Present	117	2.27	1.63–3.14	<0.0001

HR = hazard ratio; CI = confidence interval; LNM = lymph node metastasis.

reported. However, a phase III trial (JCOG 0212) of the effectiveness of pelvic sidewall dissection is ongoing in Japan and will recruit 600 patients in total.

In conclusion, we found no differences in the rates of local recurrence between the pelvic sidewall dissection group and the non-pelvic sidewall dissection group, although there might be a selection bias for pelvic sidewall dissection. Lateral pelvic lymph node metastasis is a risk factor for both local recurrence and overall survival. A randomized controlled trial will be essential to test the survival benefit of pelvic sidewall dissection in patients with advanced lower rectal cancer.

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Timing of Relapse and Outcome after Curative Resection for Colorectal Cancer: A Japanese Multicenter Study

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Key Words

Colorectal cancer · Treatment for relapse · Curative resection · Time to relapse · Recurrence

Abstract

Background: The aim of this multicenter study was to clarify the influence of timing of relapse after curative resection for colorectal cancer on prognosis. ***Methods:*** We enrolled 5,230 consecutive patients who underwent curative resection for colorectal cancer at 14 hospitals from 1991 to 1996. All patients were intensively followed up. Time to relapse (TR) was classified into three groups as follows: group A, TR ≤1 year; group B, TR >1 year and ≤3 years, and group C, TR >3 years. The prognoses after relapse were compared among the three groups. ***Results:*** Of the 5,230 patients, 906 experienced relapse (17.3%). The curative resection rates for recurrent tumors were 35.2% in group A, 46.6% in group B, and 45.1% in group C ($p = 0.0045$). There were significant differences in the prognoses after relapse among the three TR groups in patients with relapse to the liver ($p = 0.0175$) and in those with local relapses ($p = 0.0021$), but not in those with pulmonary or anastomotic recurrence. There were no differences in prognoses after relapse in any recurrence site among the three groups in patients who underwent curative resection for relapse. ***Conclusion:*** If patients can undergo curative resection for relapse, they receive a survival benefit regardless of the timing of relapse.

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Introduction

Colorectal cancer is the second most common cause of cancer death in both the USA and Japan, and is one of the most rapidly expanding diseases in Japan [1, 2]. Although the most promising treatment for colorectal cancer is curative resection, some of the patients with curative resection for colorectal cancer develop relapse [3]. Therefore, it is important to improve the outcome of treatment for relapse of colorectal cancer.

Recent remarkable advances of multiagent chemotherapies, including those using molecular target drugs, have improved the prognosis of metastatic colorectal cancer [4–6]. However, the complete resection of metastatic tumors is still the best treatment for this disease. There have been many studies investigating the outcome of resection for metastatic tumors of colorectal cancer. The 5-year survival rates after resection for hepatic and pulmonary metastases ranged from 27 to 58% and from 29 to 64%, respectively [7–17]. Most of the relapses occur within 5 years after curative resection for colorectal cancer [3]. However, it remains uncertain whether there is an association between the timing of relapse and the outcome. Kornprat et al. [18] demonstrated that the disease-free interval from colorectal surgery to liver metastases was not associated with the prognosis after hepatectomy. On the other hand, it has been reported that the disease-free survival after hepatectomy in patients with metachronous liver metastasis is better than that in patients with synchronous liver metastasis [19].

The relationship between the time to relapse (TR) and the rate of resection after relapse remains unclear. Further, the association between the outcome in patients treated with resection for relapse and the TR is also obscure.

The aim of this retrospective multicenter study was to clarify the association between TR after resection for colorectal cancer and prognosis after relapse.

