DISCUSSION

Lateral lymph node dissection (LLND) was introduced in Japan in the 1970s and results in good survival and low local recurrence rates.[7–9] Since approximately 1984 several forms of nerve-sparing techniques, combined with LLND, have been developed. Bilateral and even unilateral complete autonomic nerve preservation (ANP) combined with LLND often maintains urinary function, but reports vary about the results in sexual function.[16–20] In the many decades of LLND surgery in Japan constant evaluation has taken place with the purpose of preventing overtreatment and minimizing morbidity.[21] Nowadays the policy in many Japanese hospitals is highly case-oriented, adapting the degree of surgical resection and ANP to the extent of cancer spread.[22] Whereas in the 1970s and 1980s in the National Cancer Center Hospital (NCCH) in Tokyo the standard procedure was to perform bilateral LLND in case of advanced rectal cancer, lately also unilateral LLND has been performed. The purpose of this study was to evaluate the treatment between 1993 and 2002 at the National Cancer Center Hospital for rectal carcinoma, at or below the peritoneal reflection, looking at the patterns of local recurrence and the risk factors for local recurrence. To our knowledge, there are no published results of unilateral lymph node dissection in rectal carcinoma.

The results of this study show 5-year local recurrence rate of 6.6% in rectal cancer at or below the peritoneal reflection by Japanese surgery. This primarily surgical approach compares favorably with results in Western countries, where neoadjuvant treatment is adopted as the standard in order to reduce local recurrence rates. Therefore, the Japanese concept of removing the lateral basins of lymph nodes spread can be considered successful. However, some questions still remain to be answered. The etiology of locally recurrent disease is not completely understood yet.

This study, although retrospective, provides further evidence of disease outside the TME envelope in higher-stage tumors. Bilateral LLND (5-year local recurrence rate 14%) resulted in better local control than unilateral LLND (5-year LR rate 33%) in N+ patients. Persistent disease in lateral lymph nodes that is left behind may account for some of the local recurrences, as would occur in standard TME surgery. However in that case, it would be expected that most of the recurrences would occur originating in this lateral basin. In this study we noted that only a part of the local recurrences was present in the lateral side walls. Most of the recurrences could not be explained by the anatomical position of the lateral lymph nodes. One can only speculate about other mechanisms of how tumor cells seed into the surgical resection volume. Maybe removal of the lateral lymph nodes also removes (microscopic) tumor cells which are in transit in the lateral lymph flow route, which could otherwise leak back into the surgical wound. This would explain why unilateral dissection is inferior to bilateral dissection, having more local recurrence in also the presacral, perineal, and anastomotic subsite, not only the lateral.

The rationale behind the unilateral LLND is that the contralateral autonomic nervous system stays untouched, decreasing the chance of autonomic nerve injury. Studies report that, after LLND with nerve-sparing surgery, urinary function is maintained. Between 50% and 100% of males are sexually active, however with compromised ejaculation.[16,18,19,23] This is ascribed to traction and injury to nerves during the mobilization and electrocautery required for LLND.[18] Unfortunately we have no data on urinary and sexual function of this cohort, being unable to report on the results after unilateral LLND with nerve preservation. Therefore, the question of whether functional results are truly better remains unanswered.

The tumors of the patients who had TME without LLND were smaller and less advanced compared with those of LLND patients. This better staging is reflected in better survival. That only one patient who had standard TME surgery had local relapse (5-year local recurrence 0.8%) is striking. The selection for low-risk disease by pre- and intraoperative evaluation has obviously been accurate. Interesting however, is that pathology (Tables 1 and 2) showed that about 30% of the patients operated by TME had T3-stage or N-positive disease. Pathology seems to filter out more metastatic lymph nodes than preoperative imaging, but these (micro)metastases obviously have no oncologic consequences. Jump metastases (mesorectal negative, lateral positive) occurred in only 3% of the LLND patients, thus when mesorectal lymph nodes are unsuspected, risk for lateral lymph node recurrence is very low.

Preoperative evaluation in advanced disease is difficult. In this study local recurrence developed on the contralateral side after unilateral lymph node dissection, while these contralateral lymph node metastases were not suspicious on preoperative CT imaging. Meta-analysis report that assessment of lymph node status by CT is unreliable for clinical decision making, because the radiologist can only look at lymph node size.[24,25] Since 2002 in the NCCH magnetic resonance imaging (MRI) has been used, which is reported to be superior to CT because it can rely on additional morphological criteria, such as signal intensity and border contour.[26–28] Furthermore, lymph-node-specific contrast agents or molecular imaging might play a role in detecting micrometastases in the near future.[29]

In the West, (chemo)radiation is used instead of LLND. There are no (randomized) studies comparing preoperative

(chemo)radiotherapy and TME with LLND in similar patients, making it difficult to make a statement about which regimen is preferred in advanced rectal carcinoma. Western surgeons are hesitant to do lateral lymph node dissections for three reasons. First, in Western patients with a higher body mass index, nerve-sparing techniques are more difficult and the fear of excess morbidity is realistic. Further, it is well known that lateral lymph node status is reflective of overall mesenteric lymph node status and lateral lymph node positivity results in poor prognosis.[13,30] Lastly, although LLND has improved oncologic results in Japanese patients in historical studies and also the current study suggests that LLND is able to prevent residual tumor cells from developing into local recurrence, the clinical effectiveness of LLND has not been proved in a randomized fashion. Currently, the National Cancer Center Hospital is coordinating a multicenter randomized clinical trial comparing conventional TME with bilateral LLND in patients with rectal carcinoma. The results are awaited with anticipation, but it is questionable whether they will be applicable to Western patients.

Concluding, in this study patterns of local recurrence were evaluated in the treatment of rectal cancer, at or below the peritoneal reflection, with selective LLND. Overall local recurrence was 6.6% at 5 years. Local recurrence rate after standard TME was 0.8% in low-stage disease. In lymph-node-positive patients, 33% of the unilateral LLND patients had local relapse, significantly more than in the bilateral LLND group with 14% local recurrence. Either surgical approach, with or without LLND, requires reliable imaging during work-up.

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Pelvic exenteration for clinical T4 rectal cancer: Oncologic outcome in 93 patients at a single institution over a 30-year period

Seiji Ishiguro, MD,[a,b] Takayuki Akasu, MD,[a] Shin Fujita, MD,[a] Seiichiro Yamamoto, MD,[a] Miranda Kusters, MSc,[c] *and* Yoshihiro Moriya, MD,[a] *Tokyo and Nagoya, Japan, and Leiden, The Netherlands*

Background. *Patients with stage T4 rectal cancer are known to have poor survival and often require pelvic exenteration (PE). We describe the oncologic outcome of PE for patients with clinical T4 rectal cancer over a 30-year period.*
Methods. *Data for 93 patients with primary rectal cancer who underwent PE between 1975 and 2005 were reviewed retrospectively.*
Results. *Curative resection was performed in 91 patients (97.9%). Estimated 5-year overall survival (OS) and 5-year recurrence-free survival (RFS) rates were 52% and 46%, respectively. Irradiation was administered in 18 patients (19.4%). Local recurrence was observed in 7 patients, of whom 6 had lymph node (LN) involvement. Estimated local recurrence rate at 2 years was 8.6% (2.0% in node-negative and 16.4% in node-positive patients). Multivariate analysis demonstrated that lateral pelvic LN involvement (P = .03), a carcinoembryonic antigen level of >10 ng/dL (P = .04), and lympho-vascular invasion (P = .04) were significantly associated with decreased OS. Only lateral pelvic LN involvement was significantly associated with decreased RFS (P = .01).*
Conclusion. *For patients with clinical T4 rectal cancer, PE can provide an opportunity for long-term survival and good local control. Patients with lateral pelvic LN involvement should be offered adjuvant treatment pre- or postoperatively to improve prognosis after PE. (Surgery 2009;145:189-95.)*

