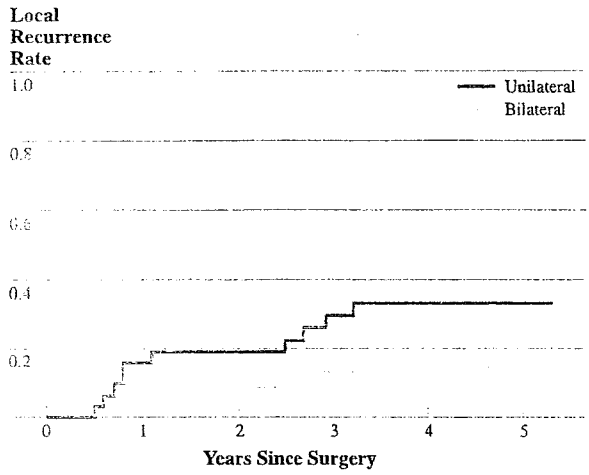

FIG. 1 Local recurrence in N+ patients

TABLE 3 Multivariate analysis for local recurrence

Variable	HR	95% CI	p
Lateral dissection			0.003
Unilateral	1.00		
Bilateral	0.25	0.10–0.64	
T-stage			0.09
T1 + T2	1.00		
T3 + T4	2.99	0.84–10.73	
N-stage mesorectal LN			0.008
0 pos	1.00		
1–3 pos	2.71	0.75–9.85	
> 4 pos	7.22	2.01–25.94	
Lateral LN status			0.007
Negative	1.00		
Positive	3.53	1.41–8.85	

Figure 2 shows the survival curves of the TME-only, and uni- and bilateral LLND patients. Overall 5-year survival was 89% for patients who had standard TME. Five-year overall survival in the unilateral LLND group was 78%, which did not differ significantly from the bilateral LLND group (77%) ($p = 0.37$).

The multivariate Cox regression analysis, when including the uni- and bilateral LLND groups, identified T-stage, mesorectal lymph node N-stage and lateral lymph node positivity as independent factors for death risk.

Two years after local recurrence diagnosis 37% of the unilateral LLND patients was still alive, as compared with 60% of the bilateral LLND patients. The number of patients is however too low to conclude significant better survival for bilateral LLND patients.

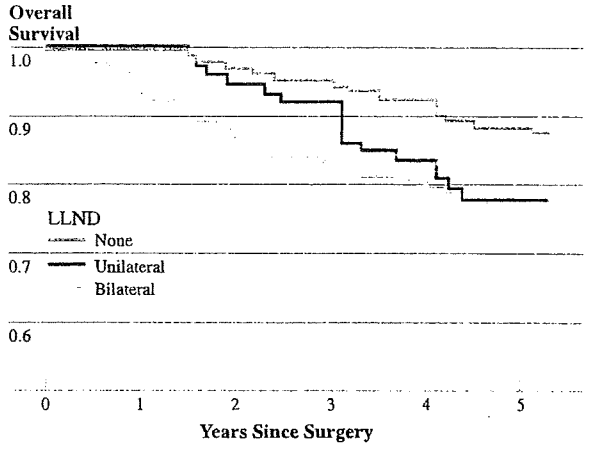

FIG. 2 Overall survival in all patients

TABLE 4 Sites of local recurrence

Site of local recurrence	All patients			Only N+ patients		
	Unilateral LLND ($n = 73$)	Bilateral LLND ($n = 133$)	p	Unilateral LLND ($n = 32$)	Bilateral LLND ($n = 74$)	p
Lateral	5 (5.6)	4 (3.3)		4 (13.2)	3 (4.6)	
Ipsilateral	*3 (3.4)*			*3 (9.9)*		
Contralateral	*2 (2.2)*			*1 (3.3)*		
Presacral	2 (2.8)	0 (0)		2 (6.7)	0 (0)	
Perineal	2 (2.8)	2 (1.7)		1 (3.1)	2 (3.4)	
Anterior	0 (0)	1 (0.9)		0 (0)	1 (1.8)	
Anastomotic	3 (4.2)	2 (1.6)		3 (9.8)	2 (3.0)	
Unknown	0 (0)	1 (0.8)		0 (0)	1 (1.4)	
Total	12	10		10	9	
5-Year LR rate	15.4%	8.3%	0.06	32.8%	14.2%	0.04

Values in parentheses are the 5-year local recurrence rates per subsite

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.

ACKNOWLEDGEMENTS The authors would like to express their gratitude to the Japan Prizewinners Program of the Dutch Government who financed the stay of M. Kusters in Tokyo and the Japan–Netherlands Institute (Executive Director Dr. W. G. J. Remmelink) for practical support.

The authors would also like to thank Drs. S. Ishiguro and Y. Kobayashi, from the Colorectal Surgery Department of the National Cancer Center Hospital, for help with obtaining data; as well as Drs. Y. Arai and M. Takahashi from the Department of Radiology, National Cancer Center Hospital, for assistance with imaging.

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A Comparison Between the Treatment of Low Rectal Cancer in Japan and the Netherlands, Focusing on the Patterns of Local Recurrence

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Purpose: Differences exist between Japan and The Netherlands in the treatment of low rectal cancer. The purpose of this study is to analyze these, with focus on the patterns of local recurrence.

Methods: In The Netherlands, 755 patients were operated by total mesorectal excision (TME) for low rectal cancer, 379 received preoperative radiotherapy (RT+TME). Applying the same selection criteria resulted in 324 patients in the Japanese (NCCH) group, who received extended surgery consisting of lateral lymph node dissection and a wider abdominoperineal excision. The majority received no (neo) adjuvant therapy. Local recurrence images were examined by a radiologist and a surgeon.

Results: Five-year local recurrence rates were 6.9% for the Japanese NCCH group, 5.8% in the Dutch RT+TME group, and 12.1% in the Dutch TME group. Recurrence rate in the lateral pelvis is 2.2%, 0.8%, and 2.7% in the Japanese, RT+TME group, and TME group, respectively. The incidence of presacral recurrences was low in the NCCH group (0.6%), compared with 3.7% and 3.2% in the RT+TME and TME groups, respectively.

Conclusions: Both extended surgery and RT+TME result in good local control, as compared with TME alone. Preoperative radiotherapy can sterilize lateral extramesorectal tumor particles. A wider abdominoperineal resection probably results in less presacral local recurrence. Comparison of the results is difficult because of differences in patient groups.

(*Ann Surg* 2009;249: 229–235)

The main purpose of curative surgical treatment for rectal cancer is en bloc excision of the primary tumor with its locoregional lymph nodes. It has been demonstrated that nonradical removal of the tumor leads to persistence of tumor cells that contributes to the development of recurrent rectal cancer growth.[1,2] Local recurrence is known to cause severe morbidity.

With the total mesorectal excision (TME) procedure the rectum with its primary lymphovascular field of drainage is removed as an intact package, by dissection under direct vision along preexisting embryologically determined planes. Since its introduction, the TME approach has led to striking results, reflected by lower local recurrence rates and improved survival, and has been advocated as being superior to conventional surgery.[3,4]

However, the results of the TME technique for low tumors are not as good as for midrectal or higher tumors, with still a considerable local recurrence rate.[5,6] This is ascribed to the difficulty to obtain a wide circumferential margin (CRM) and the higher rate of perforations of the mesorectum and bowel wall, especially in the case of abdominoperineal resection (APR).[5,7,8]

In Western countries, the addition of (neo)adjuvant therapy to improve the local recurrence rate has been well studied. Both short and long course of preoperative (chemo)radiation have been shown to be effective.[9–12] However, it has also been shown that short-term radiotherapy cannot prevent local recurrence development when advanced tumor growth or surgical failure results in a positive CRM.[13]

In Japan, extended surgery is the gold standard and the APR technique involves a wide perineal skin incision, together with resection of ischiorectal adipose tissue and the levator ani muscle,[14] aiming for a wider circumferential tumor-free margin than in a standard Western APR. However, in Japan, the main focus is on the immediate harvesting of lymph nodes from the fresh specimen, which precludes assessment of the CRM at a later stage. Lateral lymph node dissection (LLND), in which dissection of the iliac and obturator lymph nodes with the primary tumor is performed, is the standard treatment for advanced rectal cancer located at or below the peritoneal reflection.[15,16] It has been reported that local recurrence and survival rates have improved since the introduction of LLND and are known to be significantly better than Western series with surgery only.[15,17]

The question remains whether local recurrence can be prevented best by more frequent use of adjuvant (chemo)radiation or by more extended surgery. The aim of this study was to compare the patterns of local recurrence after TME surgery, TME surgery with short-term preoperative radiotherapy, and Japanese extended surgery. The prospective databases of the Dutch TME trial and the National Cancer Center Hospital in Tokyo, with accurate follow-up, were used. The hypothesis is that recurrences in the lateral pelvic subsite would occur less often in the Japanese group than in the Dutch TME group, because the lateral lymph nodes are excised, with the mesorectum and perirectal fat tissue. In addition, the Japanese APR technique is more wide than the one used during the Dutch TME trial, also possibly leading to different patterns of recurrence in other pelvic subsites.

