Effects of Chemoradiotherapy on Lymph Nodes in Patients with Rectal Adenocarcinoma: Evaluation of Numbers and Sizes of Retrieved Lymph Nodes Inside and Outside the Radiation Field

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Abstract. *Background: Preoperative chemoradiotherapy (CRT) decreases the number of retrieved lymph nodes (LNs) in rectal cancer. LNs inside the irradiation field are affected by CRT, whereas those outside the irradiation field are affected only by concurrent chemotherapy. Patients and Methods: The study cohort comprised of 210 patients with clinical stage II/III rectal adenocarcinoma. One hundred and eight received surgery alone (S group), and 102 received preoperative CRT (40 or 45 Gy) with concurrent oral UFT or S-1 uracil/tegafur or S-1 (CRT group). Results: The number of LNs inside the irradiation field was significantly smaller in the CRT group (4±4) than in the S group (6±6, p<0.01), but the number of LNs outside the irradiation field did not differ (5±4 in both groups). The longest diameters of LNs in the S group were significantly smaller than those of the CRT group both inside and outside the irradiation fields (p<0.01). Conclusion: The effects of CRT on LNs in patients with rectal adenocarcinoma differed inside and outside the radiation field.*

In patients with colorectal cancer, retrieval of 12 or more lymph nodes (LNs) has been reported to be associated with better outcomes than retrieval of less than 12 LNs (1-3). Retrieval of at least 12 LNs has, therefore, been recommended to ensure reliable staging of disease (4, 5).

Preoperative radiotherapy or chemoradiotherapy (CRT) reduces local recurrence in patients with locally advanced adenocarcinoma of the rectum and is, therefore, used as standard treatment. Preoperative radiotherapy or CRT can reduce the number of retrieved LNs (6-11). Consequently, the recommended number of retrieved LNs remains unclear in patients with rectal adenocarcinoma who receive preoperative radiotherapy or CRT. LNs inside the irradiation field are affected by radiotherapy and concurrent chemotherapy, whereas LNs outside the irradiation field are affected only by concurrent chemotherapy. Therefore, we should evaluate the numbers of retrieved LNs inside and outside the radiation field separately if the effects of chemoradiotherapy on LNs differ between inside and outside the radiation field.

In the present study the number of retrieved LNs, the number of metastatic LNs, and sizes of LNs inside and outside the radiation field were compared between patients with rectal adenocarcinoma who underwent surgery alone and those who received CRT before surgery.

Patients and methods

Patients. The study group comprised of 108 patients with pathological stage II or III adenocarcinoma of the middle or lower rectum who received radical surgery alone (S group) and 102 patients with a preoperative diagnosis of clinical stage II or III adenocarcinoma of the middle or lower rectum who underwent radical surgery after CRT (CRT group) at Tokai University Hospital from January 1991 through December 2010. The initial evaluation included digital examination of the rectum, chest x-ray, colonoscopy, barium enema as well as computed tomography of the abdomen and pelvis. Endorectal ultrasonography and magnetic resonance imaging of the pelvis was also performed since 1994.

In Japan, both radical surgery with lateral lymph-node dissection (12) and preoperative CRT plus mesorectal excision are currently used to treat locally advanced rectal adenocarcinoma. Therefore, during the study period, patients selected therapy after receiving a detailed explanation of each treatment from their physicians.

This study was approved by the institutional review board of our university (08R-032).

CRT and surgery. Preoperative radiotherapy was performed with 18 MeV X-ray beams delivered by a linear accelerator (Clinac 2100C, Varian Medical Systems, Inc., Palo Alto, CA, USA), using a four-field