Patients and Methods

The study group of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) on postsurgical surveillance of colorectal cancer collected data on 5,230 consecutive patients who underwent curative resection at 14 member institutions from January 1991 to December 1996. The patients with T1 cancers which were removed by endoscopical or transanal resection were excluded from this study. The patients with cancers associated with familial adenomatous polyposis, ulcerative colitis or Crohn's disease were also excluded. Treatment of recurrent tumors was decided according to the criteria of each institution. The local ethics committee of each institution approved this study. Recurrence sites were classified into liver, lung, local, anastomosis, and others. Other recurrence sites consisted of bone, brain, ovary, distant lymph node, and so on. Peritoneal carcinomatosis was also classified into others.

Table 1. A Cox proportional hazards model for prognosis after relapse

	n	p value	Hazard ratio	95% CI
Age				
<63 years	456	NS	1	
≥63 years	450		1.15	0.99–1.33
Histologic grade				
Well- or moderately differentiated adenocarcinoma	835	0.012	1	
Poorly differentiated adenocarcinoma or mucinous carcinoma	70		1.40	1.08–1.82
Unknown	1			
Direct invasion of the primary tumor to other organs				
Absent	840	0.0010	1	
Present	65		1.58	1.20–2.07
Unknown	1			
TNM stage				
Stage I	51	NS	1.14	0.81–1.60
Stage II	255		0.85	0.72–1.01
Stage III	600		1	
Time to relapse (TR)				
A	358	NS	1.16	0.93–1.46
B	395		1.07	0.86–1.34
C	153		1	
Resection for relapse with curative intent				
Absent	527	<0.0001	1	
Present	379		0.26	0.22–0.31

CI = Confidence interval. A = TR ≤ 1 year; B = 1 year < TR ≤ 3 years; C = 3 years < TR.

Follow-Up Examination

All patients had intensive prospective follow-up after surgery according to the follow-up protocols of each institution. Most institutions established a follow-up examination period of 5–10 years. The standard follow-up protocol was as follows: measurement of a serum tumor marker and hepatic imaging (ultrasonography and/or computed tomography) every 3 months for the first 3 years and every 6 months for the next 2 years, and chest X-ray every 6 months, pelvic CT for rectal cancer every year, and colonoscopy every 1–2 years.

Timing of Relapse

Patients were classified into three groups according to the TR: group A, TR ≤ 1 year; group B, 1 year < TR ≤ 3 years, and group C, 3 years < TR. The prognosis after relapse was compared among the three groups, and between group A and a combined group including groups B and C. The resection rates for metastatic tumors were also compared among the three groups.

Table 2. Characteristics of patients

	Patients with relapse	Patients with-out relapse	p value
Gender			
Male	559 (18.0)	2,546 (82.0)	NS
Female	347 (16.3)	1,778 (83.7)	
Age	62 ± 11	63 ± 11	NS
Primary tumor site			
Colon	506 (14.1)	3,077 (85.9)	<0.0001
Rectum	400 (24.3)	1,247 (75.7)	
TNM stage			
Stage I	51 (3.7)	1,316 (96.3)	<0.0001
Stage II	255 (13.3)	1,657 (86.7)	
Stage III	600 (30.8)	1,351 (69.2)	
First recurrence site			
Liver	373		
Lung	250		
Local	209		
Anastomosis	22		
Others	199		
Follow-up period	3.5 ± 2.9	7.1 ± 3.1	<0.0001

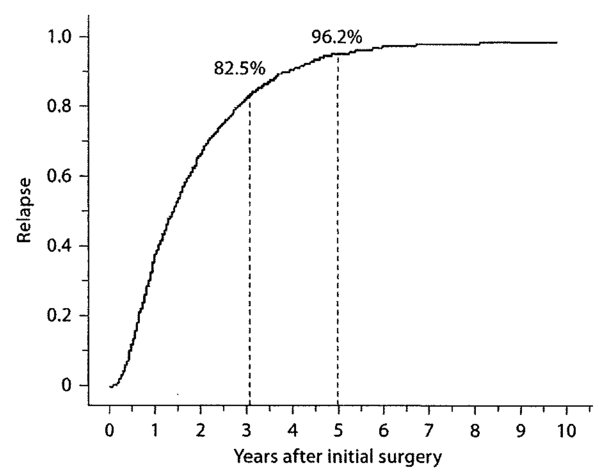

Fig. 1. Curve showing the accumulated relapse rate of patients who underwent curative resection for colorectal cancer. More than 80% of the relapses occurred within 3 years, and 96.2% occurred within 5 years after curative resection for colorectal cancer.