PATIENTS AND METHODS

Study Population

Patients were selected from the databases of the Dutch TME-trial and of the National Cancer Center Hospital (NCCH) in Tokyo.

A selection was made from a large prospective randomized multicenter study, the radiotherapy plus TME trial, in which 1530 Dutch patients were included between January 1996 and December

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The Japan Prizewinners Program (www.jpp-japan.nl) of the Dutch Government financed the stay of Miranda Kusters in Tokyo. There was no other financial support to any of the authors for this study.

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ISSN: 0003-4932/09/24902-0229
DOI: 10.1097/SLA.0b013e318190a664

1999. This trial analyzed the effect of short-term preoperative radiotherapy (5 × 5 Gy) in patients operated with a total mesorectal excision (RT+TME), compared with patients with TME alone (TME).[10] Inclusion criteria were the presence of a primary adenocarcinoma of the rectum, without evidence of metastatic disease at time of surgery, and tumor location within 15 cm from the anal verge. Patients with other malignant diseases or with fixed tumors were excluded. Standardized techniques for surgery, radiotherapy, and pathology were used.[18] Follow-up of all patients was conducted according to the trial protocol.[7] For the current study, the following patients were excluded from the analysis: no resection (n = 37), distant metastasis at operation (n = 91), and no tumor at operation (n = 15).

In the prospective database of the NCCH, Tokyo, a selection was made from January 1993 to April 2002, resulting in 923 consecutive patients operated for confirmed primary adenocarcinoma of the rectum. The patients underwent a low anterior resection (LAR), Hartmann, APR, or when a stage T4 tumor was suspected, pelvic exenteration. Surgery at the NCCH is performed according to the guidelines of the Japanese Research Society for cancer of the colon and rectum.[19] Lateral lymph node dissection was performed in low rectal cancer, when based on preoperative evaluation or intraoperative findings, TNM stage II or III disease was suspected. A decision was made for each patient individually, based on the side and the extension of the tumor, whether a uni- or bilateral LLND was performed. Accurate documentation of lymph node status and localization was obtained because all lymph nodes were dissected from the fresh specimen and their location and numbers were mapped in relation to the major arteries. After that, the specimen and all lymph nodes were examined histopathologically. Follow-up of all patients consisted of thoracic CT, abdominal CT, and pelvic CT-imaging every 6 months. For this study, similar selection criteria were applied to the patients from the NCCH as for the TME-trial patients, excluding the following patients: metastasis at the time of surgery (n = 134), other malignant diseases or double colorectal carcinoma (n = 62), fixed tumor during rectal examination (n = 15), and in situ carcinoma (n = 22).

The median follow-up of the Dutch RT+TME and TME patients alive was 7.0 years and of the Japanese NCCH patients 7.9 years.

Patient Selection

For both the Dutch and the Japanese groups, patients with low rectal tumors were selected. To match the groups as closely as possible, 2 different definitions of low rectal tumors had to be interpreted. In the Dutch TME trial, low rectal cancer was defined as tumors of which the lower edge was within 5 cm of the anal verge as measured by endoscopy. In Japan, the peritoneal reflection is the most important landmark in defining the location of the tumor and "low" rectal carcinoma is defined as a tumor of which the major part is located at or below the reflection.[20] The distance from the anal verge is often unreported. The anterior peritoneal reflection has been measured to be at 9 cm from the anal verge by intraoperative endoscopy.[21] With a mean tumor diameter of 4 cm in the Dutch TME trial, the distance between the lower border and the anal margin of the Japanese low cancers can thus be estimated as maximal 9−(4/2) = 7 cm. To match the tumors of the Japanese group, we therefore selected tumors from 0 cm up to 7.0 cm from the anal verge in the Dutch groups. Using these criteria, 324 Japanese patients were selected with rectal tumors at or below the peritoneal reflection and 755 patients from the Dutch database with tumors with the lower border from 0 cm up to 7.0 cm.

Definitions

In the Japanese group, the total amount of harvested lymph nodes consisted of mesorectal lymph nodes, and when LLND was done, also the lateral lymph nodes. In the Dutch group, the lymph node harvest consisted only of the mesorectal lymph nodes. The UICC 5th edition, 1997, classification system was used for both groups to define TNM-staging. All patients who developed local recurrence, defined as any recurrence of rectal cancer in the small pelvis, were identified from the databases. Local recurrence was either diagnosed clinically, radiologically, or histologically.

Methods

Analysis were made comparing 3 groups; the RT+TME group, the TME group, and the NCCH group. For all locally recurrent patients the available preoperative images and the images at the time of discovery of the local recurrence were retrieved. A specialized oncologic radiologist (R.B.) and a surgeon (G.B.) reviewed the images together for both the groups.

Examining the images, the site of the local recurrence was determined. The sites were classified into the following regions: lateral, presacral, perineal, anterior, or anastomotic. The same borders for the respective sites were used as defined by Roels et al.[22] When no images were available, the location of recurrence was classified using the radiology reports and clinical data. In 1 patient in the RT+TME group and in 2 patients in the NCCH group, insufficient information was provided to determine the location of recurrence with certainty.

Statistical Analysis

Statistical analysis was performed using SPSS package (SPSS 12.0 for Windows; SPSS Inc, Chicago, IL). χ^2 tests and one-way ANOVA tests, Bonferroni corrected, were used to compare individual variables. The cancer-specific survival was defined as the time between rectal cancer surgery and death caused by cancer. Survival was estimated using the Kaplan-Meier method. Cox regression was used to assess differences in survival outcomes between groups; results are reported as hazard ratios with associated 95% confidence intervals. All P values were 2-sided and considered statistically significant at 0.05 or less. For local recurrence, cumulative incidences were calculated accounting for death as competing risk.[23] Similarly, cumulative incidences were calculated for subsite of local recurrence, with death and other types of local recurrence as competing risks, and for cancer-specific survival, with death due to other causes as competing risk. To account for possible confounding factors, multivariate analyses of local recurrence and cancer-specific survival were performed by first testing the effect of covariates in a univariate Cox regression. Covariates with trend-significant effects ($P < 0.10$) and group (RT+TME, TME, NCCH) were then selected for multivariate Cox regression.

RESULTS

Patient Characteristics

Patient characteristics and treatment details are listed in Table 1. The age at operation of the Japanese patients was significantly lower than that of the Dutch patients. In the Japanese group significantly more sphincter saving procedures had been performed, compared with the Dutch group. Lateral lymph node dissection was not performed in the Dutch patients, whereas 59% of the Japanese patients underwent unilateral or bilateral LLND.

Table 2 shows an overview of the pathology results of the Japanese and the Dutch groups. Early T-stage cancer was found significantly more in the Japanese group, whereas stages T3 and T4 cancer were found more in the Dutch. The average amount of

TABLE 1. Patient Characteristics and Treatment Details

	RT+TME 379 patients	TME 376 patients	NCCH 324 patients	*P*
Sex				0.52
Male	244 (64)	234 (62)	215 (66)	
Female	135 (36)	142 (38)	109 (34)	
Age (yrs)				<0.001
Mean (SD)	64 (11)	64 (11)	58 (11)	
Type of resection				<0.001
Low anterior resection	160 (42)	159 (42)	195 (60)	
Abdominoperineal resection	193 (51)	199 (53)	113 (35)	
Hartmann	24 (6)	15 (4)	3 (1)	
Pelvic exenteration	2 (1)	3 (1)	13 (4)	
Lymph node dissection				<0.001
Standard TME	379 (100)	376 (100)	134 (41)	
Unilateral LLND	0	0	69 (21)	
Bilateral LLND	0	0	121 (38)	
Neoadjuvant therapy				<0.001
Preoperative radiotherapy	379 (100)	0	0	
None	0	376 (100)	324 (100)	
Adjuvant therapy				<0.001
Postoperative radiotherapy	3 (1)	52 (14)	5 (2)	
Postoperative chemotherapy	16 (4)	13 (3)	23 (7)	
None	360 (95)	315 (84)	297 (92)	

Values in parentheses are percentages.