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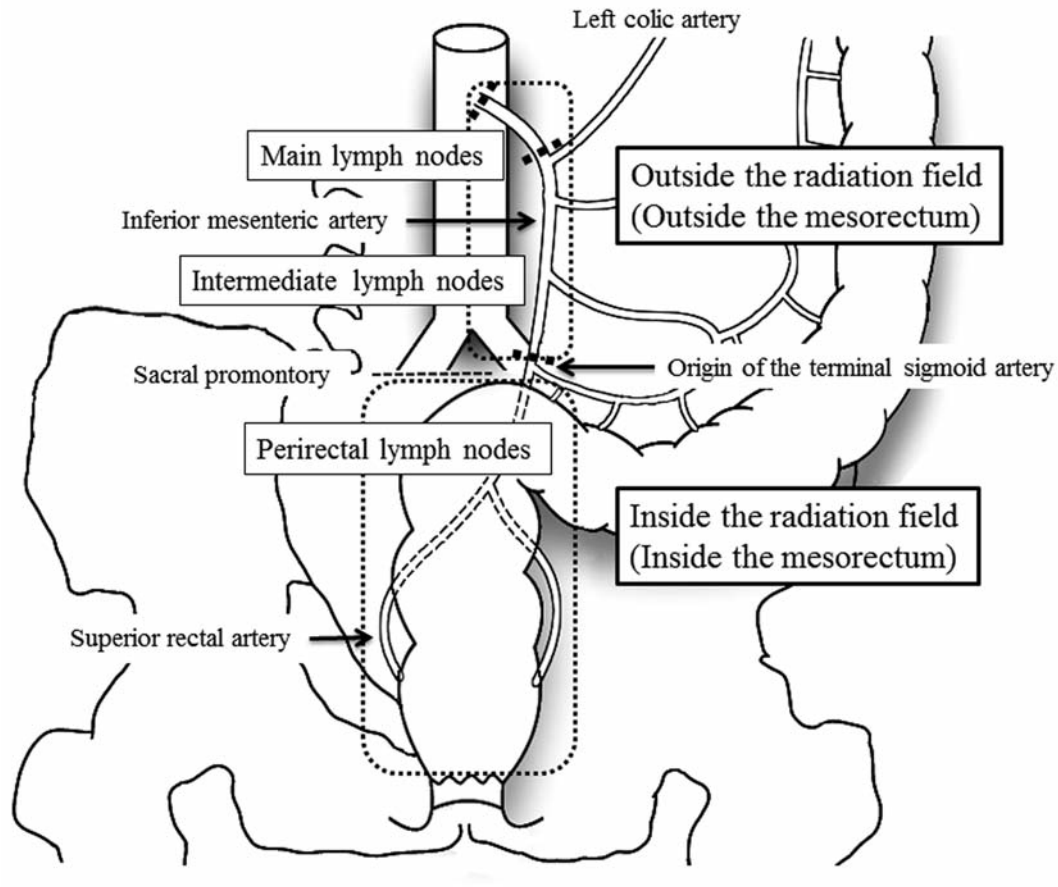

Figure 1. *Definition of lymph node distribution.*

technique. Irradiation was performed once (1.8 or 2.0 Gy) daily to a total dose of 40 or 45 Gy. The superior border of the radiation field was the lumbosacral L5/S1 junction, and the lateral borders were 1 cm lateral to the widest bony margin of the true pelvic sidewalls. The inferior border was at the level of the inferior edges of the obturator foramen or 3 cm below the site of the tumor. The field size ranged from 15×15 cm to 16×18 cm. Surgery was done 6 to 8 weeks (range 30 to 65 days) after the completion of radiotherapy. For concomitant chemotherapy, 21 patients received oral uracil/tegafur (UFT, 400 mg/m^2 Taiho Pharmaceutical CO., LTD. Tokyo, Japan) and 81 received oral S-1 (80 mg/m^2 Taiho Pharmaceutical CO., LTD. Tokyo, Japan), starting at the same time as radiotherapy. Oral UFT was given for 5 days, followed by a 2-day rest. This cycle was repeated. Oral S-1 (80 mg/m^2) was given for 2 consecutive weeks, followed by a 1-week rest, and was then given for 2 more weeks (13).

All patients underwent mesorectal excision. The inferior mesenteric artery was ligated at its aortic origin in all patients. In patients in the S group, lateral lymph-node dissection was routinely performed; however, the lateral LNs were not evaluated in the present study.

In Japan, LNs along the inferior mesenteric artery have conventionally been divided into 3 groups: peri-rectal LNs, intermediate LNs, and main LNs. The border between the perirectal LNs and the intermediate LNs is the origin of the terminal sigmoid artery (Figure 1) (14).