From the Colorectal Surgery Division, National Cancer Center Hospital,[a] Tokyo, Japan; the Division of Surgical Oncology, Department of Surgery, Nagoya University Graduate School of Medicine,[b] Nagoya, Japan; and the Department of Surgery, Leiden University Medical Centre,[c] Leiden, The Netherlands

LOCALLY ADVANCED RECTAL CANCER IN THE PELVIS remains a challenge to surgeons. The key factor influencing local control and survival is margin-negative resection.[1] Patients with T4 rectal cancer, which directly invades adjacent organs or structures,[2] have poor survival.[1]

Pelvic exenteration (PE) is defined as operative resection of the rectum, distal colon, bladder, lower ureters, internal reproductive organs, draining lymph nodes (LN), and pelvic peritoneum.[1,3] PE allows rectal tumors invading adjacent organs to be resected en bloc and the provision of a margin-negative operation. It has been reported that PE is associated with high morbidity and mortality rates.[4] In our opinion, however, the key factor in reducing these rates and in guaranteeing optimal results is skill of the surgical teams.

Here, we evaluated the outcome of clinical T4 primary rectal cancer treated with PE and factors predicting long-term survival and recurrence based on our data set covering a period of >30 years.

PATIENTS AND METHODS

Patients. PE with curative intent was performed in 93 patients with primary rectal cancer between January 1975 and September 2004 at our institution. All patients had biopsy-proven adenocarcinoma and were suspected of having cancer invasion to adjacent organs without distant metastases on the basis of either or both preoperative examination and intraoperative findings. Data for these patients came from a prospectively collected colorectal division database and were reviewed retrospectively with a focus on recurrence, survival, and clinicopathologic factors. The patients were followed until September 2007.

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Reprint requests: Seiji Ishiguro, MD, Colorectal Surgery Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: sishigur@ncc.go.jp.

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Preoperative evaluation and operative procedure. Preoperative examination included physical examination, digital rectal examination, bimanual examination (in women), and computed tomography. Tumors were grouped into lower rectum (0–7.0 cm from the anal verge), middle rectum (7.1–12.0 cm), and upper rectum and rectosigmoid (12.1–17.0 cm).[5] All tumors were confirmed to be located below the sacral promontory by contrast enema. Magnetic resonance imaging was introduced after 1988, and endoscopic ultrasonography was used after 1989. Either or both modality was performed for evaluation of the depth of tumor invasion and LN involvement.

PE with extended lateral pelvic LN dissection was performed, in principle, for tumors that were suspected to have extensive invasion to the trigone of the bladder, the prostate, or the urethra. LN dissection was performed around the inferior mesenteric artery in the upper lymphatic system, and laterally with combined resection of the bilateral internal iliac vessels. Periaortic LNs and inguinal LNs were not dissected unless the LNs were found to be swollen by preoperative imaging or intraoperatively. Details of extended LN dissection have been precisely described in previous reports.[3,6]

In some female patients, modified (anterior or posterior) PE was performed to preserve urinary or fecal continence and to reduce postoperative morbidity. In anterior PE, the lower rectum was retained in situ, with removal of the upper rectum, reproductive organs, and bladder. In posterior PE, the bladder was preserved and the uterus, vagina, and rectum were resected with preservation of the superior vesical artery and division of the distal internal iliac vessels.[7] Sacral invasion was treated by en bloc resection.[3,6] Most urinary reconstruction procedures were done using an ileal conduit.

Radiotherapy and chemotherapy. Radiotherapy was provided in cases of large or far-advanced tumors, in accordance with the surgeon's preference. Hypofractionation short-course radiation was performed before 1985. After that, our policy of preoperative radiotherapy was long-course radiation with or without chemotherapy because of adverse events. The doses varied from 30 to 50.4 Gy with hyperfractionation. In principle, intraoperative or postoperative radiation therapy was administered according to intraoperative findings, when extension of tumor into the operative margin was suspected or confirmed. In some patients, preoperative chemotherapy as well as radiotherapy was given, although no definite criteria for this treatment were available. Some patients with LN involvement received postoperative adjuvant chemotherapy. The standard regimen varied across the study period.

Determination of recurrence and survival. Local recurrence was defined as clinical or radiologic recurrence in the prior pelvic treatment field, and distant metastasis was defined as clinical or radiologic recurrence at any other site. Overall survival (OS) was the period from the date of surgery to the date of death or the date of the most recent follow-up. Recurrence-free survival (RFS) was the period from the date of surgery to the date of death, the first observation of local, or distant recurrence, or the date of the most recent follow-up, whichever occurred first.

Statistical analysis. Statistical analyses were performed using Stata Version 9.2 (Stata Corporation, College Station, Tex). OS and RFS curves were calculated using the Kaplan–Meier method. Cox regression analysis was used to identify factors significantly associated with OS and RFS. Results were considered significant when $P < .05$.

RESULTS

Patients and operation. Patient demographics are summarized in Table I. The study group was composed of 80 men (86%) and 13 women (14%), with a median age of 55 years (range, 26–80). Total PE was performed for 83 patients (80 men and 3 women), anterior PE for 9, and posterior PE for 1. Median operation time was 496 minutes (range, 220–1,073) and median blood loss during surgery was 1,850 mL (range, 370–8,000). In 6 patients, combined resection of the distal sacrum was done.[8]

Radiotherapy and chemotherapy. Radiotherapy of the pelvis was performed in 17 patients (18.8%), preoperatively in 13, postoperatively in 2, and both intraoperatively and postoperatively in 2. Doses varied between 20 and 50.4 Gy. Preoperative hypofractionation short-course radiation was done in 4 cases. Of 13 patients who received preoperative irradiation, 8 received preoperative chemoradiotherapy with a 5-fluorouracil–containing regimen, intravenously in 6 and orally in 2.

Postoperative adjuvant chemotherapy was performed in 25 patients. Among these, 3 received intravenous 5-fluorouracil plus leucovorin, 3 received intravenous mitomycin C, 1 received intravenous cisplatin and etoposide, and 18 received oral chemotherapy (carmofur in 14, uracil-tegafur in 4).

Pathologic analysis. Pathologic outcomes are listed in Table II. The mean number of LNs harvested was 51 (range, 2–110). All resected LNs were investigated histologically, and LN involvement

Table I. Characteristics of 93 patients undergoing PE for rectal cancer

	No. of patients
Age (yrs)	
<60	57
≥60	36
Gender	
Male	80
Female	13
Primary site	
Upper rectum and rectosigmoid	25
Middle rectum	13
Lower rectum	55
CEA level (ng/dL)	
<10	59
≥10	34
Type of operation	
Total PE	83
Modified PE	10
Radiotherapy	
Preoperative (chemoradiotherapy)	13 (8)
Intraoperative and/or postoperative	5
None	76
Postoperative adjuvant chemotherapy	
Done	25
None	68

CEA, Carcinoembryonic antigen.