TABLE 2. Pathologic Results

	RT+TME 379 patients	TME 376 patients	NCCH 324 patients	*P*
Amount of lymph nodes resected				<0.001
Mean (SD)	7.3 (6.0)	9.3 (6.4)	33.7 (18.5)	
T-stage				<0.001
T1	19 (5)	21 (6)	52 (16)	
T2	143 (38)	131 (35)	107 (33)	
T3	209 (55)	210 (56)	160 (49)	
T4	8 (2)	14 (4)	5 (2)	
N stage			*/†	0.82/0.62
N0	244 (64)	229 (61)	198/192 (61/59)	
N1	80 (21)	82 (22)	75/80 (23/25)	
N2	55 (15)	64 (17)	51/52 (16/16)	
TNM-stage*				0.27
Stage I	129 (34)	123 (33)	125 (39)	
Stage IIa	111 (29)	100 (27)	72 (22)	
Stage IIb	4 (1)	6 (2)	1 (0)	
Stage IIIa	27 (7)	19 (5)	26 (8)	
Stage IIIb	53 (14)	63 (17)	49 (15)	
Stage IIIc	55 (15)	64 (17)	51 (16)	
Tumor size (cm)				0.09
Mean (SD)	4.0 (1.6)	4.6 (1.7)	4.3 (2.1)	
Distal margin (cm)				0.46
LAR (SD)	2.1 (1.5)	1.9 (1.7)	1.9 (0.9)	
APR (SD)	4.3 (1.7)	4.1 (1.9)	4.2 (2.7)	

Values in parentheses are percentages.
*On basis of mesorectal lymph nodes.
†With extra positive lateral lymph nodes.

harvested lymph nodes was 34 in Japanese group and 8 in the Dutch groups. The N stages, whether lateral nodes were included or not, did not differ significantly. TNM stage did not differ significantly between the groups.

The cancer-specific survival was higher in the Japanese extended surgery group than both in the Dutch TME group as in the Dutch RT+TME group (Fig. 1A). The hazard ratios for death (95% CI) of the Dutch TME and RT+TME groups with respect to the Japanese group were 2.0 (1.2–3.3) and 1.7 (1.1–2.8), respectively.

Local Recurrence Patients

Twenty-three patients (6.9% 5-years percentage) in the Japanese extended surgery group, 24 patients (5.8%) in the Dutch RT+TME group, and 46 patients (12.1%) in the Dutch TME group were diagnosed with local recurrence (Table 3, Fig. 1B). The hazard ratio for local recurrence (95% CI) of the Dutch TME group compared with the Japanese group was 1.6 (1.0–2.8). The hazard ratio (95% CI) of the Dutch RT+TME compared with the Japanese group was 1.0 (0.6–1.8). The mean time to local recurrence in the Japanese group is 2.1 years, 1.5 years in the TME-group, and 2.6 years in RT+TME-group.

In the Japanese patients with local recurrence, 11 patients (48%) had distant metastases before or at the time of local recurrence diagnosis. In the Dutch TME patients with local recurrence this was the case in 9 patients (20%), in the RT+TME local recurrence this was the case in 13 patients (54%). When distant metastases diagnosed within 1 month of local recurrence diagnosis were considered as being simultaneous, these distant metastases rates were 62%, 30%, and 88% for the Japanese, Dutch TME, and Dutch RT+TME local recurrence patients, respectively. At the time of last follow-up or death 95%, 77%, and 88% had metastases in the respective groups.

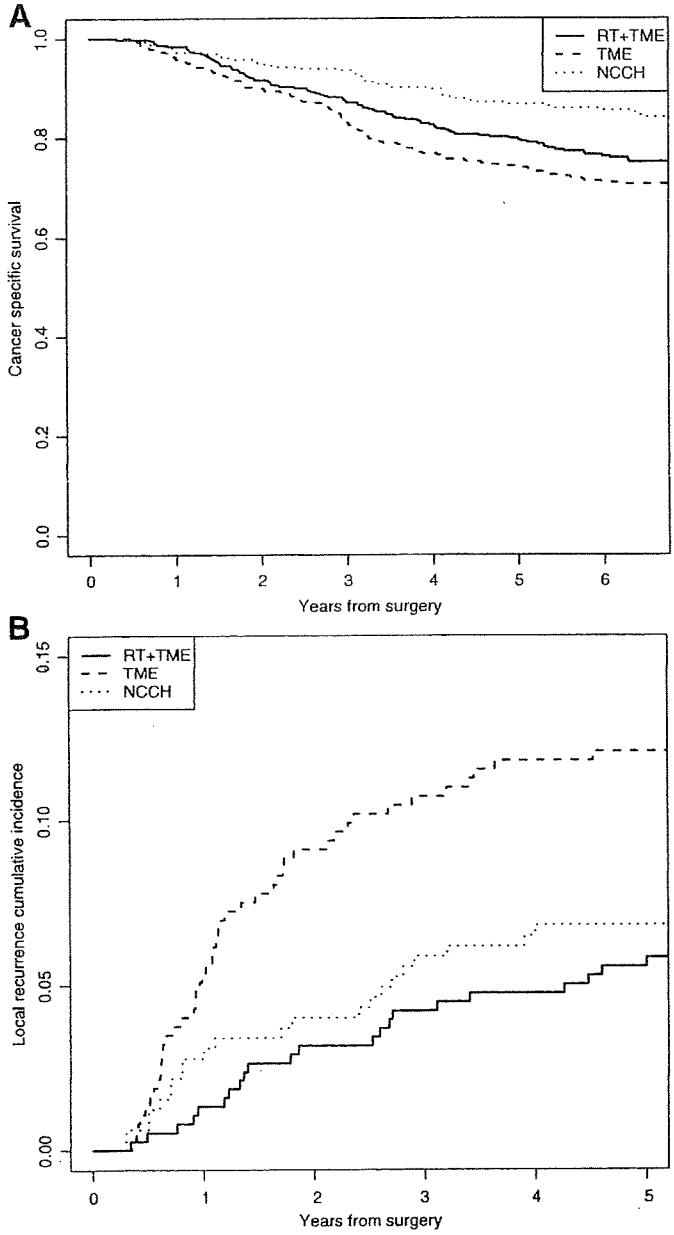

FIGURE 1. A, Cancer-specific survival, B,Local recurrence incidence.

Patterns of Local Recurrence

In Table 3 the patterns of local recurrence for the 3 groups are shown. Presacral recurrences (Fig. 2) occurred in 3.7% of the RT+TME patients and in 3.2% of the TME patients. In the Japanese group only 0.6% of the patients developed presacral recurrence. When only looking at the patients operated by APR, 5-year local recurrence rates in the presacral subsite were 6.5% in the RT+TME group, 4.4% in the TME group, and 1.8% in the Japanese group.

In this study, the lateral recurrence (Fig. 3) rate in the nonirradiated TME-group is 2.7%, comprising 24% of all local recurrences. The hazard ratio of lateral recurrence in the RT+TME group (0.8%) versus the TME group (2.7%) is significantly different from zero (HR = 5.3, 95% CI: 0.6–43.9). In the Japanese group, 2.2% developed local recurrence in the lateral pelvic subsite, not differing significantly from the Dutch groups. When only T3 and T4 tumors are selected, similar trends are observed.

Circumferential Resection Margin and Lateral Lymph Nodes

In the Dutch TME-group, 23% (88/376) of the patients showed CRM involvement on pathologic examination. Of these CRM-positive patients, the 5-year local recurrence percentage was 33%. In the CRM-negative cases, this was 9%. In the RT+TME-group, 20% (77/379) of the patients showed CRM involvement. Of these CRM-positive patients, the 5-year local recurrence rate was 25%. In the CRM-negative cases, 3% developed local recurrence in 5 years, versus 9% in the TME-group (HR = 0.4, 95% CI: 0.2–0.8).

Of the Japanese group it is not possible to report on CRM involvement; the immediate harvesting of lymph nodes from the fresh specimen precludes assessment of the CRM at a later stage. For the 190 patients operated by uni- or bilateral LLND, the 5-year local recurrence rate was 36% in the lateral node positive patients and 7% in the lateral negative patients (HR = 6.4, 95% CI: 2.6–15.7).

