Lateral Lymph-node Dissection for Rectal Cancer: Meta-analysis of all 944 Cases Undergoing Surgery During 1975-2004

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Abstract. *Background: Colorectal cancer is the third most common cancer and leading cause of cancer-related death in Japan. One of the major problems in rectal cancer surgery is local recurrence. Pelvic sidewall dissection (PSD) has the potential to reduce local recurrence. Patients and Methods: This study included all 994 patients with rectal cancer who underwent curative surgery from January 1975 until December 2004, at the Kurume University Hospital in Fukuoka, Japan. The patients were analyzed to determine whether lateral lymph node (LLN) metastasis correlates with clinicopathological factors, and to determine a diagnostic tool based on magnetic resonance imaging (MRI) findings. Results: The rate of positive LLNs in patients who underwent PSD was 7.5% in the upper rectum, and 14.5% in the lower rectum. Logistic regression analysis disclosed that perirectal lymph nodes metastasis was associated with an increased incidence of positive LLNs and had a greater hazard ratio. Positive LLNs were frequently found to be located along the internal iliac artery (47 patients; 89%) or around the oburator vessels and nerve (17 patients; 32%). MRI has become a promising diagnostic tool in patients with rectal cancer including LLN estimation. Conclusion: We speculate that PSD may be a good candidate as an effective strategy for lower rectal cancer. In further studies, it is important to investigate the validity of PSD for its potential clinical use in lower rectal cancer therapy and prognosis.*

Colorectal cancer is a major cause of death in Japan, where it accounts for the largest number of deaths from malignant neoplasms in women and the third largest number in men (1). The most important prognostic factor in colorectal cancer is nodal status, and node metastasis is a determining factor for adjuvant chemotherapy and subsequently key to predicting disease-free and overall survival (2, 3).

One of the major problems in rectal cancer surgery is local recurrence. There are some reports of a local recurrence rate at 21% to 46% in the early 1990s (4-7). To improve local control, adjuvant radiotherapy, total mesorectal excision (TME) (8, 9) and extended lateral lymph node (LNN) dissection (10, 11) have been introduced. One of the standard surgical approaches for rectal cancer is tumor-specific mesorectal excision (TSME) in which the rectum and mesorectum are removed with an appropriate distal resection margin en bloc together with the proper rectal fascia (12, 13).

Furthermore, significant prognosis was made in terms of using chemoradiotherapy to achieve local control and favorable survival rates (14, 15). Although randomized controlled trials show that preoperative adjuvant radiotherapy has reduced local recurrence by 50% (4-6), a survival benefit has only been observed in a Swedish trial (6). Some other meta-analyses of adjuvant radiotherapy shows that preoperative radiotherapy yields a significant reduction in local recurrence and a significant of although small increase in survival (16, 17).

The technique of TME alone, however, does not address the potential nodal spread to the lateral compartments of the pelvis thus leading to potential local recurrence. The introduction of TME has raised awareness among surgeons regarding the importance of anatomic mobilization of the rectum along the proper rectal fascia without destruction of the lymphovascular network in the mesorectum (8, 9). The local recurrence rate has been found to be reduced to around 10% after TME was introduced (18-20).

Since the late 1970s, extended pelvic node dissection has been applied in Japan to remove the lymphatic network, including not only the proximal lymphatic stream in the mesorectum but also the lateral lymphatic stream. In this

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procedure, the dissection plane is further outside than that of TME. However, this aggressive procedure is complicated by a high frequency of severe urinary and sexual dysfunctions (21). The introduction of pelvic autonomic nerve preservation combined with extended pelvic node dissection achieves a lower local recurrence rate of 5.6% in urinary dysfunction, and 4.8% in male sexual dysfunction (22, 23). Therefore cases in Japan are now pre-selected for those needing LLN dissection.

Extended pelvic node dissection is a combination of TSME and pelvic sidewall dissection (PSD), and TME is a combination of TSME and complete distal mesorectal excision. In order to pre-select patients with LLN spread preoperatively using pelvic imaging, we have undertaken this retrospective study to investigate the indication and possible benefit of PSD for rectal cancer.

The aim of this study was to analyze the correlation, if any, between LLN metastasis and various clinicopathological factors, and to investigate the efficacy of PSD in patients with rectal cancer.

Patients and Methods

Patients and tissue samples. This study included 994 patients with rectal cancer who underwent curative surgery, from January 1975 until December 2004, at the Kurume University Hospital in Fukuoka. Informed consent was obtained from each of the patients before performing surgical resection, and approval was received from the Institutional Review Committee for Research on Human Subjects at the Kurume University Hospital (#12135). Tumor differentiation and the degree of invasion were examined by pathologists, and histopathological classification was performed according to the General Rules for Colorectal Cancer Study (24). Clinicopathological factors were assessed according to the tumor node metastasis (TMN) classification of the International Union Against Cancer (UICC) (25).