Prognostic Factors after Relapse

Age, gender, location of tumor, histologic grade, direct invasion of the primary tumor to other organs, TNM staging, lymphatic invasion, venous invasion, TR, and resection for relapse with curative intent were analyzed as risk factors for overall survival after relapse (table 1).

Statistical Analysis

Statistical analysis was performed with the StatView statistical package (StatView 5.0; Abacus Concepts, Inc., Berkeley, Calif., USA). All data are expressed as the median ± SD. The χ^2 test for independence was used to investigate the frequency of resection in relapsed cases for each of the three TR groups. We used the Kaplan-Meier method to calculate the actuarial survival of patients. Overall survival rates for each of the three patient groups were assessed by log-rank test. A Cox proportional hazards model was used to determine which risk factors had an independent effect on survival after relapse. Differences in results were considered significant at $p < 0.05$.

Results

Relapse

Of the 5,230 patients, 906 (17.3%) had relapse after curative resection for colorectal cancer during the median follow-up time of 6.6 ± 3.1 years. Among them, 39.5% developed recurrence within 1 year (group A), 82.5% within 3 years, and 96.2% within 5 years (fig. 1). There were no differences in gender or age between patients with relapse and those without (table 2). Relapse was significantly more frequent in patients with rectal cancer than in those with colon cancer. The more advanced the stage, the more frequent the relapse. The most common recurrence site was the liver, followed in order by the lungs and local recurrence sites.

Overall Survival after Initial Colorectal Surgery according to Timing of Relapse

There was a significant difference in overall survival after colorectal surgery in patients with liver, lung, and local relapse, but not in those with anastomotic relapse (table 3). The later the relapse occurred, the better the prognosis was after initial colorectal surgery.

Overall Survival after Relapse according to the Timing of Relapse

There was a significant difference in overall survival after relapse in patients with liver or local relapse (table 3) according to the timing of relapse ($p = 0.0175$ and $p = 0.021$, respectively). The survival after relapse in group A patients with liver metastasis was worse than that in group B or group C patients, but there was no difference

