

ORIGINAL RESEARCH ARTICLE

## Histopathological characteristics of lateral lymph nodes dictate local or distant metastasis and prognosis in low rectal cancer patients

Takeshi Suto, Toshihiko Sato and Hazime Iizawa

*Department of Gastroenterological Surgery, Yamagata Prefectural Central Hospital, Yamagata, Japan*

### Abstract:

**Objectives:** The therapeutic value of lateral lymph node dissection in low rectal cancer (RC) patients remains a matter of debate. The present study evaluated the dissection value of each lateral lymph node, based on its histopathological characteristics. **Methods:** This study enrolled 381 consecutive RC patients with bilateral lateral lymph node dissection, from 1995 to 2014. We investigated their clinicopathological characteristics, and the therapeutic value of each lymph node dissection. The therapeutic values of the distal internal iliac and obturator lymph nodes were further investigated on the basis of histopathological classifications, as follows: minimum metastasis (Type A), massive metastasis (Type B) without capsular invasion, and invasive metastasis (Type C) with capsular invasion and were evaluated by the local or distant recurrence and 5 year overall survival. **Results:** Among the lateral lymph nodes, the therapeutic values of distal internal iliac (6.1) and obturator (7.4) lymph node dissection were higher than those of common (0.4) and proximal iliac (1.2) lymph node dissection. However, our further investigation revealed that the 5 year overall survival rates of Type C (obturator/distal iliac) were 12.5%/22.9%, whereas those of Type A and Type B were 100%/91.6% and 77.8%/50.0%, respectively. **Conclusions:** Metastasis and prognosis of RC patients depend on the histopathological characteristics of the distal internal iliac and obturator lymph nodes. The present study provides new insights for choices of appropriate treatments for RC patients.

### Keywords:

rectal cancer, lateral lymph node dissection, chemoradiotherapy, therapeutic value, histopathological characteristic

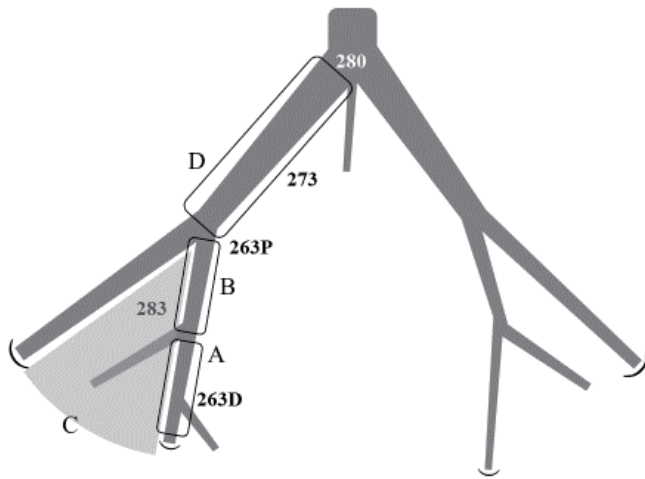
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### Introduction

The indication or concept of lateral lymph node dissection for rectal cancer (RC) patients is still under debate. Previous studies reported that the prevalence of lateral lymph node metastasis was 13.9% to 25.5% in RC patients treated with lateral lymph node dissection<sup>1-3</sup>. Several studies in Japan revealed that the 5 year overall survival rate was 37.9% to 49% in RC patients with lateral lymph node metastasis<sup>4-9</sup>. Lateral lymph node metastasis is a risk factor of local recurrences in RC patients<sup>10</sup>. A Japanese study reported that more than 80% of RC patients with lateral lymph node metastasis

involved the internal iliac, internal pudendal, and obturator lymph nodes<sup>11</sup>.