Anatomic definition in the pelvic cavity. The rectum was divided into three regions according to the Japanese Classification of Colorectal Carcinoma (24), rectosigmoid (RS), upper rectum (Ra), and lower rectum (Rb). RS is defined as the region of the rectum between the promontrium and the lower border of the second sacral vertebra, which is equivalent to 12 cm from the anal verge; Ra is located between the lower border of the second sacral vertebra and peritoneal reflection, which is equivalent to 8 cm from the anal verge; and Rb is between peritoneal reflection to the upper border of the anal canal. In this study, we distinguished between the upper rectum (RS+Ra) and the lower rectum (Rb).

The LLN were defined as the lymph nodes located outside the pelvic plexus, along the internal iliac (inside area: I) and common iliac vessels and in the obturator cavity (extra area: E).

PSD. PSD was performed based on the preoperative staging by colonoscopy, barium enema examination, computed tomography (CT), and/or magnetic resonance imaging (MRI). An Rb tumor was a common condition for the indication of PSD when the LLN appeared to be swollen on MRI (Figure 1). Almost all patients underwent bilateral PSD in the early and middle periods (from 1975 to 1994), pre-selected patients underwent selective PSD in the latter period (from 1995 to 2004).

Surgical procedure. The basic procedure was TSME with a distal resection margin >2 cm. In PSD, the fatty and connective tissue outside the pelvic plexus, around the intestinal iliac and common iliac vessels, and in the obturator cavity were removed, resulting in the iliac vessels being skeletonized, with or without pelvic autonomic nerve preservation.

Statistical analysis. Statistical analysis was performed using JMP version 10.0 (SAS Institute Inc., Cary, NC, USA). Statistical comparisons were made using Fisher's exact test, the x^2 test, or the Wilcoxon rank-sum test, depending on the type of data. Values of $p<0.05$ were considered to indicate statistical significance.

Results

The clinical characteristics of the patients are summarized in Table I.

A total of 994 patients with rectal cancer underwent curative surgery. The tumor was located in the upper rectum (RS and Ra) in 645, and in the lower rectum (Rb) in the other 349. Out of 994 patients, PSD was performed in 450 patients (45.3%): for 126 patients (28.0%) in the upper rectum, and for 324 patients (72.0%) in the lower rectum. Positive LLNs were identified in 59 patients (13.1%): in 12 in the upper rectum, and in 47 in the lower rectum. The rate of positive LLNs among patients who underwent PSD was 7.5% in the upper rectum, and 14.5% in the lower rectum. Because of these findings, the cases involving the upper rectum were excluded from further analysis.

Almost all patients underwent bilateral PSD in the early and middle periods (from 1975 to 1994), pre-selected patients underwent PSD in the latter period (from 1995 to 2004).

Out of the 994 patients with a rectal tumor, low anterior resection was performed in 533, abdominoperineal resection in 235, and Hartman's operation in 6. PSD was combined in 450 patients, and the rate of PSD was dependent on the tumor location, type of surgery, autonomic nerve preservation, histological grade, tumor size, and depth of invasion (data not shown).

LLN. The median number of dissected LLNs was 23 (range: 0-66). Positive LLNs were found in 59 patients (in 13.1% of patients with PSD). A significantly increased incidence of positive LLNs were found in patients with the following factors: female gender, Rb tumor, non-well-differentiated adenocarcinoma, depth of invasion (T3 and T4), perirectal lymph node metastasis, lymphatic invasion, and venous invasion (Table I). Among Rb tumors at T3-T4, 17.3% had positive LLNs. Among those with involved perirectal lymph nodes, 24.5% had positive LLNs. Thirteen patients (5.9%) had positive LLNs without perirectal lymph node metastasis.