Table II. Pathologic outcome of 93 patients undergoing PE for rectal cancer

	No. of patients
Tumor differentiation	
Well or moderately differentiated	80
Poorly differentiated or mucinous	13
T status	
pT4	46
Non-pT4	47
N status (direction)	
pn0	53
Upper LN involvement	18
Upper and lateral LN involvement	22
Lymphovascular invasion	
Absent	35
Present	58
Surgical margin	
Negative	91
Positive	2

LN, Lymph node.

was found in 40 patients. Of these 40, 18 patients had LN involvement in the mesorectum or along the inferior mesenteric artery (upper LN involvement) and 22 had involvement along the internal iliac artery (lateral LN involvement) as well as upper LN involvement. In patients with lower rectal cancer, 36.4% (20/55) had lateral LN involvement, and 7.7% (1/13) with middle and 4.0% (1/25) with upper rectal cancer had lateral LN involvement. Of 14 patients who received preoperative radiotherapy, 10 did not have LN involvement, 1 had only upper LN involvement, and 3 had both upper and lateral LN involvement.

Histologically, 46 (49.5%) of 93 patients who were suspected of having T4 cancer at preoperative or intraoperative evaluation had definite invasion into adjacent organs. Of 47 patients who did not have pathologic T4 disease, 16 had involved LNs that had invaded neighboring organs, mimicking the penetration of rectal cancer, and 7 had cancer deposits between the rectum and adjacent organs. The others had inflammatory changes resulting from abscess formation or radiotherapy, which caused fixation of the tumor. The surgical margin was positive in 2 patients (2.2%).

Mortality and morbidity profile. Surgery-related complications were observed in 34 of 83 (41.0%) patients who underwent total PE (Table III). The most frequent complication was perineal wound dehiscence (20.3%), followed by urinary tract infection (10.8%) and pelvic sepsis (8.4%). Eight patients required an additional operations, including stoma reconstruction in 4, reconstruction of the urinary tract in 2, and bypass operation because of anastomotic leakage in 2. Three patients who undergone anterior PE developed a complication, namely pelvic sepsis, leakage of the ureter, and acute colitis.

Two patients (2.2%) died within 30 days after surgery, 1 from cerebral hemorrhage and the second from sepsis after leakage of the intestine. One patient died of perineal infection followed by sepsis 7 months after surgery.

OS. Thirty-seven patients survived for 5 years and 28 patients for 10 years. With a median follow-up of 40 months (range, 1–305), the estimated 3-, 5- and 10-year survival rates were 61%, 52% and 50%, respectively (Fig 1).

RFS and pattern of local and distant recurrence. Recurrence occurred in 27 (29.0%) patients (Table IV). Of these, 4 had local recurrence, 20 had distant recurrence, and 3 had both local and distant recurrence. The estimated 3-, 5-, and 10-year RFS rates were 51%, 46% and 46%, respectively (Fig 1). The sites of distant metastases included the liver in 9, lung in 10, inguinal LN in 5, paraaortic LN in 2, and bone in 2. Among patients with lateral LN involvement, 59.1% developed recurrence by the last follow-up compared with 38.9% in those with upper LN involvement and 13.2% in those with no LN involvement.

Table III. Morbidity profile of 83 patients after total PE procedures

	No. of cases	*%*
Perineal wound dehiscence	17	20.5
Urinary tract infection	9	10.8
Pelvic sepsis	7	8.4
Leakage of intestine	3	3.6
Leakage of ureter	3	3.6
Acute renal failure	3	3.6
Bowel obstruction	2	2.4
Abdominal wound infection	2	2.4
Others	3	3.5

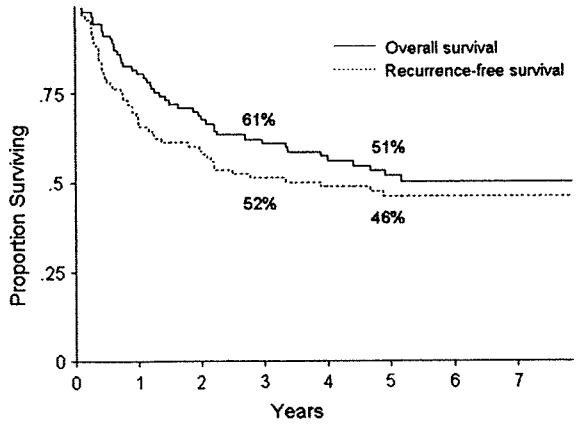

Fig 1. OS and RFS after PE in patients with clinical T4 rectal cancer. Estimated 3- and 5-year survival rates were 61% and 52%, respectively. Estimated 3- and 5-year RFS rates were 51% and 46%, respectively.

The estimated local recurrence rate at 2 years was 8.1%. Of the 18 patients receiving radiotherapy, 1 experienced local recurrence. Of the 7 patients with local recurrence, 6 had LN involvement (upper LN involvement in 3, upper and lateral LN involvement in 3). The patient who had no LN involvement followed by local recurrence was 1 of 2 who had a positive operative margin and who had received intraoperative and postoperative radiation therapy. The other patient with a positive operative margin did not develop local recurrence. The cumulative local recurrence rate was plotted by stratified LN involvement (Fig 2). The estimated 2-year local recurrence rate was 2.0% in patients with no LN involvement and 16.4% in those with involvement, with this difference being significant ($P = .01$). Even after the exclusion of patients who received preoperative radiotherapy, no patient without LN involvement experience local recurrence at 2 years.

Four of 6 patients who had inguinal LN recurrence underwent resection. With regard to liver metastasis, 1 patient had a hepatectomy, and 1 patient received radiofrequency ablation. None of the patients who developed pulmonary metastases underwent metastasectomy.

Factors associated with OS and RFS. The estimated OS at 5 years for patients without LN, with upper LN involvement, and with lateral LN involvement were 62%, 49%, and 31%, respectively. In the univariate model, lateral LN involvement was significantly associated with reduced survival (Fig 3). A carcinoembryonic antigen (CEA) level of ≥10 ng/dL, as well as lymphovascular invasion and poorly differentiated or mucinous carcinoma, were also significantly associated with poor survival (Table V). OS between patients with T4 and non-T4 rectal cancer did not significantly differ ($P = .92$).

On multivariate analysis, lateral LN involvement ($P = .03$), a CEA level of ≥10 ng/dL ($P = .04$), and lymphovascular invasion ($P = .04$) were significantly associated with decreased survival (Table VI). With regard to RFS, lateral LN involvement and lymphovascular invasion were significantly associated with a reduced RFS on univariate analysis ($P = .01$ and .05, respectively; Table V). On multivariate analysis, only lateral LN involvement was significantly associated with a reduced RFS ($P = .01$; Table VI).

DISCUSSION

To our knowledge, this study represents the largest single institution analysis to date of long-term outcome in patients with clinical T4 rectal cancer treated by PE. Estimated 5-year OS was 52% and estimated 5-year RFS was 46%, with an estimated local recurrence rate at 2 years of 8.1%. Lateral LN involvement was significantly associated with both decreased OS and RFS; a CEA level ≥10 ng/dL and lymphovascular invasion were also significantly associated with decreased survival. These factors are predictive of patients who are candidates for adjuvant therapy.

In previous articles on oncologic outcomes of primary rectal cancer in patients treated by PE, estimated 5-year survival rates were in the range of 43% to 64%.[9-15] However, none of these papers provided details of local recurrence rate in patients in the disease group. Comparison of our long-term results with those in similar reports is hampered by our less frequent use of preoperative or postoperative radiotherapy and differences in operative procedure, which in our case involved PE with lateral pelvic LN dissection. Nevertheless, it is interesting that the estimated 5-year survival rate in our series is quite similar to these previous rates.