Total mesorectal excision for RC, which was proposed by Heald et al., is a surgical procedure to control the local recurrence<sup>12</sup>. The Japanese Clinical Oncology Group (JCOG)<sub>0202</sub> study revealed that the noninferiority of mesorectal excision with lateral lymph node dissection was not confirmed in the intent-to-treat analysis and that total mesorectal excision with lateral lymph node dissection had a lower prevalence, compared with total mesorectal excision alone<sup>13</sup>. The Japanese Society for Cancer of the Colon and Rectum guidelines recommend total mesorectal excision with lateral



**Figure 1.** Schematic image showing the locations of the right lateral lymph nodes. The common iliac lymph node region (273), proximal internal iliac lymph node region (263P), distal internal iliac lymph node region (263D), and obturator lymph node region (283).

lymph node dissection as the gold standard procedure for RC patients<sup>1</sup>. In Western countries, based on the Guideline 2000 for colon and RC surgery, lateral lymph node metastasis is a metastatic disease that requires chemoradiotherapy, and thus, preventative lateral lymph node dissection is not indicated for every RC patient but for patients with suspected lateral lymph node metastasis before preoperative diagnosis<sup>14,15</sup>. The treatment strategy or different concept for lateral lymph nodes may affect the local recurrence and prognosis of RC patients. Recent reports suggested that lateral lymph node dissection decreased the local recurrence and had prognostic benefits<sup>16,17</sup>. However, even in RC patients with lateral lymph node metastasis, some patients had a good prognosis and others had a poorer one. The underlying cause of this difference remains unknown.

In the present study, we evaluated the therapeutic value of each lateral lymph node dissection. Next, we classified the dissected metastatic internal iliac and obturator lymph nodes into three types, as follows: minimum, massive, and invasive metastasis types, by their histopathological characteristics. Finally, we investigated the dissection effects of the three representative types of lymph nodes on the local or distant recurrence and the 5 year survival of RC.

## Methods

### *Rectal cancer patients and lateral lymph node dissection*

The study included patients who were diagnosed with advanced lower RC and underwent radical surgery with bilateral lateral lymph node dissection at the Yamagata Prefectural Central Hospital, from January 1995 to December

2014. Inclusion criteria were as follows: histologically confirmed RC and lymph node metastasis and no preoperative chemoradiotherapy. The lateral lymph node dissection is indicated for clinical stages T3 and T4 lower RC patients, according to the clinical guidelines for colorectal cancer. Lower RC is defined as existing between the peritoneal reflection and the upper border of the anal canal and includes tumors with lower borders located caudal to the peritoneal reflection. The histological type and the clinical stage of RC patients were defined according to the tumor node metastasis classification system. Clinicopathological and laboratory information was available at our hospital database. After surgery, the RC patients were initially followed every 3 months for 3 years and consequently followed every 6 months for 2 years. A whole-body computed tomography scan or abdominal echogram was performed every 6 months for 5 years.