DISCUSSION

We compared Western and Japanese treatment results, looking at the patterns of local recurrence. The Japanese group differs from the Dutch groups in that the patients received extended surgery consisting of lateral lymph node dissection and a wider APR.

The main limitation of the present study is the difficult comparison of the group of Japanese patients with the group of Dutch patients. There are many sources of potential bias, such as nonrandomization and upstaging, as described previously.[24] Japanese patients are younger and have tumors with lower T-stage,

TABLE 3. Patterns of Local Recurrence

	Absolute No. LR 5-yrs (%)			Relative Distribution of LR*		
	RT+TME 379 pts	TME 376 pts	NCCH 324 pts	RT+TME 24 pts	TME 46 pts	NCCH 23 pts
presacral	14 (3.7%)	12 (3.2%)	2 (0.6%)	58%	26%	9%
lateral	3 (0.8%)	11 (2.7%)	8 (2.2%)	13%	24%	35%
anterior	4 (0.8%)	11 (3.0%)	1 (0.3%)	17%	24%	4%
anastomosis	2 (0.5%)	8 (2.1%)	5 (1.6%)	8%	17%	22%
perineum	0 (0%)	4 (1.1%)	5 (1.6%)	0%	9%	22%
unknown	1 (0%)	0 (0%)	2 (0.6%)	4%	0%	4%
	24 (5.8%)	46 (12.1%)	23 (6.9%)			
Hazard Ratio	1.0	1.6	1.0			
95% CI†	0.6–1.8	1.0–2.8				

*Local recurrence per pelvic subsite, as a percentage of all local recurrences.
†Hazard Ratio for local recurrence after multivariate analysis, with 95% CI as compared to the NCCH group.

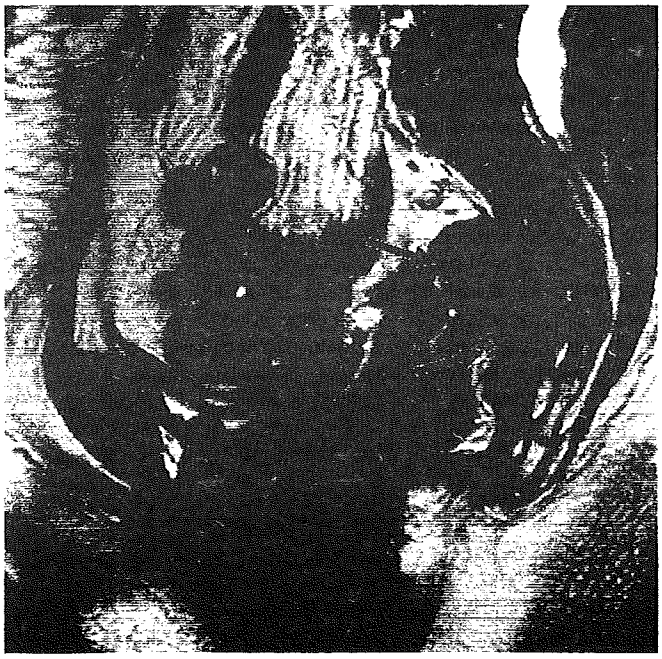

FIGURE 2. MR image of presacral local recurrence, sagittal MR image of locally recurrent mass in the presacral subsite.

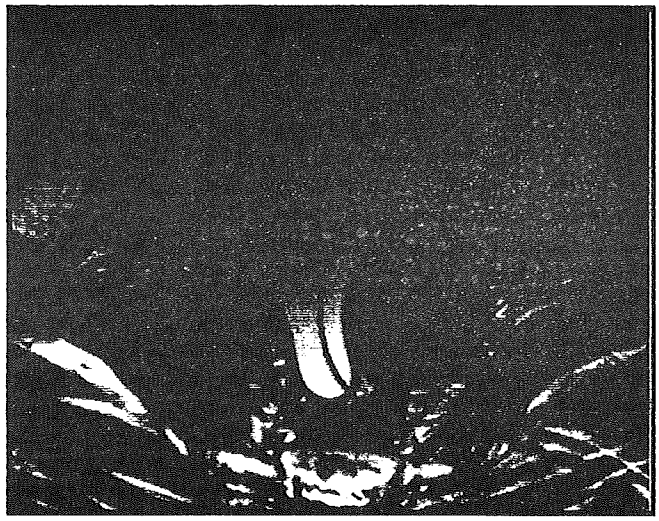

FIGURE 3. MR image of lateral recurrence, transverse MR image of local recurrence in the extramesorectal region (lateral subsite), highly suggestive of local relapse from nodal metastasis in the lateral lymph nodes.

although differences in local recurrence are still significant after multivariate analysis. Lymph node yield is much higher in the Japanese patients, which is probably because of differences in pathologic examination methods.[17] The differences in survival are undoubtedly more related to these differences than to any treatment effect. The definition and measurement of distal rectal cancer is different in the 2 countries, and although we tried to match the 2 groups as closely as possible, 1 or the other group may contain more distal tumors. The findings of the present study and the interpretation of the results therefore require some caution. Notwithstanding these limitations, the present study can give insight in the merits of the approaches and the mechanism of preventing local recurrences.

In this study extended surgery, as performed in the NCCH in Japan, results in good local control (5-year local recurrence rate, 6.9%). This is significantly less than after TME-surgery alone, which showed 12.1% local recurrence. Preoperative radiotherapy and TME-surgery also results in good local control (5.8%). The better local control is also reflected in the fact that the recurrences develop later when radiotherapy is given (2.6 years postoperatively) or more extended surgery is performed (2.1 years), compared with the 1.5 years after TME surgery. The high percentage of distant metastases at time of local recurrence diagnosis after RT+TME or extended Japanese surgery can also be seen as a marker of good local control, because now mainly patients with the worst disease get local recurrence, as if local recurrence is a sign of systemic disease.

The Japanese wider perineal resection is likely to result in less positive margins than in standard perineal resections, where the "coning in" is probably responsible for the high percentage of 23% involved margins in standard TME. Almost in 1 of 4 of these margin positive patients developed a local recurrence in this study. Unfortunately, pathology techniques differ between Japan and The Netherlands, making it impossible to draw firm conclusions on CRM involvement in the Japanese group. It has been described that recurrence rates after APR are far worse than after LAR. Even the pioneer of TME surgery, professor Heald, reported local recurrence in only 5% of cases 10 years after LAR, but in his patients who

underwent an APR, the local recurrence rate was as high as 36%.[25] Heald et al recently published an anatomic and radiologic study, in which they observed that in the lowest part of the rectum the mesorectum tapers and terminates at the pelvic floor.[26] Also Nagtegaal et al[5] concluded that following the mesorectum downward along the sphincter muscles is associated with increased occurrence of positive CRM. In the TME-trial, perforations in the anal canal were described, stressing the need for a more extended approach.[8,27] Holm et al recently reported on extended abdominoperineal resection, showing a low risk of CRM involvement.[28] It could be suggested that a wider perineal approach has a major contribution to good local control.

In the Dutch TME trial presacral recurrences were the most common type of recurrences. This was also reported in a large overview reported by Roels et al.[22] It is intriguing that this type of recurrence was uncommon in the Japanese group. The exact pathogenesis of presacral recurrences has been puzzling, as it is the easiest plane of dissection of a rectal cancer operation with often a wide margin of mesorectal fat. One could hypothesize that presacral recurrences result from implants of tumor cells originating from positive margins or tears or perforations at the tumor site. Through the force of gravity these implants would occur most often in the midline in the low/mid presacral area. Seventy-five percent of the presacral recurrences develop after APR surgery in the Dutch group, and radiotherapy apparently cannot sterilize these tumor particles. If this hypothesis were to be correct, presacral recurrences would occur less often with surgical techniques that avoid tumor spill, such as the wider perineal resections in the Japanese group. Of course this theory remains speculative.