Table IV. Recurrence profile after PE

		N0 (n = *53*)	*Upper LN involvement* (n = *18*)	*Lateral LN involvement* (n = *22*)
	All (n = *93*)	*No. (%)*	*No. (%)*	*No. (%)*
Recurrence	27	7 (13.2)	7 (38.9)	13 (59.1)
Local	7	1 (1.9)	3 (16.7)	3 (13.6)
Distant	23	6 (11.3)	5 (27.8)	12 (54.5)
Liver	9	2	2	5
Lung	10	3	2	5
Others	9	2	1	6

LN, Lymph node.

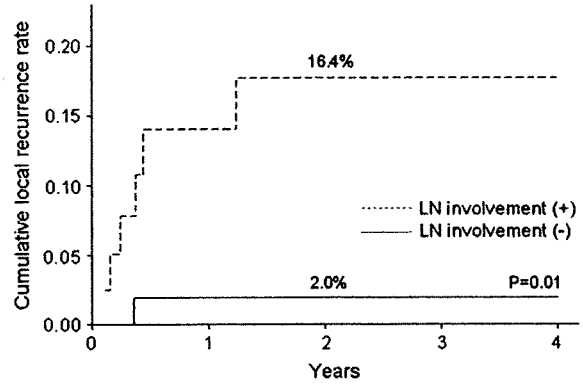

Fig 2. Cumulative local recurrence rate after PE in patients with clinical T4 rectal cancer stratified by LN involvement. Estimated 2-year local recurrence rate was 2.0% in patients without LN involvement (LN involvement [−]) and 16.4% in those with involvement (LN involvement [+]). The difference was significant ($P = .01$).

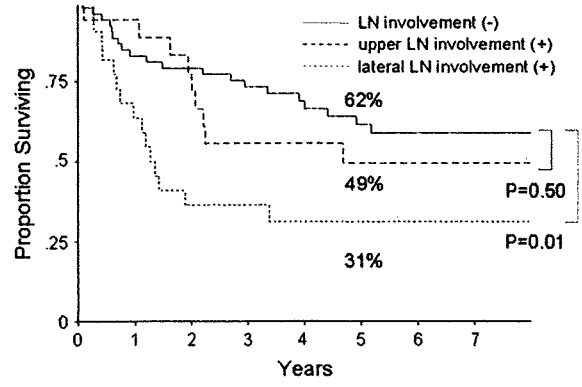

Fig 3. OS after PE in patients with clinical T4 rectal cancer stratified by the direction of LN involvement. Compared with patients without LN involvement (LN involvement [−]), those with lateral LN involvement (lateral LN involvement) had significantly decreased survival ($P = .01$), whereas those with only upper LN involvement (upper LN involvement) had no difference in survival ($P = .50$).

Inadequate excision seems to be the major determinant of a poor outcome in rectal cancer.[1,16] It has been reported that the status of circumferential resection margin strongly predicts local recurrence and poor survival.[17,18] The greatest benefit of PE is that it offers a much higher probability of resecting the tumor package without exposing malignant cells to the dissection plane.[19] We routinely combine PE with lateral pelvic LN dissection, and although the effectiveness of lateral pelvic LN dissection has not been confirmed,[20] en bloc resection of pelvic structures along with tissues lateral to the rectum likely minimizes the chance of a positive margin. Previous studies have reported that the number of resected LNs is closely correlated with increased survival for colorectal cancer,[21-23] indicating that the number of LNs suggests the adequacy of the operation and of pathologic examination.[21] The median number of harvested LNs in the study was 51. We believe this large number of LNs, as well as high frequency of curative resection, indicate that we performed optimal operations.

The efficacy of radiotherapy for local control in patients with rectal cancer has been consistently demonstrated.[24,25] In this study, however, only one fifth of patients received perioperative radiotherapy. It has been reported that LN involvement is associated with a higher risk of local recurrence.[26,27] Here, node-positive patients had a local recurrence rate of 16.4% at 2 years, indicating the limitation of surgery alone for clinical T4 rectal cancer with LN involvement. To improve local control, radiotherapy may be mandatory in positive-node patients with clinical T4 rectal cancer. On the other hand, the local recurrence rate at 2 years for node-negative patients was 2.0%. Furthermore, no local recurrence was seen in node-negative patients, even though they did not receive preoperative radiotherapy. We, therefore, assume that radiotherapy is not always indicated for node-negative patients, even those with T4 rectal cancer.

The fact that only 49.5% of patients diagnosed as having T4 rectal cancer had tumors invading

Table V. Univariate analysis of factors associated with OS and RFS

	OS			*RFS*		
Variable	*HR*	*95% CI*	P	*HR*	*95% CI*	P
Gender						
Male	1.00	—	—	1.00	—	—
Female	0.77	0.33–1.81	.55	0.94	0.43–2.09	.88
Age (yrs)						
<60	1.00	—	—	1.00	—	—
≥60	1.30	0.74–2.28	.36	1.32	0.77–2.25	.32
Primary site						
Upper rectum	1.00	—	—	1.00	—	—
Middle rectum	0.97	0.36–2.60	.96	1.07	0.42–2.72	.89
Lower rectum	1.67	0.86–3.24	.13	1.75	0.91–3.37	.09
CEA level (ng/dL)						
<10	1.00	—	—	1.00	—	—
≥10	**1.80**	**1.03–3.14**	**.04**	1.51	0.89–2.58	.13
Tumor differentiation						
Well or moderate	1.00	—	—	1.00	—	—
Poor or mucinous	2.08	1.00–4.33	.05	1.82	0.88–3.76	.10
T Status						
Non-pT4	1.00	—	—	1.00	—	—
pT4	1.03	0.59–1.78	.92	1.08	0.64–1.83	.78
LN involvement						
pN0	1.00	—	—	1.00	—	—
Upper LN involvement	1.29	0.58–2.52	.50	1.43	0.71–2.88	.32
Lateral LN involvement	**2.61**	**1.34–4.62**	**.01**	**3.07**	**1.68–5.63**	**.01**
Lymphovascular invasion						
Absent	1.00	—	—	1.00	—	—
Present	**2.08**	**1.13–3.83**	**.02**	**1.79**	**1.01–3.16**	**.04**
Radiation therapy						
None	1.00	—	—	1.00	—	—
Done	1.25	0.62–2.50	.53	1.08	0.56–2.09	.82
Adjuvant chemotherapy						
None	1.00	—	—	1.00	—	—
Done	1.14	0.63–2.04	.67	1.00	0.57–1.78	.99

Table VI. Multivariate model of factors associated with OS and RFS

Variable	*HR*	*95% CI*	P *value*
OS			
Lateral LN involvement	2.09	1.06–4.10	.03
CEA ≥10 ng/dL	1.84	1.04–3.25	.04
Lymphovascular invasion	2.00	1.05–3.82	.04
RFS			
Lateral LN involvement	2.61	1.38–4.92	.01

adjacent organs also deserves consideration. Balbay et al[28] reported that only 61% of 46 patients who underwent total PE for suspicion of bladder involvement had definite invasion, whereas in their series of 71 patients, Ike et al[13] reported that 50% of patients diagnosed with T4 rectal cancer who underwent total PE actually had T3 tumors. In this study, magnetic resonance imaging or endoscopic ultrasonography was introduced after 1988. The rate of actual T4 cancer was not different even after introduction of such modalities (51% before 1988 and 50% in/after 1989). These low rates of accuracy indicate the difficulty in reaching a precise preoperative diagnosis of tumor invasion even with current diagnostic modalities.