### *Definition of lateral lymph nodes*

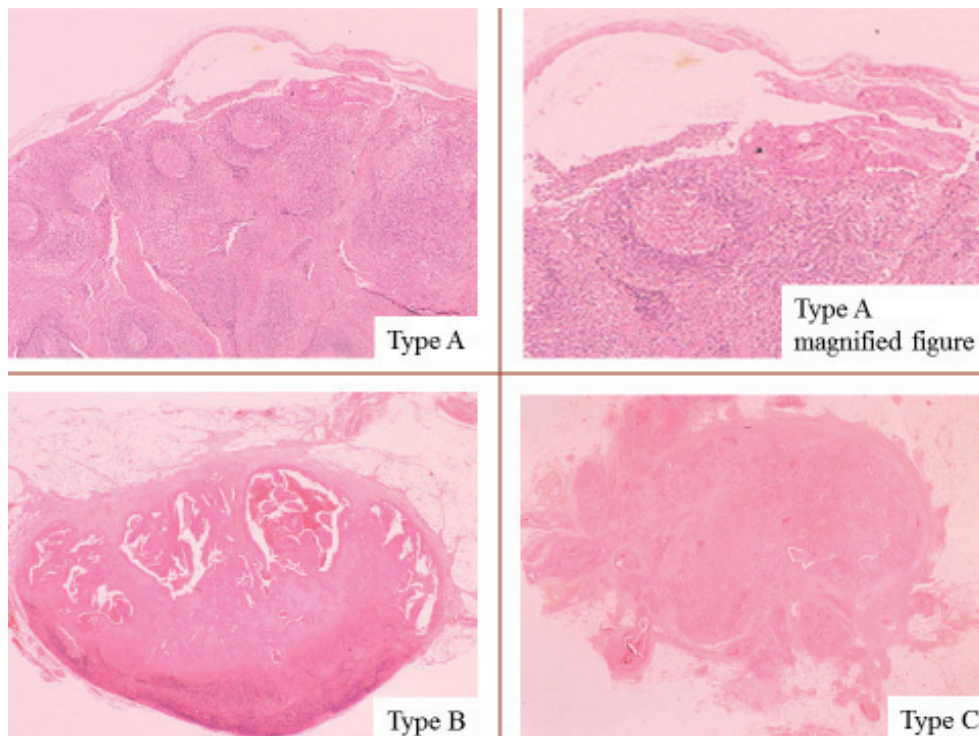
The dissection of lateral lymph nodes was set to the common iliac lymph node region (273), proximal internal iliac lymph node region (263P), distal internal iliac lymph node region (263D), and obturator lymph node region (283), according to the 7th edition of the Japanese Society for Cancer of the Colon and (Figure 1). The intermediate lymph nodes between the left colic artery and final branch of the sigmoid artery and around the inferior mesenteric artery were regarded as the 252 and 253 lymph nodes, respectively. The right lymph node below RC was regarded as 251-T. The superior lymph nodes from the cancer margin to 5 and 5-10 cm were defined as 251-1-O and 251-2-O, respectively, and the inferior lymph node from the cancer margin to 2 cm as 251-1-A. When both lymph nodes were positive for metastasis, they were individually counted and evaluated. In the operative procedure, the central lymph nodes around 253 were initially dissected, and subsequently the lateral lymph nodes were dissected. The lymph nodes and their surrounding adipose and connective tissues were totally dissected.

### *Evaluation of the effect of lateral lymph node dissection on 5 year overall survival rates*

The effect of lateral lymph node dissection was estimated by the therapeutic value, by multiplying the frequency of lymph node metastasis (A; %) and the 5 year survival rate (B; %) of RC patients with lateral lymph node metastasis<sup>18</sup>. The therapeutic value was calculated as  $A \times B/100$ . When both lymph nodes were positive for metastasis, they were individually counted and evaluated.

### *Histopathological classification of metastatic lateral lymph nodes and the dissection effect on local or distant metastasis and 5 year overall survival*

The metastatic internal distal iliac (263D) and obturator



**Figure 2.** Representative figures of the histopathologic patterns of 263D and 283 lymph node metastasis.

Type A: Minimum metastasis.

Type B: Massive metastasis.

Type C: Invasive metastasis.

(283) lymph nodes were classified into three types by their histopathological characteristics, as follows: minimum metastasis (Type A), marginal sinus metastatic lesions; massive metastasis (Type B), without capsular invasion; and invasive metastasis (Type C), with capsular invasion and not tumor nodules. These are not cancer nodules (Figure 2). Dissected lymph nodes were fixed in 10% buffered-formalin solution for about 48 h. After fixation, the characteristics of the lymph nodes were judged by hematoxylin-eosin staining of the maximum cut surface and classified into the three types. The dissection benefits of the three types of lymph nodes were individually estimated by local or distant recurrence and 5 year overall survival.

### Statistical analysis

All statistical analyses were performed using the statistical analysis software, JMP, Version 11 (SAS Institute Inc., Cary, NC). The survival rate was calculated by employing the Kaplan-Meier method, and the log-rank test was used to compare the overall survival between the two groups. Differences between groups were considered significant at value of  $p < 0.05$ .