The effect of the application of uni- or bilateral LLND on prevention of lateral recurrence is questionable. In the Japanese group, 2.2% developed local recurrence in the lateral pelvic subsite, not differing significantly from the Dutch groups. In this study, the lateral recurrence rate in the nonirradiated TME-group is 2.7%, comprising 24% of all local recurrences. The difference in lateral recurrence in the RT+TME group (0.8%) versus the TME group (2.7%) shows that radiotherapy plays a significant role in the reduction of local recurrence in the lateral pelvic subsite. Further, the significant lower local recurrence rate of CRM-negative RT+TME patients compared with CRM-negative TME-patients suggests the sterilization of tumor deposits outside the mesorectum. Only few reports are published about local recurrence in the lateral pelvis. In the overview report of Roels et al,[22] 6% of all patients and 21% of the patients with local recurrence had a relapse in the lateral pelvic subsite. Also Kim et al[29] reported recently that even after preoperative chemoradiotherapy combined with TME 24 of 366 (6.6%) patients with stage T3 or T4 tumors up till 8 cm from the anal verge developed lateral recurrence. Syk et al[30] reported only 2 of the 33 recurrent tumors originating from lateral pelvic lymph nodes in a population-based cohort. However, the study did not focus on low rectal tumors only and might be biased because patients who had a R1-resection or short distal resection margin were excluded. In the current report only low rectal tumors were studied and incomplete resection was not an exclusion criterion.

In the choice between more extensive surgery or preoperative radiotherapy as a means to improve the local recurrence rate, the morbidity associated with the treatment plays a major role. Patients who undergo radiotherapy have been shown to have an increased risk of sexual dysfunction and incontinence. In the Dutch TME-trial, 76% of the TME and 67% of the RT+TME male patients who were previously active were still active.[31] For female patients, these figures were 90% and 72%, respectively. Preoperative radiotherapy resulted in more erection and ejaculation problems in men, and vaginal dryness and pain during intercourse in women. Fecal incontinence was observed in 51.3% of the RT+TME patients, as compared with 36.5% in the TME patients. Regarding the lateral lymph node dissection, before nerve-sparing surgery, sexual dysfunction was present in as many as 96% of the patients.[32] LLND with nerve-sparing techniques 50% to 75% of the men are reported to be sexually active, although ejaculation is often compromised.[33,34] Urinary function is maintained well, but there are no reports on fecal continence. Although in Japan nerve-sparing techniques in LLND surgery are used to minimize damage the autonomic nervous system in the pelvis,[15,35] most Western surgeons feel that in Western patients, with a higher body mass index, nerve preserving techniques are more difficult and will lead to an excess morbidity. There is 1 report on results in 9 Western patients with locally advanced rectal cancer operated by LLND and ANP, with 1 patient with erection dysfunction and 1 patient suffering from retrograde ejaculation.[36] Currently, the National Cancer Center Hospital in Tokyo coordinates a multicenter randomized clinical trial comparing conventional TME versus LLND in patients with low rectal carcinoma, addressing the questions of survival benefit and morbidity. The inclusion of about 600 patients will be completed by the end of 2009.

Magnetic resonance imaging (MRI) is currently considered as the most reliable in staging rectal cancer. Preoperative MRI modalities are further improving and techniques are developed to distinguish better between nonmetastatic and metastatic lymph nodes by, for example, lymph node specific contrast enhancement.[37] With present day MRI, sometimes patients are identified with clearly involved or suspected lateral lymph nodes. As often preoperative chemoradiation is the choice of treatment in these cases, it is doubtful whether the lateral lymph nodes can be fully sterilized. Also, the risk for disseminated disease is high and prognosis is unfavorable for lateral lymph node positive patients. For these patients, it may be wise to consider a combination of treatments: neoadjuvant chemoradiation, a lateral lymph node dissection, and possibly even systemic therapy.

In conclusion, both extended surgery and preoperative radiotherapy with standard TME surgery result in good local control in the treatment of distal rectal cancer, as compared with TME alone.

ACKNOWLEDGMENTS

The authors thank all participating clinical investigators of the Dutch TME trial, Dr. M. den Dulk, E. Klein Kranenbarg from the Data center of the Department of Surgery, Leiden University Medical Center, for providing the data; and Dr. S. Ishiguro and Y. Kobayashi, from the colorectal surgery department of the National Cancer Center Hospital, for the help with obtaining data; as well as Dr. Y. Arai and Dr. M. Takahashi from the department of Radiology, National Cancer Center Hospital, for assistance with respect to imaging.They express their gratitude to the Japan Prizewinners Program of the Dutch Government who financed the stay of M. Kusters in Tokyo and the Japan-Netherlands Institute (Executive Director Dr. W.G.J. Remmelink) for the practical support.

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Int J Colorectal Dis (2009) 24:1085–1090
DOI 10.1007/s00384-009-0704-4

ORIGINAL ARTICLE

Risk factors of lateral pelvic lymph node metastasis in advanced rectal cancer

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Accepted: 1 April 2009 / Published online: 23 April 2009

Abstract
Background To clarify the risk factors of lateral pelvic lymph node (LPLN) metastasis of rectal cancer, we examined associations between LPLN status and clinicopathological factors including LPLN status diagnosed by computed tomography (CT).
Methods We reviewed a total of 210 patients with advanced rectal cancer, of which the lower margin was located at or below the peritoneal reflection, who underwent preoperative CT with 5-mm-thick sections and lateral pelvic lymph node dissection at the National Cancer Center Hospital between February 1998 and March 2006.
Results Forty-seven patients (22.4%) had LPLN metastasis. Multivariate analysis showed that LPLN status diagnosed by CT, pathological regional lymph node status, tumor location, and tumor differentiation were significant risk factors for LPLN metastasis. Among 45 patients with well-differentiated adenocarcinoma who were LPLN-negative and in whom CT had found no regional lymph node metastasis, none had LPLN metastasis. On the other hand, among 13 patients with moderate or less differentiated lower rectal adenocarcinoma who were LPLN-positive and in whom CT had revealed regional lymph node metastasis, 12 (92.3%) had LPLN metastasis.
Conclusions LPLN status diagnosed by CT, pathological regional LN status, tumor location, and tumor differentiation are significant risk factors for LPLN metastasis. Using these factors, patients can be classified as having a low or high risk of LPLN metastasis.

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Keywords Rectal cancer · Lymph node dissection · Lateral pelvic lymph node · Risk factor

Introduction

Lateral pelvic lymph node dissection (LPLD) is widely performed for advanced lower rectal cancer in Japan, and the incidence of lateral pelvic lymph node (LPLN) metastasis has been demonstrated to be 15–30% [1–3]. In spite of the relatively high incidence of LPLN metastasis, most surgeons, except for those in Japan, do not perform LPLD, and instead adjuvant chemoradiotherapy and total mesorectal excision (TME) have become the standard therapy for rectal cancer. In order to clarify the indications for, and the possible benefits of, LPLD, a retrospective multicenter study was conducted in Japan, and this demonstrated that LPLD was effective for local control, and might be indicated for patients with T3–T4 lower rectal cancer [3]. The 5-year survival rate of patients with LPLN metastasis is about 40% [1–3], which is comparable with that of patients with resectable liver or lung metastasis. From this viewpoint, LPLN metastasis should be classified as distant metastasis, and resected if at all possible. Kim et al. demonstrated that LPLN metastasis is a major cause of local recurrence in patients who receive preoperative chemoradiotherapy without LPLD [4]. This indicates that LPLD should not be neglected even in the era of neo-adjuvant therapy for rectal cancer. Therefore, accurate preoperative diagnosis of pelvic lateral node metastasis is important. Although Yano et al. showed that conventional CT accurately predicted LPLN status [5], validation studies are necessary. In this study, therefore, we examined the association between clinicopathological factors, including CT diagnosis of lymph nodes and LPLN status, and

selected high-risk factors for LPLN metastasis, enabling classification of patients according to LPLN metastasis risk.

Patients and methods

Patients

We reviewed a total of 210 patients with advanced rectal cancer, of which the lower margin was located at or below the peritoneal reflection, who underwent preoperative computed tomography (CT) with 5-mm-thick sections and lateral pelvic lymph node dissection (LPLD) at the National Cancer Center Hospital between February 1998 and March 2006. All the patients underwent TME or tumor-specific mesorectal excision. Pelvic autonomic nerves were preserved completely or partially in 187 patients (89%). The patients were followed up at 3-monthly intervals for 2 years, and at 6-monthly intervals thereafter. Tumor markers were examined at every patient visit. CT of the liver and lung or abdominal ultrasonography with chest X-ray was performed at least every 6 months. Colonoscopy was performed twice within 5 years after surgery. Median follow-up time was 3.8 years. Six patients received preoperative or postoperative radiotherapy. Pathological stage III patients were given adjuvant chemotherapy.