PE has functional, psychological, and psychosexual implications for patients postoperatively, and indications should therefore be determined with caution. The efficacy of preoperative chemoradiotherapy has been also improved and the frequency of complete sterilization of the tumor has increased, even for advanced rectal cancer.[29] Our policy for T4 rectal cancer has changed to more frequent adoption of preoperative chemoradiotherapy for better local control. Further improvement in sterilization or shrinkage of the tumor might allow the use of organ-preserving surgery in

patients with T4 rectal cancer. Until that time, we believe organ-preserving surgery in patients with T4 rectal cancer is risky. We now have a plan to conduct a new protocol using preoperative chemoradiotherapy for clinical T4 rectal cancer for better local control and organ preservation, but a policy of obtaining radical margins by PE is the safest way to prevent local recurrence.

In conclusion, this retrospective review of the oncologic outcome of PE with lateral pelvic LN dissection for patients with clinical T4 rectal cancer at a single institution over a period of >30 years showed a 5-year OS of 52% and a 5-year RFS of 46%. Lateral LN involvement was significantly associated with both decreased OS and RFS. A CEA level ≥10 ng/dL and lymphovascular invasion were also significantly associated with decreased survival. In addition to optimal surgery, patients with these factors should be offered pre- or postoperative adjuvant treatment. Confirmation of these findings in an additional data set is required.

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特別寄稿

JCOG0212
(臨床病期Ⅱ・Ⅲの下部直腸がんに対する側方リンパ節郭清術の意義に関するランダム化比較試験)

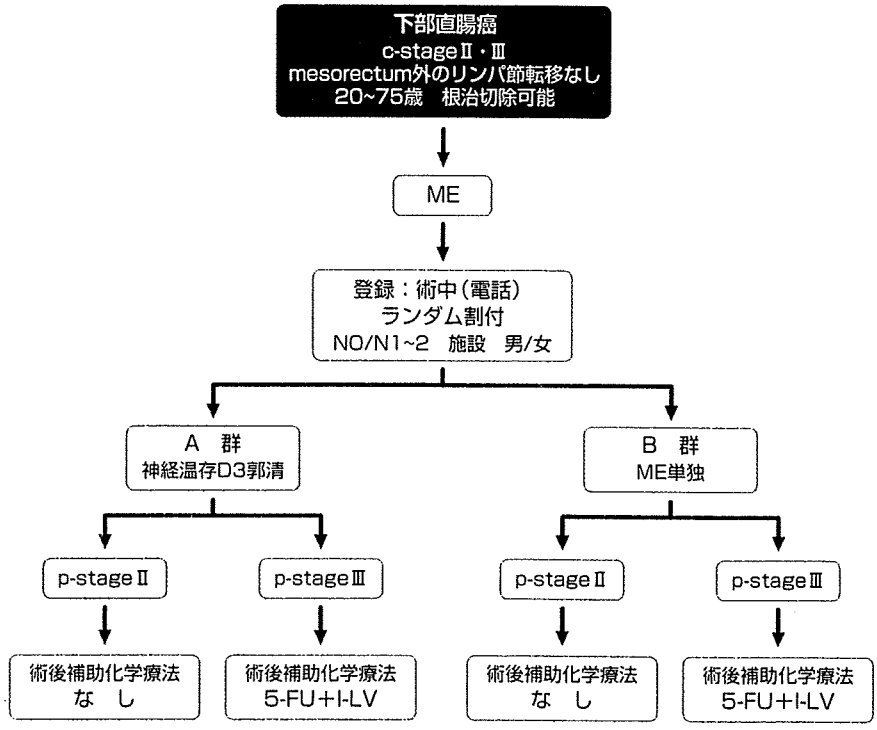
藤田　伸
国立がんセンター中央病院大腸外科 医長

はじめに

JCOG0212とは，Japan Clinical Oncology Group(日本臨床腫瘍グループ)の大腸がんグループが行っている臨床試験「臨床病期Ⅱ・Ⅲの下部直腸がんに対する側方リンパ節郭清術の意義に関するランダム化比較試験(研究代表者・事務局：藤田　伸)」のことである。本稿では，その目的，進捗状況，意義について概説してみたい。

試験の目的

試験の目的は，術前画像診断および術中開腹所見にて，明らかな側方転移を認めない臨床病期Ⅱ・Ⅲの切除可能な腫瘍下縁が腹膜翻転部以下の進行直腸癌を対象にして，国際的標準手術となっているtotal mesorectal excision(TME)と本邦で広く行われている自律神経温存側方郭清の臨床的有用性を比較評価することを目的としている。プライマリーエンドポイントは，無再発生存期間，セカンダリーエンドポイントは，生存期間，局所無再発生存期間，有害事象発生割合，重篤な有害事象発生割合，手術時間，出血量，性機能障害発生割合，排尿障害発生割合である。試験の概略を図❶に，現在までに1例以上の登録があった施設を表に示す。試験の詳細はJCOGホームページ(http://www.jcog.jp/basic/clinicaltrial/index.html)，さらにはUMIN(http://www.umin.ac.jp/ctr/index-j.htm：UMIN試験ID C000000034)，ClinicalTrials.gov(http://



図❶　試験概略

clinicaltrials.gov/：ClinicalTrials.gov　ID NCT00190541)の臨床試験登録に掲載されているので，興味のある方はこれらも参照されたい。

研究仮説とサンプルサイズ

この臨床試験の研究仮説は「TMEの無再発生存期間が本邦の標準治療である自律神経温存側方郭清と同等であった場合，自律神経温存側方郭清に比べ手術が容易で，かつ，有害事象発生割合が低いと考えられるTMEを有用な治療法と判断する」としている。つまり，側方郭清に対してTMEの非劣性を証明する，いわゆる非劣性試験デザインである。非劣性試験を組むにあたって，無再発生存率が何%以下の差であれば，TMEが側方郭清に対して劣っていないと判定するかという臨床的判断基準を決める必要があった。この基準に関して試験開始前の大腸がんグループ班会議において検討した結果，TMEが側方郭清に対して5年無再発生存割合として8%以上劣っていなければ，TMEは非劣性であると判断すると決定した。さらに試験対象症例(臨床病期Ⅱ・Ⅲの下部直腸癌)の5年無再発生存率を過去の報告に基づき70%と推定して，登録期間，サンプルサイズを計算し，予定登録数：600例，登録期間：5年，追跡期間：登録終了後5年として2003年6月より登録を開始した。

進捗状況

登録開始から6年以上経過した現在，予定登録数の600例近い登録がなされている。したがって，当初の予定通りであれば，そろそろ登録終了という段階であるが，定期モニタリングによる予後解析の結果，研究計画時に予想していた最もよい5年無再発生存率(75%)となると推定され，600例では検出力不足と判断された。この結果，症例登録開始から5年経過した2008年にプロトコール改訂を行い，登録期間7年，

表　登録施設

●国立がんセンター中央病院	●市立吹田市民病院
●国立がんセンター東病院	●新潟県立がんセンター新潟病院
●静岡県立静岡がんセンター	●国立病院機構四国がんセンター
●愛知県がんセンター中央病院	●千葉県がんセンター
●大阪府立病院機構大阪府立成人病センター	●昭和大学横浜北部病院
●横浜市立大学医学部附属市民総合医療センター	●市立堺病院
●岡山済生会総合病院	●東邦大学医療センター大橋病院
●国立病院機構京都医療センター	●関西労災病院
●石川県立中央病院	●埼玉県立がんセンター
●東京医科大学	●群馬県立がんセンター
●神奈川県立がんセンター	●慶應義塾大学病院
●久留米大学医学部	●藤田保健衛生大学
●東京医科歯科大学	●市立広島市民病院
●国立病院機構大阪医療センター	●宮城県立がんセンター
●大阪市立総合医療センター	●兵庫医科大学
●山形県立中央病院	