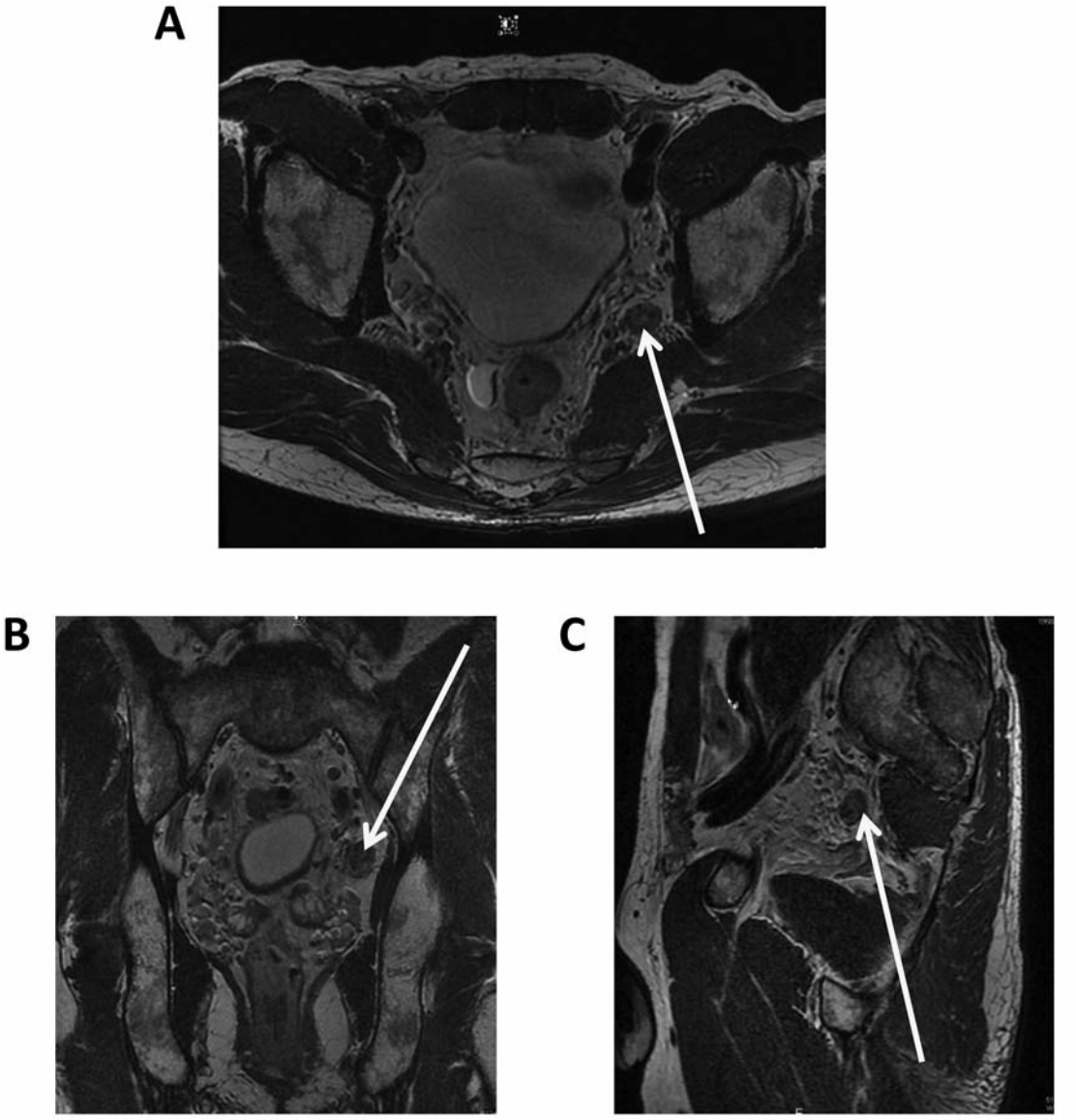

Figure 1. *Typical magnetic resonance imaging findings of a clearly swollen lateral lymph node. The lymph node was located in the left internal iliac area, and in this case, extended pelvic lymph nodes were dissected. A: T2-weighted high-resolution axial image; B: T2-weighted high-resolution coronal image; C: T2-weighted high-resolution sagittal image.*

Logistic regression analysis disclosed that perirectal lymph node metastasis was associated with an increased incidence of positive LLNs and had a greater hazard ratio (Table II).

Location of LLN metastasis. We analyzed the location of the positive LLNs. We divided the area into two parts: area I, and area E. We defined those with positive LLNs located along the internal iliac artery as being in area I (47 patients; 89%) and those around the oburator vessels and nerve as being in area E (17 patients; 32%) (Figure 2). The location in thirteen patients, who had positive LLNs without perirectal lymph node metastasis, was in the internal iliac lymph nodes (eight cases) and oburator lymph nodes (five cases).