## Results

### *Clinicopathological characteristics and operation types of RC patients with lateral lymph node dissection*

In total, 544 RC patients were enrolled. The eligible study population comprised 381 RC patients with lateral lymph node dissection (Table 1). The clinicopathological characteristics and operation types of the RC patients are shown in Table 1. There were about twice as many male RC patients (258) than female ones (123). Most histologic types of RC comprised well (tub1)-and moderately (tub2)-differentiated types. The lateral lymph node metastasis was detected in 64 RC patients (16.8%). The median duration of follow-up was 61.5 months (range: 28 to 228 months). Most RC operation types comprised low anterior resection and abdominal perineal resection. Figure 3 showed the cumulative 5 year overall survival rates in RC patients with (56.5%) or without (76.6%) lateral lymph node metastasis. The lateral lymph node metastasis decreased the 5 year overall survival of RC patients.

### *Therapeutic value of lateral lymph node dissection*

The therapeutic value of each lymph node dissection is

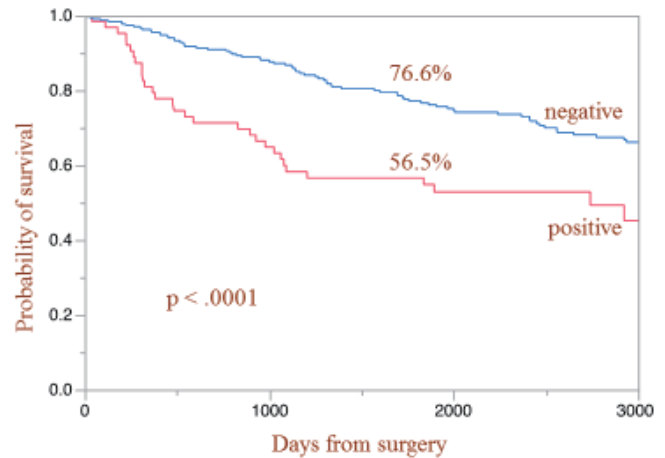
**Table 1.** Clinicopathological Characteristics of Our RC Patient Cohort (381).

Parameters	Number
Age (years) [median (range) ]	66 (31-86)
Gender	
Male	258 (67.7)
Female	123 (32.3)
Tumor size: median (range) (cm)	5.0 (0.9-17.0)
Histological type	
tub1	189 (49.6)
tub2	164 (43.0)
por, muc	28 (7.4)
Pathological lateral lymph node metastasis	
Yes	64 (16.8)
No	317 (83.2)
pStage	
I	74 (19.4)
II	114 (29.9)
III	177 (46.5)
IV	16 (4.2)
Type of operation	
Low anterior resection	209 (54.8)
Inter sphincteric resection	40 (10.5)
Abdomino perineal resection	123 (32.3)
Total pelvic exenteration	6 (1.6)
Hartmann	3 (0.8)

shown in Table 2. The prevalence of lymph node metastasis was higher in the 251-1-T and 251-1-O lymph nodes than the 251-2-A and 253 lymph nodes. The metastatic prevalence of the 251-1-A lymph node was low, and its 5 year survival rate was low. The therapeutic values of the 251-1-T and 251-1-O lymph nodes were also higher than those of the 251-2-A and 253 lymph nodes. The prevalence of the 263D and 283 lymph nodes was 9.7% and 11.5%, respectively, but their 5 year survival rates were higher than 252 and 253, and those of the other lateral lymph nodes. These results relatively increased their therapeutic values.

**Three types of 263D and 283 lymph nodes revealed different effects on local or distant metastasis and 5 year overall survival**

The effects of metastasis and the 5 year overall survival for the three types of 263D and 283 lymph nodes are shown in Table 3 and Figure 4. Among the 283 lymph nodes (44 in total), there were 20 Type C (invasive metastasis; local/distant, 7/16; and 5 year survival, 22.9%), 18 Type B (massive metastasis; 1/5 and 77.8%), and 6 Type A (minimum metastasis; 0/1 and 100%). For the 263D lymph nodes (34 total), there were 16 Type C (local/distant; 6/14 and 5 year survival; 12.5%), 6 Type B (2/3 and 50.0%), and 12 Type A (0/1 and 91.6%). For both lymph nodes, Type A revealed few



**Figure 3.** The 5 year overall survival rates in patients with and without lateral lymph node metastasis.

local or distant metastases, and a prominent 5 year overall survival, whereas Type C increased the prevalence of local and distant metastases, including the liver, lung, and paraaortic lymph nodes, and reflected a poor 5 year overall survival. Expectedly, for both lymph nodes, Type B exhibited the intermediate prevalence of local and distant metastases and a 5 year overall survival between those of Type A and Type C. These findings indicated that the histopathological characteristics of the 263D and 283 lymph nodes dictated the local or distant metastasis and the prognosis.