予定登録数700例と改訂し，現在にいたっている。症例集積状況を図❷に示す。ほぼ予定登録ペースで症例集積が進行しており，予定登録期間の7年で症例集積が終了する見込みである。

手術手技の質の確保

この試験は，手術の比較試験であるので，手術手技の質を確保しなくてはならない。本邦では側方郭清の歴史が長く，細かな相違はあるものの，側方郭清手技がほぼ完成したものとなっていたことは，この試験を行うにあたっては幸いであった。手術の質は，判定委員による全症例の術中写真評価と，さらに年2回行われるグループ会議において各参加施設の側方郭清ビデオ供覧でその質を確保している。術中写真は，TME群では，上方の郭清状態（1枚）と自律神経温存状態（左右1枚ずつ），さらに標本の直腸固有筋膜の破損の有無をみるために切除標本を開く前の標本の前，後の直腸固有筋膜の状態（前後1枚ずつ）の計5枚の撮影を行っている。一方，側方郭清群では，上方郭清の状態（1枚），左右の骨盤内自律神経の温存状態（左右1枚ずつ）（図❸），標本写真（前後1枚ずつ），内腸骨血管周囲の郭清状況（左右1枚ずつ），閉鎖腔の郭清状況（左右1枚ずつ）（図❹），摘出したリンパ節を含む側方脂肪織（左右1枚ずつ）の計11枚の撮影を行っている。提出された術中写真は，判定委員が神経温存，郭清程度を定期的に評価し，班会議で問題ある症例を提示し，手術の質の確保と向上を図っている。郭清，神経温存が不十分と判断される症例がないわけではないが，おおむね問題のない郭清，神経温存が行われている。

予想される結論

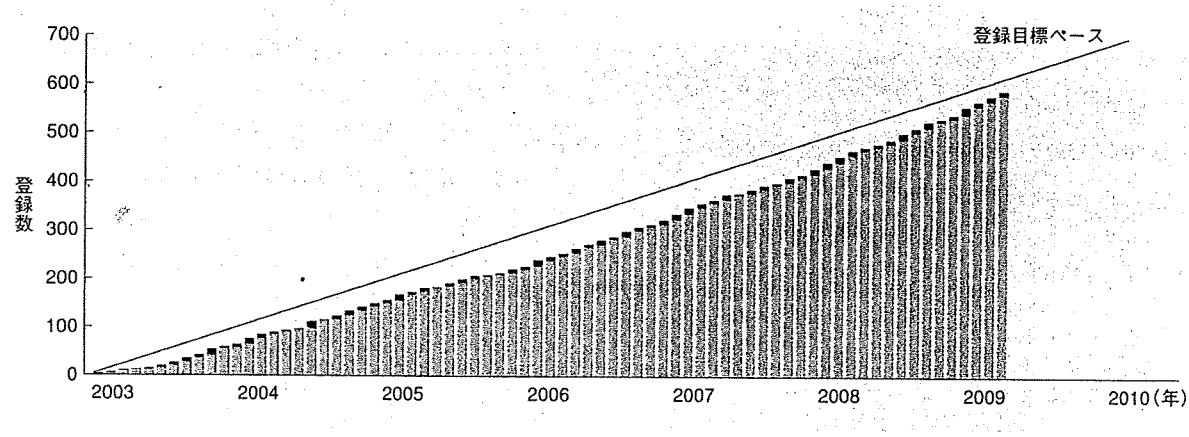
この臨床試験で予想される結論は，以下の3つである。

①TMEが側方郭清に対し，無再発生存期間が劣っていないことが証明され，さらにその優越性が証明されるか，その他のエンドポイント（有害事象発生割合，重篤な有害事象発生割合，手術時間，出血量，性機能障害発生割合，排尿機能障害割合）で優越性が証明された場合：TMEが有用な治療法であると判断。

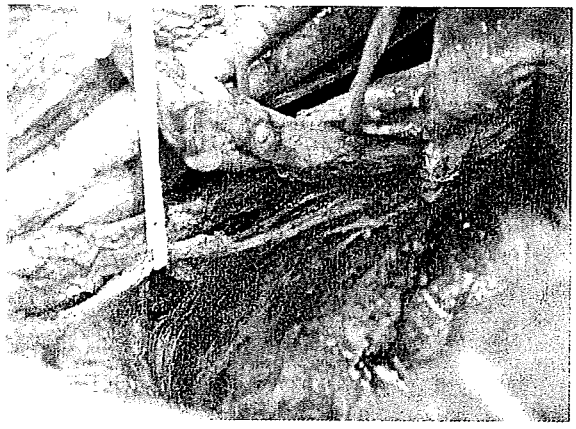
②TMEが側方郭清に対し，無再発生存期間が劣っていることが証明された場合：側方郭清が有用な治療法であると判断。

③TMEが側方郭清に対し，無再発生存期間が劣っていないことが証明されたが，その他のエンドポイントで優越性が証明されない場合：側方郭清が有用な治療法と判断。

①の場合には，これまで本邦で行われてきた側方郭清の有用性が否定されることになり，日本の大腸外科医にとって残念な結果となるが，重要な結論である。ただし，この場合の側方郭清とは，あきらかな側方転移のない場合の側方郭清，すなわち予防的側方郭清のことであるので，明らかな側方転移のある症例の側方郭清である治療的側方郭清の意義が否定されるものではない。②の場合には，側方郭清の意義を証明することができ，日本の大腸外科医としてはうれしい結果

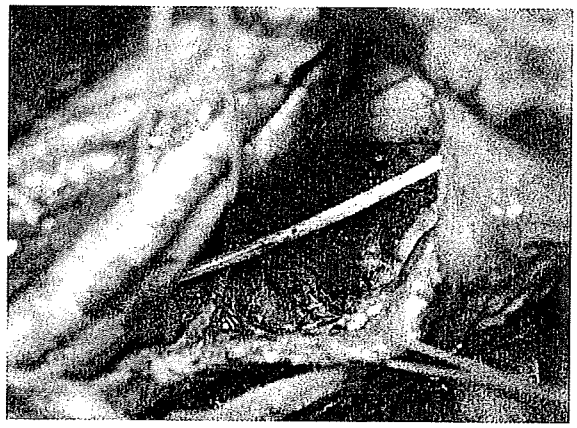


図❷ 症例集積状況



図❸ 骨盤内自律神経温存術中写真

(p.1 写真1参照)



図❹ 閉鎖腔郭清術中写真

(p.1 写真2参照)

であるが，この手技を国際的に普及させることが可能かどうかは，側方郭清に伴う手術時間，出血量の増加の程度，有害事象の程度，頻度が重要となるであろう。③の場合は，この臨床試験においては可能性が低いものの，一般の非劣性臨床試験では，あり得る判断である。

今後の予定

現在の登録状況であれば，来年5月までには登録を終了する。その後，すべてのプロトコール治療の終了(この臨床試験では半年間の術後補助化学療法もプロトコール治療として規定しているので，術後補助化学療法が終了した時点)を目処に中間解析が行われる。その際，側方郭清に対してTMEの非劣性が証明され，さらに優越性も示された場合，あるいは許容範囲を超えてTMEの治療成績が悪い場合には，試験中止として，その結果を公表するが，そうでなければ，登録終了から5年経過した時点で最終解析が行われ，そこで結果を公表する予定である。