Discussion

This study demonstrated that among those patients who underwent PSD, the rate of positive LLNs was higher in the lower rectum than in the upper rectum, and logistic regression analysis confirmed that perirectal lymph node

Table I. *Pelvic sidewall dissection and lateral lymph node metastasis in regard to clinicopathological characteristics (n=994).*

	No. of patients (A)	Pelvic sidewall dissection (B)	Positive lateral lymph node (C)	C/B (%)	*p*-Value
Gender					
Male	645	302	39	12.9	0.009
Female	349	148	18	12.1	
Location					
RS+Ra	503	126	12	7.5	0.001
Rb	491	324	47	14.5	
Type of surgery					
AR	110	1	0	0	
LAR	533	212	18	8.4	
Hart	6	1	0	0	
APR	282	235	41	17.4	
Other	63	1	0	0	
Histological grade					
Well	690	295	29	10.9	Well *vs*. non-well,
Mod	223	122	21	17.2	0.0011
Poor	14	10	3	30.0	
Muc	39	23	6	26.0	
Other	28	0	0	0	
Depth of invasion					
T1	134	8	1	12.5	T1+T2 *vs*. T3+T4
T2	180	80	7	8.8	0.3459
T3	403	255	34	12.9	
T4	277	107	17	15.9	
Perirectal lymph node metasitasis					
No	543	249	14	5.6	<0.0001
Yes	367	197	45	22.8	
Unknown	81	4	0		
Lymphatic invasion					
No	500	200	15	7.5	<0.0001
Yes	486	248	41	16.5	
Unknown	8	2	1	50.0	
Venous invasion					
No	247	79	7	8.9	0.0002
Yes	736	369	52	14.1	
Unknown	11	2	0	0	

AR: Anterior resection, LAR: low anterior resection, Hart: Hartmann's operation, APR: abdominoperineal resection, Well: well-differentiated adenocarcinoma, Mod: moderately-differentiated adenocarcinoma, Poor: poorly-differentiated adenocarcinoma, Muc: mucinous adenocarcinoma, RS: rectosigmoid, Ra: upper rectum, Rb: lower rectum.

metastasis was associated with an increased incidence in positive LLNs and had a greater hazard ratio. We also found a high frequency of positive LLNs in those located along the internal iliac artery and around the oburator vessels and nerve. MRI has become a promising diagnostic tool in rectal cancer for LLN estimation.

Patients with lower rectal cancer have an increased risk of LLN metastasis, because the lower rectum has been shown to drain both upward, along the superior rectal vessels and laterally along the middle rectal vessels and then to the internal iliac vessels. The rates of LLN metastases in rectal cancer have been reported to range from 8.6% to 29% (26-28). Based on this, PSD has become a standard procedure for lower rectal cancer in Japan, although it is rarely performed in other countries. One reason that PSD is not performed in other countries may be because positive LLNs would represent systemic spread rather than regional disease (18). The standardization of the technique of TME with accurate dissection of the anatomical plane enveloping the rectum and mesorectum constitutes major progress in rectal cancer surgery. TME has achieved much lower local recurrence rates (8). Moreover, progress in chemoradiotherapy has achieved good local control and better survival rates (14, 15) in many Western countries. These studies have shaped the current Western practice of combining TME with chemoradiation to achieve the best oncological results for rectal cancer.