Diagnosis

All the patients underwent preoperative CT with 5-mm-thick sections using intravenous contrast media, and lymph nodes more than 5 mm in diameter were considered positive (Fig. 1). A radiologist interpreted the CT images preoperatively, and one author (SF) interpreted the images postoperatively. The author finally determined the lymph node status. Lymph nodes were classified according to their location. Lymph nodes in the lateral pelvic area outside the pelvic plexus and hypogastric nerves along the internal ileac, external ileac, common ileac vessels, and in the obturator space were considered LPLN. Patients with LPLN metastasis were classified as stage III in this study. Lymph nodes in the area lying along the inferior mesenteric vessels were considered regional lymph nodes. Tumor size and annularity were determined preoperatively by colonoscopy, barium enema, or virtual colonoscopy. Depth of invasion (T) and tumor location were determined preoperatively by CT or magnetic resonance imaging (MRI), and tumor location was finally confirmed during surgery. All the cancers were biopsied and a pathological diagnosis obtained before surgery.

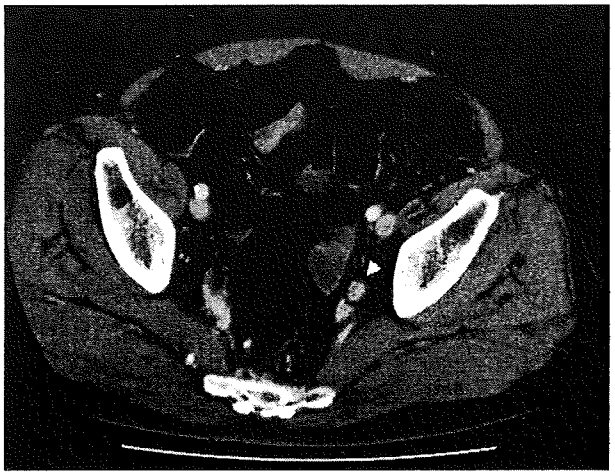

Fig. 1 Representative lateral pelvic lymph node swelling detected by CT. Left lateral pelvic lymph node swelling is seen (*arrowhead*). The lymph node diameter is 10 mm. This patient underwent lateral pelvic lymph node dissection and metastasis was found by pathological examination 201 × 285 mm

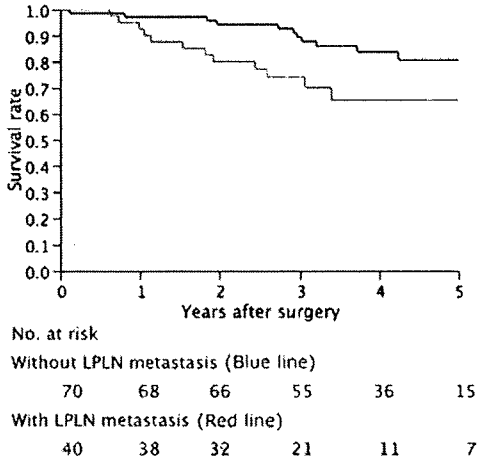

Fig. 2 Survival curves for patients with stage III rectal cancer with and without LPLN metastasis. 201×285 mm

Statistical analysis

Statistical analysis was carried out by the chi-squared test. Survival rates were calculated by the Kaplan–Meier method, and survival curves were compared by the log-rank test. A logistic regression model was used for multivariate analysis. Data differences between groups were considered statistically significant at $P<0.05$.

Results

Incidence of LPLN metastasis and prognosis

Among the 210 patients, 47 (22.4%) had LPLN metastasis. The survival curves for stage III patients are shown in

Fig. 2. The survival rate of stage III patients with LPLN metastasis was significantly poorer than that of stage III patients without LPLN metastasis (P=0.014). Although the follow-up period was insufficient, the estimated 5-year survival rate for the patients with LPLN metastasis was 54%. The incidence of local recurrence in stage III patients with LPLN metastasis was 22.5% (9/40) and that in stage III patients without LPLN metastasis was 10.0% (7/70). Although the incidence of local recurrence in stage III patients with LPLN metastasis was higher than that in stage III patients without LPLN metastasis, the difference was not statistically significant (P=0.074).

Table 1 Incidence of LPLN metastasis and preoperative clinicopathological factors

	LPLN metastasis positive (n=47)	LPLN metastasis negative (n=163)	P
Age (years)			0.749
<60	25	91	
≥60	22	72	
Sex			0.336
Male	30	116	
Female	17	47	
CEA (ng/ml)			0.072
≤5	25	110	
>5	22	53	
Tumor location			0.018
Ra	3	35	
Rb	44	128	
Clinical T			0.616
T1, 2	4	14	
T3	31	118	
T4	12	31	
Regional LN status			0.014
Negative	13	78	
Positive	34	85	
LPLN status			<0.001
Negative	18	147	
Positive	29	16	
Tumor size (cm)			0.673
≥5	22	82	
<5	25	81	
Annularity			0.197
≤2/3	23	97	
>2/3	24	66	
Tumor differentiation			<0.001
Well	14	92	
Moderate	26	66	
Poor, mucinous	7	5	

Ra tumor center located above the peritoneal reflection; *Rb* tumor center located below the peritoneal reflection

Table 2 Incidence of LPLN metastasis and postoperative clinicopathological factors

	LPLN metastasis positive (n=47)	LPLN metastasis negative (n=163)	P
Pathological T			0.058
T1, 2	4	38	
T3	40	111	
T4	3	14	
Pathological regional LN status			<0.001
Negative	7	84	
Positive	40	79	
Lymphatic invasion			<0.001
Negative	17	116	
Positive	30	47	
Venous invasion			0.002
Negative	11	80	
Positive	36	83	
Perineural invasion			0.001
Negative	27	131	
Positive	20	31	
Tumor budding			0.073
Negative	15	76	
Positive	32	87	

Associations of LPLN metastasis with clinicopathological factors

Associations of LPLN metastasis with preoperative clinicopathological factors are shown in Table 1. LPLN status and regional lymph node status diagnosed by CT, tumor location, and tumor differentiation were significantly associated with LPLN metastasis. Associations of LPLN metastasis with postoperative clinicopathological factors are shown in Table 2. Pathological regional lymph node status, lymphatic invasion, venous invasion, and perineural invasion were significantly associated with LPLN metastasis. Multivariate analysis showed that LPLN status diagnosed by CT, pathological regional lymph node status, tumor location, and tumor differentiation were significant risk factors for LPLN metastasis (Table 3).

Incidence of LPLN metastasis according to risk factors

In order to identify patients at low risk and high risk for LPLN metastasis preoperatively, patients were classified into four groups according to the significant risk factors of LPLN metastasis. Although pathological regional lymph node status was a significant risk factor for LPLN metastasis, regional lymph node status diagnosed by CT

Table 3 Multivariate analysis of clinicopathological factors associated with LPLN metastasis

	Odds ratio (95% C.I.)	*P*
LPLN status (positive/negative)	28.00 (9.19–102.46)	<0.001
Pathological regional lymph node status (positive/negative)	7.21 (2.19–28.08)	0.002
Tumor location (Rb/Ra)	12.56 (2.35–107.87)	0.009
Tumor differentiation (moderate, others/well)	4.05 (1.47–12.23)	0.009

C.I. confidence interval

was used for the classification, because pathological lymph node status was not clarified preoperatively. Tumors located at Ra (tumor center located above the peritoneal reflection) and tumors located at Rb (tumor center located below the peritoneal reflection) were analyzed separately, and other risk factors were used for the classification. Group I was the group with no risk factors. Group II was the group with negative LPLN status diagnosed by CT but with at least one of the other two risk factors. Group III was the group with positive LPLN status diagnosed by CT but without at least one of the other two risk factors. Group IV was the group with all of the risk factors. Incidences of LPLN metastasis according to this classification are shown in Table 4. Irrespective of tumor location, no patients (0/45) had LPLN metastasis in group I. On the other hand, in group IV, 50.0% (2/4) of the patients with Ra tumors and 92.3% (12/13) of the patients with Rb tumors had LPLN metastasis. When pathological regional lymph node status was used for this classification instead of regional lymph node status diagnosed by CT, 75 patients were classified into group I or group II without pathological lymph node metastasis, and these patients also had no LPLN metastasis.