おわりに

中間解析で試験中止という判断とならない限り，この試験の結果が明らかになるのはこれから6年後となる。この試験により側方郭清のきわめて重要なエビデンスが形成されること，その価値を考えるとこの6年は決して長いものでない。

特集 ・・・直腸癌に対する側方リンパ節郭清と術前化学放射線療法の治療成績・・・

進行下部直腸癌の治療成績と補助放射線療法の必要性

藤田　伸[*1]　山本聖一郎[*1]　赤須孝之[*1]　森谷宜皓[*1]

Outcome of Patients with Lower Rectal Cancer and Indications for Adjuvant Radiotherapy: Fujita S[*1], Yamamoto S[*1], Akasu T[*1] and Moriya Y[*1] ([*1]National Cancer Center Hospital)

To clarify the indications for adjuvant radiotherapy for clinical stage Ⅱ or Ⅲ lower rectal cancer, the outcome of patients who underwent lateral pelvic lymph node dissection without adjuvant radiotherapy was investigated.A total of 359 patients between 1988 and 2002 were reviewed. The 5-year survival and local recurrence rates of the patients was 71.6% and 10.5%, respectively.Multivariate analysis identified lymph node status and sex as statistically significant risk factors for local recurrence. Local recurrence rates of the patients with clinical or pathological stage Ⅲ lower rectal cancer were more than 10%. These patients should be given preoperative or postoperative adjuvant radiotherapy.

Key words: Rectal cancer, Lymph node dissection, Lateral pelvic, Lymph node, Risk factor

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はじめに

直腸癌において補助放射線療法の有効性が多数報告され，術前，あるいは術後に補助放射線治療を行うことが標準治療となっている[1]．さらに術後よりも術前補助放射線療法が直腸癌局所再発を低下させたとする臨床試験結果が報告され[2]，現在では術後よりも術前補助放射線療法が主流となっている．他方，わが国においては，側方リンパ節郭清が行われ，かつ直腸癌術後局所再発率が低いこともあり，補助放射線療法はいまだ標準治療と言えない状況である．しかしながら，側方リンパ節郭清を行っても局所再発は生じるため，局所再発の高リスク群を選別し，補助放射線療法を施すなら，直腸癌治療成績の一層の向上が期待できる．そこで，進行下部直腸癌（腫瘍下縁が腹膜翻転部以下 cStage Ⅱ，Ⅲ）で側方リンパ節郭清が行われた症例の局所再発リスク因子を検討し，補助放射線療法が必要と思われる症例を明らかにしてみたい．

1 対象と方法

1988年から2002年までに国立がんセンター中央病院で側方リンパ節郭清が行われた腫瘍下縁が腹膜翻転部以下 cStage Ⅱ，Ⅲ直腸癌359例の術前診断し得る臨床病理学的背景因子（性別，年齢，術前 CEA，腫瘍占居部位，AV からの距離，分化度，肉眼型，腫瘍径，環周度，臨床的深

*1 国立がんセンター中央病院外科

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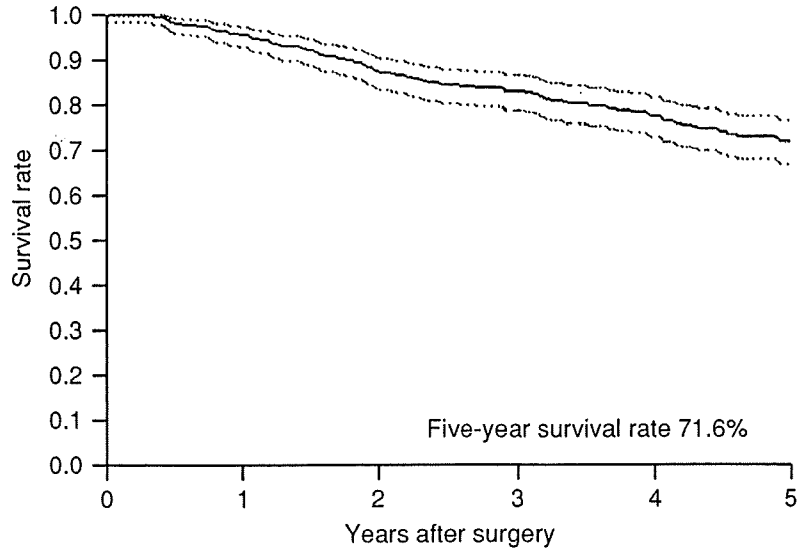

図1　生存曲線

達度，臨床的リンパ節転移）と局所再発との関連を単変量ならび多変量解析で検討した．さらに術後に判明する臨床病理学的因子（病理学的深達度，病理学的リンパ節転移，ly，v，RM）と局所再発との関連も検討し，すべての因子を用いての多変量解析も行った．

2 結　果

1 生存率と局所再発率

検討対象の生存曲線と局所再発曲線を図1に示す．累積5年生存率は71.6%，累積5年局所再発率は10.5%であった．Stage Ⅰが43例（12.0%），Stage Ⅱが106例（29.5%），Stage Ⅲが202例（56.3%），Stage Ⅳが8例（2.2%）という内訳であった．

2 術前臨床病理学的背景因子と局所再発

術前診断し得る臨床病理学的背景因子と局所再発率の関係を表1に示す．臨床病理学的背景因子のうち，局所再発と有意に相関があったのは，分化度，深達度（cT），リンパ節転移（cN）であった．さらに多変量解析を行うと，cNと性別の2因子が有意な因子として選択された（表2）．この2因子と局所再発との関連を表3に示した．臨床的にリンパ節転移が疑われる症例の局所再発率は男性12.9%，女性19.4%といずれも高率であった．

3 術後臨床病理学的因子と局所再発

術後にわかる臨床病理学的因子と局所再発の関係を表4に示す．深達度（pT），リンパ節転移（pN），ly，v，RMいずれも有意に局所再発と関連した．術前，術後にわかるすべての臨床病理学的因子を用いて多変量解析を行うと，リンパ節転移（pN）と性別が有意な因子として選択され，pN，性別と局所再発率との関連を表5に示した．病理学的にリンパ節転移がある症例の局所再発率は，臨床的にリンパ節転移が疑われる症例とほぼ同程度で，男性15.0%，女性19.9%であった．

3 考　察

直腸癌に対して補助放射線療法が標準療法となっているとはいえ，放射線療法は，短期的，長期的な副作用が問題となる．短期的な問題として，術後合併症が増加することが示されている[3]．長期的には，性機能，排尿機能，肛門機能，腸管機能障害が報告されている[4~12]．これらの障害により術後のQOLも低下していることが示されている[4,8,11]．以上のような放射線治療の問題，そして今回の検討結果ならびにTME（Total Mesorectal Excision）が行われた症例のStage

表1　術前臨床病理学的背景因子と局所再発率

	患者数	局所再発率(%)	P値
性別			0.077
男	243	8.6	
女	116	14.4	
年齢			0.28
<60	203	12.2	
≥60	156	8.2	
CEA (ng/ml)			0.98
≤5	213	10.3	
>5	146	10.8	
腫瘍占居部位			0.54
RS, Ra	64	9.0	
Rb, P	295	10.7	
AV距離 (cm)			0.22
≤5	258	11.7	
>5	101	7.5	
分化度			0.002
高分化/中分化	335	9.3	
低分化/粘液	24	29.3	
肉眼型			0.086
1/2	321	9.5	
3/4	38	20.6	
腫瘍径 (cm)			0.94
≤5	177	10.6	
>5	182	10.4	
環周度			0.27
<1/2	143	7.4	
>1/2	216	11.3	
深達度 (cT)			0.024
≤A1	133	5.6	
≥A2	226	13.4	
リンパ節転移 (cN)			<0.001
−	119	1.8	
+	240	15.1	