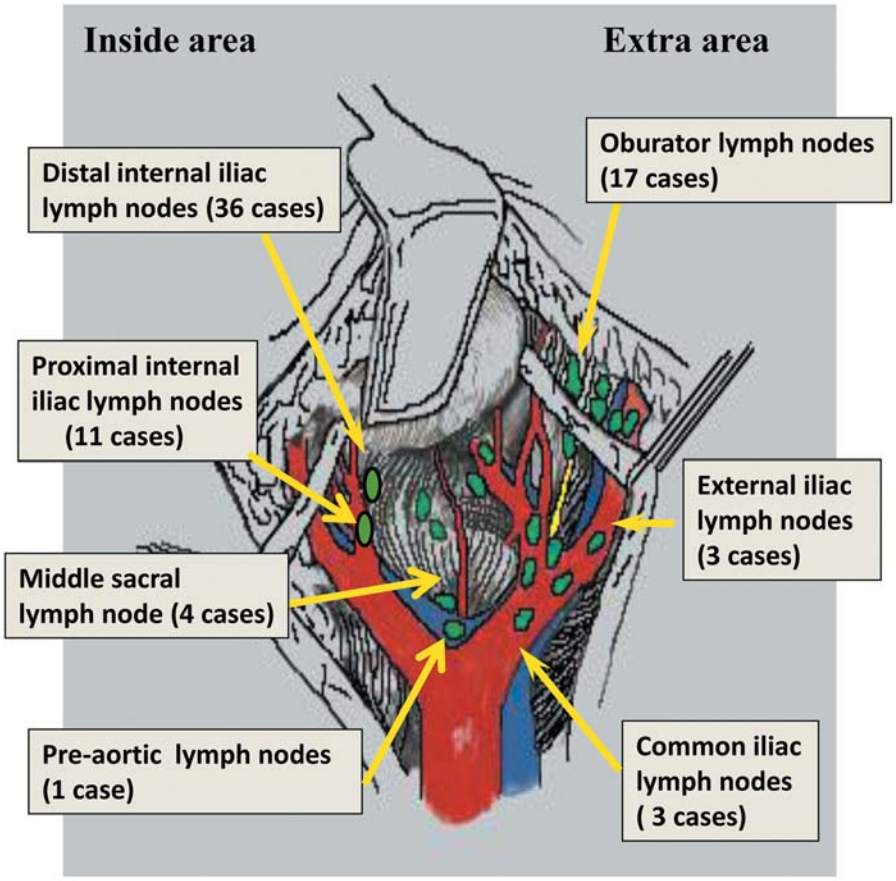

Figure 2. *Schema of lateral lymph nodes in the pelvis. Lateral lymph nodes were defined as lymph nodes located outside the pelvic plexus, along the internal iliac and common iliac vessels and in the obturator cavity. Number and location of metastatic cases with lower rectal cancer patients are shown (n=53).*

Table II. *Logistic regression analysis for the risk factors of lateral lymph node metastasis.*

	p-Value	Hazard ratio	(95% CI)
Histological grade			
Well	0.1448	1	0.8712-2.575
Non-well		1.49	
Perirectal lymph node metasitasis			
No	<0.0001	1	1.0722-6.5093
Yes		3.5198	
Lymphatic invasion			
No	0.2787	1	0.769-2.56
Yes		1.388	
Venous invasion			
No	0.3729	1	0.6536-3.717
Yes		1.458	

CI: Confidence interval.

However, there are some reports that patients with positive LLNs can survival for more than five years after PSD. Actually, some reports have shown the five-year survival rates of patients with positive LLNs after PSD to range from 37.3% to 49.3% (29-31), and the survival of patients of the PSD group with stage II disease was significantly better than those without PSD (32). These studies suggest that PSD for LLN-positive cases is an effective procedure for lower rectal cancer and PSD might reduce local recurrence and improve the five-year survival rate by removal of positive LLNs. Thus, PSD may improve prognosis in pre-selected patients.

Various factors such as gender, location, and perirectal lymph node metastasis have been suggested as significant predictors of positive LLNs. The location, histological grade, and mesenteric node metastasis have also been found to be significant predictors of positive LLNs (31). In this study, multivariate analysis, including factors that were preoperatively evaluated, showed that perirectal lymph node metastasis was the strongest predictor of positive LLNs (Table II).

Among another 1272 patients with low rectal cancer, radiological examinations showed that LLN metastasis along the internal iliac artery (73%) and in the obturator area (38%) were the most common sites of metastasis (33), consistent with the findings of the present study (Figure 2).

There remains a need to detect positive LLNs in the pelvic area. The accurate identification and characterization of lymph nodes using imaging has important therapeutic and prognostic significance in patients with a lower rectal cancer.

MRI has become a key diagnostic tool in rectal cancer. In the evaluation of depth of tumor invasion and lymph node metastasis, the diagnostic accuracy of MRI is superior to that of CT (34, 35). Some reports suggest that a 6-mm longitudinal diameter criterion is the most optimal in the evaluation of mesorectal lymph node status in patients with rectal cancer (36). Figure 1 shows that MRI can detect LLN swelling due to metastasis from low rectal cancer. Thus pelvic MRI is now usually performed to determine positive LLNs preoperatively. These MRI findings can indicate the need for selective LLN dissection in lower rectal cancer.

In the early 1980s, extended PSD was performed without full understanding of the pelvic autonomic innervations, which led to the observation of urinary and sexual dysfunction after surgery in Japan. Since then, attention had been paid to the anatomical findings and preservation of pelvic autonomic nerves in order to reduce complications after lower rectal surgery. In addition, PSD was performed in pre-selected patients.

The benefit if any of TME plus PSD over TME for pre-selected patients, with clinical stage II or III low rectal cancer, is under investigation in the Japanese JCOG 0212 trial that was started in 2003. This is a multicenter trial randomizing patients with low rectal cancers to TME or TME plus PSD. The results of JCOG 0212 will only be available in around 2016.

The management of low rectal cancer, especially with lymph node metastasis, continues to be a challenge, with numerous controversies. However, current findings suggest that PSD may be considered a good strategy for lower rectal cancer. In future studies, it will therefore be important to further investigate validity of PSD for its potential clinical use in therapy and prognosis of lower rectal cancer.

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