Pathology procedures. One of the members of the colorectal surgical team dissected the resected specimen in the operation room within 30 min after excision. LNs were identified by direct inspection and manual palpation after closely slicing the mesorectum and sigmoid mesentery. Fat clearance methods were not used in any of the cases. In Japan, surgeons dissect the surgical specimen and identify LNs. Pathologists examine all specimens considered to be LNs.

Evaluation of the numbers and sizes of the retrieved LNs. The numbers of retrieved LNs and metastatic LNs were obtained by reviewing the patients' pathological charts. The sizes of LNs (longest axis, shortest axis, and area) were measured on specimens stained with hematoxylin and eosin, using a computer digitizer (Adobe Photoshop CS5®, Adobe Systems, San Jose, California, USA).

Definition of lymph node regions. The superior border of the radiation field is the L5/S1 junction. Because the mesorectum was not marked at the level of the promontory during surgery, it was difficult to accurately determine the radiation field on resected specimens. LNs along the inferior mesenteric artery were divided into two groups at the origin of the terminal sigmoid artery according to the Japanese criteria (14): (i) the perirectal LNs and (ii) the intermediate LNs and main LNs. In the present study, the perirectal LNs were defined as being inside the radiation field while

the intermediate LNs and the main LNs were defined as being outside the radiation field.

LNs in other locations, such as lateral LNs and LNs in the sigmoid mesentery, were defined as LNs in the border field and were not evaluated in the present study.

Statistical analyses. The Student's *t*-test was used to compare continuous variables such as the numbers and sizes of LNs. The Pearson's chi-square test was used to compare discrete variables.

Results

Patients' characteristics. The distance from the anal verge to the tumor was significantly shorter in the CRT group than in the S group. The CRT group comprised significantly lower proportions of patients with lymphatic and venous invasion. After preoperative CRT, tumor downstaging was noted in 40 (39%) patients in the CRT group. All patients' characteristics are shown in Table I.

Table I. *Patients' characteristics*.

	S group* n=108 (%)	CRT group† n=102 (%)	*p*-Value
Gender			
Male	74 (69)	80 (78)	0.10
Female	34 (31)	22 (22)	
Age			
Mean±SD	62±12	64±11	0.24
Median	63	66	
Distance from anal verge (cm)			
Mean±SD	6.5±3.3	5.4±2.6	<0.01
Median	7	6	
Histologic type			
Well	37 (34)	48 (47)	0.21
Moderately	60 (56)	50 (49)	
Poorly	4 (4)	2 (2)	
Mucinous	6 (6)	2 (2)	
Signet ring cell	1 (1)	0	
Lymphatic invasion			
+	88 (81)	44 (43)	<0.01
–	20 (19)	58 (57)	
Venous invasion			
+	87 (81)	48 (47)	<0.01
–	21 (19)	54 (53)	
TNM‡ Stage			
0	0	13 (13)	<0.01
I	0	27 (26)	
II	44 (41)	35 (34)	
III	64 (59)	27 (26)	
Surgical procedure			
Low anterior resection	57 (53)	72 (71)	0.01
Abdominoperineal resection	37 (34)	28 (27)	
Hartmann procedure	8 (7)	2 (2)	
Pelvic exenteration	3 (3)	0	
Abdominosacral resection	3 (3)	0	

*S group: surgery group, †CRT group: chemoradiotherapy group, ‡Tumor-Node-Metastasis classification of the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC).

Numbers of LNs evaluated. The total number of retrieved LNs evaluated was 1,160 in the S group and 892 in the CRT group. The total number of metastatic LNs was 118 in the S group and 107 in the CRT group.

Numbers of retrieved LNs. The total number of retrieved LNs was significantly lower in the CRT group than in the S group ($p<0.01$). The number of retrieved LNs inside the irradiation field was significantly lower in the CRT group than in the S group ($p<0.01$). The numbers of retrieved LNs outside the irradiation field did not differ significantly between the groups (Table II).