表2　多変量解析

	ハザード比	95%信頼区間	P値
cN+/cN−	2.750	1.493〜6.878	<0.001
女/男	1.620	1.113〜2.379	0.012

Ⅱ症例[13,14]あるいはT1からT3の症例[15]には補助療法が不要であるという報告があることから，直腸癌症例のすべてに補助放射線療法を行うのではなく，その適応を決め，行うべきである．

今回の検討結果から，側方リンパ節郭清が適応

表3　cN，性別による局所再発率

	リンパ節転移なし	リンパ節転移あり
男	1.2%	12.9%
女	3.0%	19.4%

表4　術後臨床病理学的背景因子と局所再発率

	患者数	局所再発率(%)	P値
深達度 (pT)			0.046
≤A1	163	7.1	
≥A2	196	13.3	
リンパ節転移 (pN)			<0.001
−	152	2.3	
+	207	16.8	
ly			<0.001
−	147	2.9	
+	212	16.0	
v			0.003
−	186	5.6	
+	173	16.1	
RM			0.025
−	352	10.0	
+	7	40.0	

表5　pN，性別による局所再発率

	リンパ節転移なし	リンパ節転移あり
男	1.3%	15.0%
女	4.8%	19.9%

となる症例，すなわち腫瘍下縁が腹膜翻転部以下cStage Ⅱ，Ⅲにおいて，リンパ節転移，性別が局所再発リスク因子であり，リンパ節転移が疑われる，あるいはある場合には，男女ともに局所再発が10%を超え，これらの症例は，補助放射線療法を考慮すべきと考えられる．一方，リンパ節転移が疑われない，あるいはない症例においては，局所再発率は男女ともに5%以下であり，これら症例には補助放射線療法は不要と考えられる．

今回の検討で明らかになったように補助放射線療法の適応を決める上でリンパ節転移診断は重要である．われわれは，リンパ節転移の有無をCT，

MRIにより術前診断を行っているが，今回の検討症例におけるリンパ節転移に関する感度は87%，特異度は62%，正診率は77%という結果であった．感度はまずまずであるが，特異度は高いとはいえず，術前診断で補助放射線治療の適応を決めていくためには，より正確なリンパ節転移診断，特に特異度をさらに向上させる努力が必要である．

側方リパ節郭清は，その転移が明らかな場合，すなわち治療的な郭清に関しては，側方リンパ節転移例であっても郭清することで約40%の5年生存率が得られることから，行うべきである[16]．しかし，側方リンパ節転移が明らかでない症例の予防的な郭清に意義があるかどうかは不明である．その予防的郭清の意義に関しては，現在，わが国でTME＋側方リンパ節郭清 vs. TME単独を比較する臨床試験（臨床病期Ⅱ・Ⅲの下部直腸がんに対する側方リンパ節郭清術の意義に関するランダム化比較試験：JCOG0212）が行われており，その結果を待ちたい．

今回の検討では，女性の局所再発率が男性より高く，単変量では有意ではなかったが，多変量解析では，性別が有意な因子として選択された．男女間で臨床病理学的背景因子には大きな差はなく，その理由は明らかではない．オランダで行われたTME vs. TME＋術前補助放射線療法の臨床試験において直腸切断術で男性よりも女性の局所再発率が高いことが示されているが[17]，この試験では直腸切断術において女性の切離断端陽性率が男性よりも高く，これが女性の局所再発率が高い原因と考えられる．この検討では女性の切離断端陽性率が男性よりも高いということはないため，改めて検討が必要である．

まとめ

側方リンパ節郭清の適応となる進行下部直腸癌においては，リンパ節転移が疑われる，あるいはある症例は，側方リンパ節郭清を行っても局所再発率は10%を超え，術前あるいは術後補助放射線療法を考慮すべきである．

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ORIGINAL CONTRIBUTION

Analysis of Clinical Factors Associated with Anal Function after Intersphincteric Resection for Very Low Rectal Cancer

Masaaki Ito, M.D. • Norio Saito, M.D. • Masanori Sugito, M.D.
Akihiro Kobayashi, M.D. • Yusuke Nishizawa, M.D. • Yoshiyuki Tsunoda, M.D.

Department of Colorectal and Pelvic Surgery, National Cancer Center Hospital East, Chiba, Japan

PURPOSE: The purpose of this study was to identify factors that have a negative impact on anal function after intersphincteric resection.

METHODS: We evaluated postoperative anal function in 96 patients with very lower rectal cancer who underwent intersphincteric resection by having patients fill out detailed questionnaires at 3, 6, 12, and 24 months after surgery. Univariate and multivariate analysis based on the Wexner incontinence score were used to identify factors associated with poor anal function after intersphincteric resection.

RESULTS: The mean Wexner score at 12 months after stoma closure was 10.0. Patients with frequent major soiling showed a Wexner score of ≥16, and this score was used as a cutoff value of poor anal function. In the univariate analysis, poor anal function was significantly associated with a greater extent of excision of the internal sphincter and with preoperative chemoradiotherapy. In the multivariate analysis, preoperative chemoradiotherapy was the only independent factor associated with poor anal function after intersphincteric resection (odds ratio=10.3; 95 percent confidence interval, 2.3–46.3, $P < 0.01$).

CONCLUSIONS: Preoperative chemoradiotherapy was identified as the risk factor with the greatest negative impact on anal function after intersphincteric resection, regardless of extent of excision of the internal sphincter.

KEY WORDS: Rectal cancer; Intersphincteric resection; Preoperative chemoradiation; Anorectal function; Incontinence.

Since Miles reported abdominoperineal resection in the 1920s, this procedure has been the standard treatment for low rectal cancer.[1] However, standard abdominoperineal resection leaves many rectal cancer patients with permanent stomas. Recently, innovative treatment for lower rectal cancer has tended toward preservation of the anus. Low anterior resection with coloanal anastomosis (CAA)[2] and intersphincteric resection (ISR)[3] are advanced anus-preserving operations for treating low rectal cancer while avoiding a colostomy. Anastomoses are made near or under the dentate line in the anal canal, and the result has been a tolerable local recurrence rate that we have been able to accept clinically. Several studies[4–7] have also investigated the functional outcome after ISR. The results suggested that satisfactory anal function was preserved in most patients who underwent ISR, but some patients had severe dysfunction,[5,8] and conversion to colostomy was necessary.[5,7]

We prospectively collected questionnaires concerning anal function from our patients every three months for two years after closure of the diverting stomas. The aims of the present study were to accurately determine the status of anal function and to identify factors associated with postoperative incontinence after ISR.

PATIENTS AND METHODS

Patients

Between November 1999 and March 2007, 150 patients underwent ISR for very lower rectal cancer at the National Cancer Center Hospital East (NCCHE), Chiba, Japan. A diverting stoma was constructed in every patient, and the stoma had been closed in 109 of the patients as of March 2007. Diverting stomas had not been closed in 41 patients when the data were analyzed. The reasons were

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Address of correspondence: Masaaki Ito, M.D., Department of Colorectal and Pelvic Surgery, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa, Chiba, Japan 277-8577. E-mail: maito@east.ncc.go.jp

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