Discussion

The incidence of LPLN metastasis in patients with advanced lower rectal cancer is 15–30% [1–3]. Although the prognosis of patients with LPLN metastasis is poor, the 5-year survival rate is 40%, being comparable to that of patients with resectable liver or lung metastasis. Sugihara et al. estimated that LPLD would improve the 5-year survival rate of patients with T3–T4 lower rectal cancer by 8% [3]. Therefore, LPLD for patients with LPLN metastasis should be considered. Because accurate diagnosis of LPLN metastasis is difficult, LPLD is routinely performed in Japan for stage II or III rectal cancer located at or below the peritoneal reflection. However, it is still unproved whether LPLD is necessary for patients without LPLN metastasis. In order to acquire level 1 evidence, we are currently performing a clinical trial to compare TME alone with TME plus LPLD for rectal cancer patients without LPLN metastasis (JCOG0212) (ClinicalTrials.gov Identifier NCT00190541). Because accurate preoperative diagnosis of LPLN metastasis is important for treatment of lower rectal cancer, we selected four high-risk factors for LPLN metastasis and were able to estimate the incidence of LPLN metastasis using a combination of these factors. Patients without LN metastasis diagnosed by CT and with well-differentiated adenocarcinoma have no LPLN metastasis, and would not require LPLD. On the other hand, more than 80% of patients with LPLN metastasis diagnosed by CT and with moderate or less differentiated adenocarcinoma have LPLN metastasis, and should undergo LPLD. Therefore, our classification is thought to be useful for determining the indications for LPLD.

Late adverse effects of LPLD are sexual and urinary dysfunction [6]. Recently, TME plus LPLD with autonomic nerve preservation has been performed in Japan, and the incidences of sexual and urinary dysfunction following this treatment have been comparable to those after TME [7–9]. Because the oncological outcome of TME plus LPLD with autonomic nerve preservation is also comparable to that without autonomic nerve preservation [10], the former has become the standard therapy for rectal cancer in Japan. However, when patients have LPLN metastasis or if the tumor has invaded the autonomic nerves, nerve preservation is not possible. Therefore, the autonomic nerves were not preserved in 11% of the patients in this series.

Sex, tumor location, depth of invasion, mesorectal LN status, tumor differentiation, and tumor size are reported to be factors associated with LPLN metastasis [3, 11]. Although our findings were comparable, these previous reports did not take into account LPLN status diagnosed by

Table 4 Incidence of LPLN metastasis according to risk factors

	Incidence of LPLN metastasis
Ra (*n*=38)	
Group I (*n*=7)	0.0% (0/7)
Group II (*n*=27)	3.7% (1/27)
Group III (*n*=0)	–
Group IV (*n*=4)	50.0% (2/4)
Rb (*n*=172)	
Group I (*n*=38)	0.0% (0/38)
Group II (*n*=93)	18.3% (17/93)
Group III (*n*=28)	53.6% (15/28)
Group IV (*n*=13)	92.3% (12/13)

CT. As demonstrated in the present study, LPLN status diagnosed by CT was the most important risk factor associated with LPLN status. Therefore, accurate diagnostic imaging is important. In this study, the sensitivity, specificity, and accuracy of LPLN status diagnosis using CT were 62%, 90%, and 84%, respectively. Arii et al. demonstrated that the accuracy of LPLN status diagnosis using MRI was 83%, whereas that using CT was 77% [12]. Matsuoka et al. reported that MRI diagnosis of LPLN status had 67% sensitivity, 83% specificity, and 78% accuracy [13]. These results were comparable to ours. On the other hand, Yano et al. showed that CT diagnosis of LPLN status had 95% sensitivity, 94% specificity, and 95% accuracy [5]. However, because the number of patients they examined was small (n=39) and patients who did not undergo LPLD were excluded, the results were not directly comparable with other studies. Quadros et al. reported the preliminary results of LPLN detection using lymphoscintigraphy and blue dye [14]. However, the sensitivity and specificity were 17% and 79%, respectively. Tada et al. demonstrated the effectiveness of ultrasonographic examination for determining LPLN status, the sensitivity, specificity, and accuracy being 75%, 94%, and 93%, respectively [15]. Although this result was excellent, there were some problems and limitations; for example, obturator space lymph nodes were sometimes overlooked, and the use of ultrasonography in obese patients was difficult.

A meta-analysis of mesenteric lymph node diagnosis has indicated that the sensitivity and specificity of CT, MRI, and endoscopic ultrasonography are compatible [16]. Matsuoka et al. also demonstrated that multidetector-row CT was as equally effective as MRI for local staging of rectal cancer [17]. We preliminarily examined the capacity of MRI for diagnosis of lymph node status, and found that its sensitivity was higher and its specificity lower than that of CT, with roughly comparable accuracy. The use of new criteria for lymph node status instead of size [18], or a new MRI contrast agent [19], has been reported to yield better sensitivity and specificity for MRI diagnosis of mesenteric lymph nodes. However, further examinations will be necessary to establish an optimal approach for diagnosis of lymph node status using imaging modalities.

If patients with LPLN metastasis do not undergo LPLD, they would suffer LPLN or local recurrence. Kim et al. showed that adjuvant preoperative radiotherapy without LPLD was unable to control LPLN metastasis and local recurrence [4]: lateral pelvic recurrence was observed in 2.3%, 12.5%, and 68.8% of patients with LPLN measuring <5, 5–10, and≥10 mm, respectively, determined by MRI. On the other hand, Quadros et al. showed that patients who received preoperative adjuvant chemoradiotherapy did not develop LPLN metastasis [14]. A small randomized study that compared adjuvant radiotherapy with LPLD also suggested that LPLD was unnecessary for patients who underwent preoperative radiotherapy [20]. Syk et al. demonstrated that LPLN metastasis was not a major cause of local recurrence of rectal cancer [21]. A comparative study demonstrated that the local recurrence rate in Korean patients who received adjuvant chemoradiotherapy without LPLD was lower than that in Japanese patients who underwent LPLD alone [22]. Moreover, the local recurrence rate in patients with LPLN metastasis has been reported to be 25.6% [3]. In our study, the local recurrence rate in patients with LPLN metastasis was 22.5%, which was significantly higher than that in patients without LPLN metastasis. These facts suggest that LPLD alone is not sufficient for local control in patients with LPLN metastasis. Therefore, a combination of adjuvant radiotherapy with LPLD is thought to be important for treatment of advanced rectal cancer, and a randomized study is required to determine whether LPLD is necessary for patients with LPLN metastasis receiving preoperative chemoradiotherapy.

In conclusion, LPLN status diagnosed by CT, pathological regional LN status, tumor location, and tumor differentiation are significant risk factors for LPLN metastasis. Using these factors, patients can be classified as having a low or a high risk of LPLN metastasis. This classification suggests that LPLD should be considered in patients with advanced lower rectal cancer.

Funding Grant-in-Aid for Scientific Research from the Ministry of Health, Labor and Welfare of Japan.

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Differences in rectal cancer surgery: east versus west

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See ... page 1053

In this issue of *The Lancet Oncology*, Georgiou and colleagues[1] report the results of their meta-analysis of observational studies comparing extended lymphadenectomy (EL) for rectal cancer with non-EL. After analysing 20 studies published over the past 25 years, the authors concluded that the efficacy of EL was insufficient to recommend it instead of conventional surgery.

Although this paper is important, its role in clinical decision making for rectal cancer is unclear for a number of reasons. During the past 25 years, imaging modalities and surgical techniques have made remarkable progress. In EL, nerve-sparing surgery with lateral nodal dissection (LND) was developed, while in non-EL, total mesorectal excision has become the standard. In surgery, techniques of LND can vary from "node picking" to "en-bloc dissection". Even without accounting for time effect or bias, interpreting the results of Georgiou and colleagues is problematic.

Also problematic are the author's failure to take lateral nodal metastases (LNM) into account. The definition of low rectum is slightly different between Japan and the west. LNM are found only in cancers of the low rectum, below the peritoneal reflection. It is well-known that the deeper the invasion and the lower the tumour, the higher the risk of LNM.[2] Heald once described LNM as "a Japanese mystery": LNM are not considered of surgical importance in the west. However, progress in MRI has been made, and the preoperative evaluation of LNM has become more reliable. Whether or not the sterilisation of LNM by pre-operative radiotherapy or chemoradiotherapy (pre-[C]RT) is possible is also an important point. There are no reports on the efficacy of pre-(C)RT for the treatment of LNM, but some researchers claim that the sterilisation of LNM can be achieved.[3]

Overtreatment, which is seen in both Japanese and western populations, also needs to be addressed. LND in patients without extra-mesenteric metastasis is overtreatment. However, in Japanese hospitals, LND was done in almost all cancers of the low rectum of T2 stage or higher until 1985. Although this wide application of LND clarified the frequency and sites of LNM, LND caused dysfunction. Because of this, Japanese surgeons investigated pelvic autonomic nerve anatomy, and developed nerve-sparing surgery with LND.[4,5] A randomised trial of nerve-sparing surgery with LND versus total mesorectal excision has been started in Japan to measure the effectiveness of LND for occult LNM. For high-risk patients, such as those with obvious LNM or c-stage IIIb disease, a randomised trial of pre-CRT with extended surgery versus pre-CRT with total mesorectal excision should be done in Japan.