Forty-four patients with stage II disease in the S group were compared against 75 patients without positive LNs in the CRT group. The total number of retrieved LNs was significantly lower in the CRT group than in the S group ($p<0.01$). The number of retrieved LNs inside the irradiation field was significantly lower in the CRT group than in the S group ($p<0.01$). The number of retrieved LNs outside the irradiation field was also significantly lower in the CRT group than in the S group ($p<0.01$). Sixty-four patients with stage III disease in the S group were compared against 27 patients with stage III disease in the CRT group. The total number of retrieved LNs was significantly greater in the CRT group than in the S group ($p=0.03$).

Numbers of LNs in patients with Stage III disease. The number of metastatic LNs was significantly greater in the CRT group than in the S group within the irradiation field ($p<0.01$). Outside the irradiation field, there was no significant difference in the numbers of metastatic LNs. The numbers of negative LNs did not differ significantly between the two groups (Table III).

Sizes of negative LNs. Negative LNs inside the irradiation field as well as those outside the irradiation field were significantly smaller in the CRT group than in the S group ($p<0.01$) (Table IV). Similar results were obtained regardless of whether size was evaluated on the basis of longest diameter, shortest diameter, or area. In patients without positive LNs, LNs inside the irradiation field as well as those outside the irradiation field were significantly smaller in the CRT group than in the S group ($p<0.01$). However, in patients with stage III disease, the sizes of negative LNs, either inside or outside the radiation field, did not differ significantly between the CRT group and the S group.

Sizes of metastatic LNs in patients with Stage III disease. The sizes of positive LNs inside as well as outside the radiation field were significantly smaller in the CRT group than in the S group (Table V).

Table II. *Numbers of retrieved lymph nodes.*

	All patients			Patients without positive LNs			Patients with stage III disease		
	S group (108)	CRT group (102)	*p*-Value	S group (44)	CRT group (75)	*p*-Value	Surgery group (64)	CRT group (27)	*p*-Value
Total number	11±8*	9±6	0.04	13±10	7±4	<0.01	10±6	13±9	0.03
Inside the radiation field (Within the mesorectum)	6±6	4±4	<0.01	7±8	3±3	<0.01	5±4	7±6	0.12
Outside the radiation field (Outside the mesorectum)	5±4	5±4	0.26	6±5	4±3	<0.01	5±3	6±5	0.19

*mean±SD.

Table III. *Numbers of lymph nodes in patients with Stage III disease.*

	Negative LNs			Positive LNs		
	S group (64)	CRT group (27)	*p*-Value	S group (64)	CRT group (27)	*p*-Value
Total number	8±5*	9±7	0.36	2±2	4±4	<0.01
Inside the radiation field (Within the mesorectum)	4±4	4±4	0.91	1±2	3±4	<0.01
Outside the radiation field (Outside the mesorectum)	4±3	5±5	0.13	0.4±1	1±1	0.14

*mean±SD.

Discussion

Several studies have shown that local disease control is significantly better after CRT including preoperative long-term, low-dose conventional irradiation than after radiotherapy alone (15, 16). We concurrently used oral UFT or S-1 as a radiosensitizer. Radiation most likely affects LNs inside the irradiation field, whereas chemotherapy is considered to also have an impact on LNs outside the irradiation field.

Pan *et al*. reported good outcomes after surgery-alone in patients with rectal cancer in whom at least 12 LNs were retrieved, whereas in patients who received CRT the best outcomes were associated with 7 to 11 retrieved LNs (17). Tsai *et al*. found that patients with more than 7 retrieved LNs showed better outcomes than those with 7 or fewer retrieved LNs (18). Since the number of retrieved LNs decreases in patients who receive CRT (6-11), the recommended number of retrieved LNs remains unclear (18).

Within the irradiation field, the numbers and sizes of retrieved LNs were significantly smaller in the CRT group than in the S group. These findings were attributed to the effects of CRT. Outside the radiation field, the numbers of retrieved LNs did not differ significantly between the two groups, but LNs were significantly smaller in the CRT group than in the S group. These findings were most likely caused by the effects of concurrent chemotherapy.

The abscopal effect is a rare phenomenon in which radiotherapy causes the regression of metastatic cancer at a distance from the irradiated site. Cell-mediated immunity is thought to be involved (19, 20). Shrinkage of LNs outside the radiation field may principally be attributed to the effects of concurrent chemotherapy, but to other factors as well, including abscopal effects.