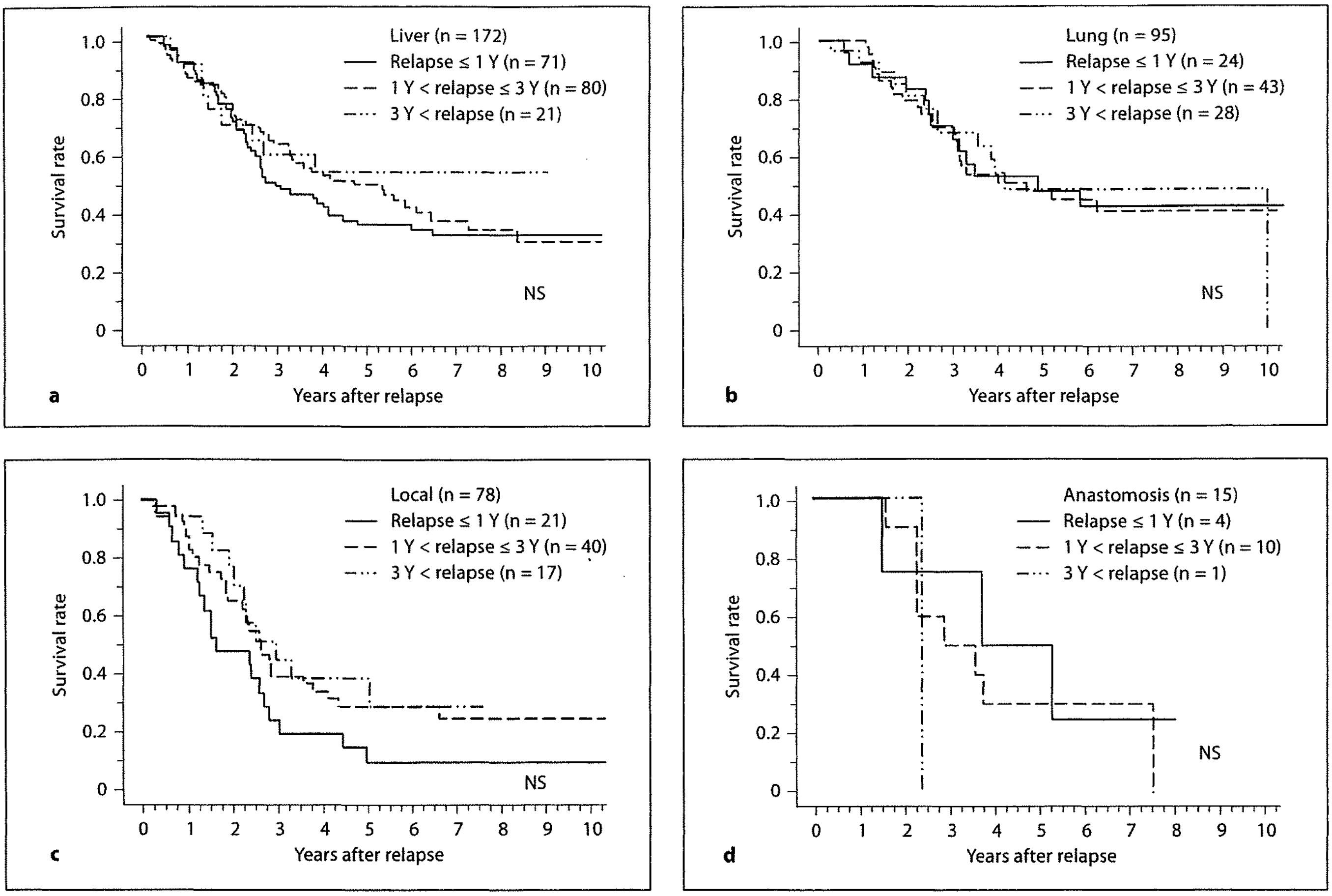

Fig. 2. There were no differences in the prognosis after curative resection for relapse among the three TR groups for patients with (**a**) liver, (**b**) lung, (**c**) local, or (**d**) anastomotic recurrence.

between group B and group C patients. There were no significant differences in survival after relapse among the three TR groups for patients with pulmonary or anastomotic relapse (table 3).

Resection Rate in Relapsed Cases

Curative resection for recurrent tumors was performed in 46.1% of cases of liver metastasis, 38.0% of cases of lung metastasis, 37.3% of cases of local recurrence, and 68.2% of cases of anastomotic recurrence. There were significant differences in the resection rates for the patients with liver ($p = 0.0023$) and pulmonary ($p = 0.038$) relapse among the three TR groups (table 4, while no differences were observed in resection rates for patients with local or anastomotic relapse among the three TR groups. The resection rate for other recurrence sites was 40.2% in total.

Survival after Curative Resection for Recurrent Tumors

Of the 906 patients with relapse, 379 (41.8%) underwent curative resection for recurrent tumors. The 5-year survival rates after resection for recurrent tumors of the liver, lungs, local sites, and anastomotic sites were 45, 48, 27, and 33%, respectively.