**Discussion**

In the present study, the prevalence of lateral lymph node metastasis and its 5 year overall survival rate in RC patients were 16.8% and 56.5%, respectively. Both findings are compatible with those of previous reports<sup>1,19)</sup>. The therapeutic values of lateral lymph node dissection were evaluated. The therapeutic values of the internal iliac (263D) and obturator (283) lymph nodes were higher, as compared with those of the 263P, 273, 252, and 253 lymph nodes. Thus, the dissection of the 263D and 283 lymph nodes was effective, whereas the dissection of the 263P and 273 lymph nodes revealed no advantages. These findings were consistent with those of a recent Japanese study<sup>20)</sup>.

The histopathological analysis classified the 44 obturator lymph nodes into 20 invasive, 18 massive, and 6 minimum metastasis types, and the 34 internal iliac lymph nodes into 16 invasive, 6 massive, and 12 minimum metastasis types. The invasive types reflected a poorer prognosis and a higher recurrence rate, as compared with the massive and minimum types. These findings suggested that the recurrence and prognosis of RC patients depend not only on the presence or absence of metastasis but also on the histopathological characteristics of the 263D and 283 lymph nodes. This may ex-

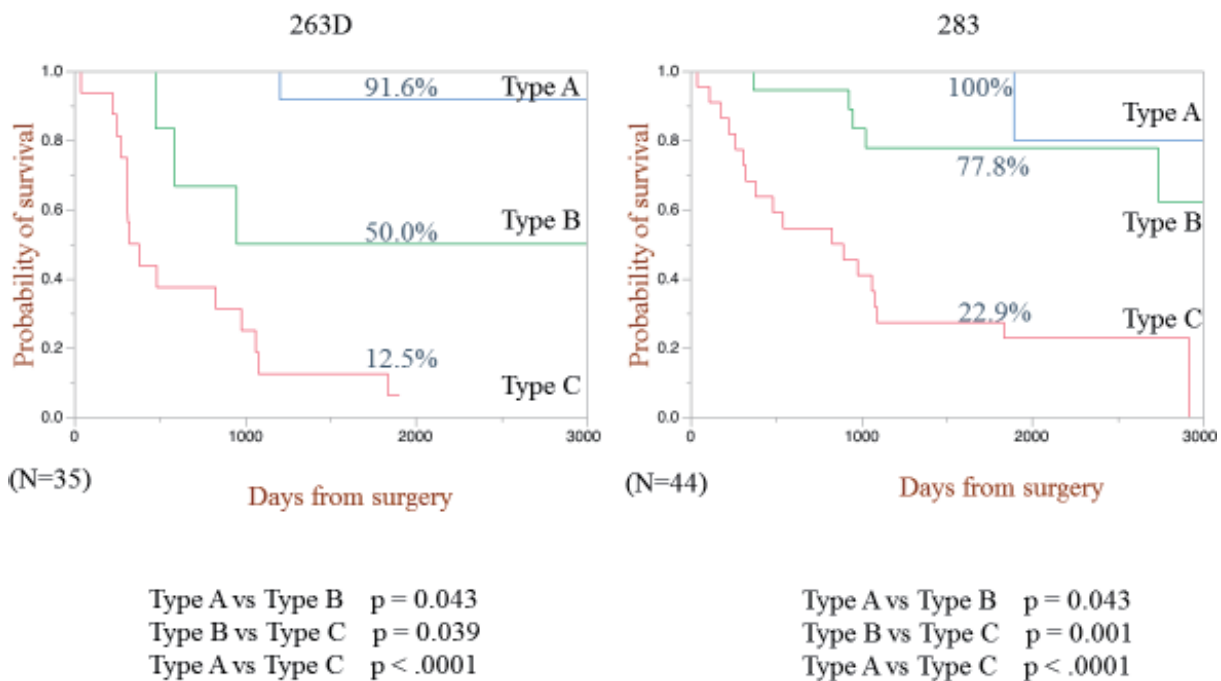
**Table 2.** Metastasis, 5 Year Survival Rates, and Index of the Effect of Lymph Node Dissection.