Overtreatment is also a problem in the west. In particular, many cases of rectal cancer that can be locally controlled by surgery alone are actually treated with pre-(C)RT. As a result, the incidence of dysfunction rises, with accompanying costs. For the treatment of rectal cancer, the role of surgery is central. In reports about neoadjuvant radiotherapy in the west, patients with T1 and T2 tumours were also included in the Swedish and Dutch trials, whereas in a German trial, the patient population was restricted to only those with T3 or T4 and N-positive disease, indicating an improvement in patient selection over time. Since the incidence of local recurrence in tumours above the peritoneal reflection is low, the clinical significance of pre-(C)RT for this population is disputed. However, in the west, tumours up to 15 cm from the anal verge are treated with pre-(C)RT. If pre-(C)RT is expected to result in downsizing of the tumour, overtreatment could be avoided by setting size criteria, in addition to T stage, in treatment protocols. Radiation increases occlusion, induces changes in hyaline in the blood and lymph vessels, and affects fibrosis over time, and brings about organ dysfunction. Owing to fibrosis, surgery for local recurrence after pre-(C)RT becomes very difficult, and radiation carcinogenesis can also develop.[6] For patients whose life expectancy is long, the adverse effects of pre-(C)RT should be taken into account. Therefore, since we now know more about the risk factors for local recurrence, and imaging modalities have been improved, high-risk tumours can be selected accurately. The east and the west should join hands and define research criteria for surgery and neoadjuvant treatment to prevent over-treatment and dysfunction, and to improve future oncological results.

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The author declared no conflicts of interest.

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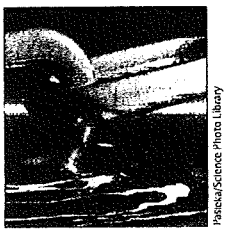
Treatment of gastric cancer in Asia: the missing link

Conventional chemotherapy for gastric cancer is known to improve overall survival, quality of life (QOL), and the length of time a patient is free of symptoms compared with best supportive care,[1] but outcomes for advanced gastric cancer are still extremely poor. Although various combinations of platinum compounds and fluoropyrimidine derivatives improve patient outcomes, no accepted global standard exists for the treatment of gastric cancer. Additionally, there are marked geographical differences in the prevalence of types of gastric cancer, with intestinal-type distal gastric cancer related to *Helicobacter pylori* predominant in Asia, compared with the predominance of proximal and diffuse types of gastric cancer in Europe and North America. There are also marked regional differences in how gastric cancer is treated.

One common trend in chemotherapy is the replacement of intravenous infusion with oral administration, thus improving patient QOL and decreasing the length of time spent in hospital. In this issue of *The Lancet Oncology*, Boku and colleagues[2] show that S-1, an oral fluoropyrimidine derivative, is as effective as continuous infusion of fluorouracil for the treatment of advanced gastric cancer. S-1 contains tegafur (a prodrug of fluorouracil), 5-chloro-2,4-dihydropyrimidine (a reversible inhibitor of dihydropyrimidine dehydrogenase), and potassium oxonate. In phase 2 trials, S-1 showed good results in Japanese patients. It has recently been suggested that S-1 should be given in adjuvant settings to Asian patients with locally advanced gastric cancer after D2 dissection.[3] The SPIRITS trial[4] comparing S-1 plus cisplatin with S-1 alone, which started 2 years after the study by Boku and colleagues, showed that the combination of S-1 plus cisplatin seems to be more effective than S-1 monotherapy (p=0·04 for overall survival). Thus the study by Boku and colleagues is a missing link: together, the study by Boku and colleagues and the SPIRITS trial indicate that the combination of cisplatin plus S-1 should replace cisplatin plus fluorouracil as the first-line treatment of choice for Japanese patients with advanced gastric cancer. However, S-1 shows a different toxicity profile in patients in Europe and the USA, including severe diarrhoea and frequent neutropenia, and is therefore not always as effective as has been seen in Japan because of low dose intensity. Although the efficacy of S-1 plus cisplatin was similar to fluorouracil plus cisplatin in the FLAGS study,[5] oral administration of capecitabine, another fluoropyrimidine derivative, is recommended for western patients because of its efficacy and lower toxicity. Cisplatin plus capecitabine is non-inferior to fluorouracil plus cisplatin in advanced gastric cancer,[6] and capecitabine and oxaliplatin are as effective as fluorouracil and cisplatin in first-line triplet therapy with epirubicin for oesophagogastric cancer,[7] suggesting cisplatin plus capecitabine or capecitabine plus oxaliplatin plus epirubicin as a standard therapy for advanced gastric cancer or oesophagogastric cancer. Therefore, there are several different standards for the treatment of advanced gastric cancer throughout the world.

A combination regimen with platinum compounds, fluorouracil derivatives, and/or taxanes is usually more effective than monotherapy.[1] Boku and colleagues also examined whether the doublet of irinotecan plus cisplatin was more effective than fluorouracil, but noted that it was not (p=0·055). This may be partly due to the design of the three-group comparison, and relatively low statistical power. Nevertheless, triple therapy is hopefully more effective than monotherapy or doublet therapy. Several phase 2 studies have indicated that docetaxel plus cisplatin and fluorouracil is promising, despite its high toxicity.[1] However, targeted agents with more favourable toxicity profiles, such as trastuzumab, combined with cytotoxic agents might substantially improve survival and reduce toxic side-effects, as was seen in the ToGA



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See Articles page 1063

J Gastrointest Surg (2009) 13:1643–1650
DOI 10.1007/s11605-009-0966-8

ORIGINAL ARTICLE

Long-Term Results of Hepatectomy After Hepatic Arterial Infusion Chemotherapy for Initially Unresectable Hepatic Colorectal Metastases

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Received: 18 May 2009 / Accepted: 22 June 2009 / Published online: 7 July 2009

Abstract
Background The prognosis of unresectable hepatic colorectal metastases is poor even if chemotherapy is administered. The purpose of this study was to evaluate the long-term efficacy of hepatic arterial infusion (HAI) chemotherapy and hepatectomy following HAI for such condition.
Methods Seventy-two patients with unresectable hepatic colorectal metastases received continuous HAI of 5-fluorouracil.
Results The overall response rate was 38%. The median survival of all patients was 18 months. The overall 3-year survival rate was 18%. Seven patients (10%) survived more than 58 months. Of the eight patients with a complete response, seven developed liver and/or lung metastases, and of these, one patient undergoing additional hepatectomy has been disease-free and the other six receiving chemotherapy died of disease. Another complete-response case died of liver abscess. Of the 19 patients with a partial response, six could undergo hepatectomy after HAI. The overall 5-year survival rate of seven patients undergoing hepatectomy was 71%, whereas for patients without hepatectomy, the rate was 0%.
Conclusions Most patients showing response after HAI for unresectable hepatic colorectal metastases had relapses. The long-term prognosis of patients undergoing hepatectomy after HAI was favorable. Therefore, when HAI makes liver metastases resectable, they should be resected.

Keywords Colorectal cancer · Liver metastasis · Hepatic arterial infusion · Neoadjuvant therapy · Liver resection

Introduction

Colorectal cancer is the leading cause of cancer death in developed countries.[1] The prognosis of patients with colorectal cancer is affected not only by surgical treatment for primary tumors but also by management of liver metastases because up to 50% of patients with primary colorectal cancer develop liver metastases synchronously or metachronously.[2,3]

The treatment strategy for hepatic colorectal metastases is still controversial. Although surgical resection is the best treatment option for resectable metastases[4] and the 5-year survival rates after hepatectomy are 37–58%,[5–10] unresectable metastases remain a serious problem. In general, systemic chemotherapy is recommended for such condition.[11] When using current systemic regimens for disease limited to the liver, chemotherapy enables resection in 15–30% of patients.[12] However, the 5-year survival rates following resection after systemic chemotherapy are still around 30%,[12] and there are circumstances that prohibit the usage of current regimens, such as drug toxicity and refractory disease.

Therefore, despite being technically demanding, hepatic arterial infusion (HAI) chemotherapy has a certain role in the treatment of unresectable liver metastases. HAI has the advantage of bringing a high concentration of cytotoxic

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