There was no difference in survival after relapse in patients who underwent curative resection for any relapse sites according to the timing of relapse (fig. 2). However, group A patients who received resection for local relapse showed significantly worse survival than the combined group of patients from groups B and C who received resection for local relapse ($p = 0.040$). In other recurrence sites, there were no differences in prognosis between group A, group B and C. Of the 379 patients who received resection for recurrent tumors, 240 (63.3%) experienced

Table 3. Overall survival rate after initial colorectal surgery and relapse according to timing of relapse

Recurrent site	TR (patients)	5-Year overall survival rate after initial colorectal surgery, %	p value	5-Year overall survival rate after relapse, %	p value
Liver	A (188)	18	<0.0001	14	0.018
	B (140)	39		31	
	C (45)	69		32	
Lung	A (82)	18	<0.0001	15	0.34
	B (113)	29		21	
	C (55)	72		26	
Local	A (74)	12	<0.0001	9	0.0021
	B (95)	26		16	
	C (40)	83		26	
Anastomosis	A (7)	29	0.22	29	0.95
	B (14)	36		21	
	C (1)	100		0	

A = TR ≤ 1 year; B = 1 year < TR ≤ 3 years; C = 3 years < TR.

re-relapse. Among them, 24 remained disease-free after surgery for re-relapse. Finally, 163 of the 906 patients with relapse (18.0%) remained disease-free.

Prognostic Factors after Relapse

In the 906 patients, age ($p < 0.0001$), histologic grade ($p < 0.0001$), direct invasion of the primary tumor to other organs ($p = 0.0075$), TNM staging of the primary tumor ($p = 0.0014$), timing of relapse ($p = 0.0035$), and the performance of curative resection for relapse ($p < 0.0001$) had effects on survival after relapse based on the log-rank test. Among them, histologic grade ($p = 0.012$), direct invasion of the primary tumor to other organs ($p = 0.0010$), and the performance of curative resection for relapse ($p < 0.0001$) were independent prognostic factors (table 1).

Discussion

This study demonstrated that, in patients who underwent curative resection for relapse of colorectal cancer, the timing of relapse did not affect the survival time after relapse. There were no differences in overall survival after hepatectomy for liver metastases according to timing of relapse in our series. Kornprat et al. [18] reported the outcome after hepatectomy for multiple colorectal metastases. In their study, there was no difference in survival between patients with a disease-free interval after colorectal surgery of <12 months and those with an interval of ≥12 months. On the other hand, Tsai et al. [19] demonstrated that synchronicity of liver metastasis is associated with disease-free survival after hepatectomy. In their study, the disease-free survival after hepatectomy in patients with metachronous liver metastasis was better than that in those with synchronous liver metastasis. Their multivariate analysis revealed that both synchronicity and primary tumor stage were independent prognostic factors that influenced disease-free survival.

In pulmonary metastases, we showed that there were no differences in prognoses after curative metastasectomy among the three different TR groups. That is, the survival curves after pulmonary resection were very similar among the three TR groups in this study. Lee and coworkers [17] demonstrated an association between timing of relapse and prognosis after pulmonary resection for metastases from colorectal cancer. In their study, the prognoses after pulmonary resection did not differ between the patients with a TR of <24 months and those with a TR of >24 months. Our study supports their results. On the other hand, a recent German study [20] showed that a disease-free interval of >36 months was a prognostic factor in a group of 153 patients. A large-scale study will be needed to clarify the association between timing of relapse and survival after pulmonary resection.

As for local relapse, the patients who underwent curative resection for recurrent tumors within 1 year after the initial colorectal resection had worse outcomes after relapse than those who underwent such resection after 1 year. In contrast, Wanebo et al. [21] demonstrated that there was no difference in prognosis between patients undergoing an abdominosacral resection for recurrent rectal cancer within 1 year and those undergoing this procedure after 1 year. One of the reasons for this discrepancy may be the difference in the populations of the two studies. That is, only patients with advanced recurrent rectal cancer were evaluated in the study of Wanebo et al.

In this study, we showed that the curative resection rates differed according to the timing of relapse for patients with liver or lung recurrence, but not for those with local or anastomotic recurrence. In other words, there were significant differences in the resection rates for distant metastases according to the timing of relapse after curative resection for colorectal cancer. In our series, the