Lymph Node Station	Metastatic numbers (%)	5-year survival rates (%)	Value (%)
251-1-T	91 (23.9)	80.4	19.2
251-1-O	91 (23.9)	67.5	16.1
251-1-A	18 (4.7)	35.3	1.6
251-2-O	34 (8.9)	51.2	4.5
251-2-A	1 (0.3)	100	0.2
252	31 (8.1)	41.6	3.3
253	6 (1.6)	16.0	0.3
273	8 (2.1)	18.7	0.4
263P	13 (3.4)	35.1	1.2
263D	37 (9.7)	65.3	6.1
283	44 (11.5)	63.9	7.4

**Table 3.** Rates of Local Recurrence and Distant Metastasis in Patients with 263D and 283 Lymph Node Metastases, Assessed by the Metastasis Morphology.

Lymph Node	Classification	Number	Site of recurrence							
			Local	Distant	liver	lung	PL	Bone	Brain	others
263D	A	12	0	1	1	0	0	0	0	0
	B	6	2	3	2	3	2	1	0	0
	C	16	6	14	4	4	3	3	1	1
283	A	6	0	1	0	1	0	0	0	0
	B	18	1	5	3	2	1	1	1	1
	C	20	7	16	3	4	4	1	1	4

PL: paraaortic lymph node



**Figure 4.** The 5 year overall survival rates of patients with 263D and 283 lymph node metastases according to the histopathological characteristics.



plain the discrepancy between good and poor prognoses in RC patients with lateral lymph node metastasis and its dissection effect.

In Western countries, RC patients with lateral lymph node metastasis were widely used as a nonadjuvant chemotherapy. Previous studies showed the same clinical outcomes between a total mesorectal excision with lateral lymph node dissection group and a group with adjuvant radiotherapy or preoperative radiotherapy<sup>21,22</sup>. The Dutch trial study suggested that late complications, including fecal incontinence and sexual dysfunction, should be addressed after radiotherapy<sup>23</sup>. The JCOG<sub>0212</sub> study found that these dysfunctional complications and postoperative mortality and morbidity were not increased after the standard lateral lymph node dissection<sup>13</sup>. Kim et al. reported that the lateral lymph nodes most frequently relapse in RC patients treated with preoperative chemoradiotherapy<sup>24</sup>. Taken together, the optimal therapy, which is not excessive but necessary and sufficient, is required for an individual RC patient. The present study may provide new insights on the prediction of a prognosis and the choice of an optimal postoperative treatment, including multimodality therapy for RC patients. However, the best multimodality therapy, with either perioperative or postoperative chemoradiotherapy, for RC patients remains undetermined. To address this issue, a phase II/III randomized controlled trial comparing perioperative versus postoperative chemotherapy with mFOLFOX6 for lower RC with suspected lateral pelvic node metastasis, JCOG<sub>1301</sub>, is underway.

In conclusion, the present retrospective study demonstrated that the recurrence and prognosis of RC patients depend not only on the presence or absence of 263D and 283 lymph node metastases but also on the histopathological characteristics. This suggests that a more precise characterization of the metastatic lateral lymph nodes is required to attain the best therapy for the individual RC patient. The present findings may contribute to appropriate judgments for treating RC patients.

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Compliance with ethical standards. The study protocol was approved by the institutional review board.

#### Conflicts of Interest

There are no conflicts of interest.

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