In the subgroup of patients without positive LNs, the numbers and sizes of retrieved LNs were significantly smaller in the CRT group than in the surgery group both inside and outside the radiation field (Tables II and IV). On the contrary, there were significantly increased numbers of retrieved LNs and of metastatic LNs in the CRT group in patients with Stage III disease.

Preoperative radiotherapy or CRT reduced the number of retrieved LNs (6-11). However, the results of the number of metastatic LNs were various. Govindarajan *et al*. and Rullier *et al*. reported that CRT reduced the number of metastatic LNs (10, 11). Marijnen *et al*. reported no change (6) while Fuente *et al*. also reported that the number of metastatic LNs was significantly greater in patients who received CRT than in those who underwent surgery-alone (8). These discrepancies, however, remain unspecified.

Table IV. *Sizes of negative lymph nodes*.

	All patients			Patients without positive LNs			Patients with stage III disease		
	S group (108)	CRT group (102)	*p*-Value	S group (44)	CRT group (75)	*p*-Value	S group (64)	CRT group (27)	*p*-Value
Inside the radiation field (Within the mesorectum)									
Long axis (mm)	4.3±2.3*	3.5±1.9	<0.01	4.5±2.4	3.5±1.8	<0.01	4.2±2.2	3.7±1.9	0.07
Short axis (mm)	3.1±1.6	2.6±1.3	<0.01	3.3±1.6	2.6±1.3	<0.01	2.9±1.6	2.6±1.4	0.08
Area (mm^2)	12.4±12.8	8.5±8.6	<0.01	13.4±13.7	8.2±8.5	<0.01	11.3±11.7	9.1±9.0	0.08
Outside the radiation field (Outside the mesorectum)									
Long axis (mm)	4.3±2.5	3.7±2.1	<0.01	4.7±2.6	3.6±2.1	<0.01	3.8±2.3	3.8±2.1	0.87
Short axis (mm)	2.8±1.6	2.4±1.3	<0.01	3.2±1.7	2.4±1.3	<0.01	2.5±1.4	2.5±1.4	0.71
Area (mm^2)	11.2±12.7	8.0±8.5	<0.01	13.7±14.1	7.7±8.3	<0.01	8.8±10.5	8.6±9.0	0.89

*mean±SD.

Lymph node cells die rapidly at inter-phase after exposure to low-dose radiation (21). Lymphocytes die without undergoing cell division within hours after irradiation, whereas tumor-cell death requires more time (6). *In vitro,* 2 to 5 rads of radiation is cytotoxic to lymphocytes (22), whereas the mean lethal dose against colonic carcinoma is 94 rads (23). Colon cancer cells are thus more radioresistant than lymphocytes. Therefore, the impact of CRT may differ substantially between normal tissue and metastatic cancer tissue in LNs.

The size of LNs following formalin fixation has been reported decrease by 52.8% for the longest diameter and 61.8% for the shortest diameter when they are compare to the original dimensions measured during surgery. (24). Therefore, our estimates are probably equivalent to less than one half of actual size *in vivo*.

Our results showed that the response of LNs to CRT differed between inside and outside of the radiation field. Effects of concurrent chemotherapy with UFT or S-1 were evident outside the radiation field. Our results suggested the that in some patients their initial metastatic LNs, become negative and are downstaged while negative LNs shrink further in patients who are more sensitive to CRT. Also, in patients who are less sensitive to CRT, positive LNs shrink, but metastases remain while the reduction in the size of negative LNs is less. Therefore, the relation of oncologic outcomes to the number of retrieved LNs and the size of negative LNs should be separately evaluated inside and outside the irradiation field in patients with rectal cancer who receive CRT.

Table V. *Sizes of metastatic lymph nodes in patients with Stage III disease*.

	S group (64)	CRT group (27)	*p*-Value
Inside the radiation field (Within the mesorectum)			
Long axis (mm)	8.1±4.7*	6.5±3.8	0.01
Short axis (mm)	5.9±3.2	4.7±2.8	0.01
Area (mm^2)	43.5±55.8	28.1±33.5	0.03
Outside the radiation field (Outside the mesorectum)			
Long axis (mm)	9.4±5.0	6.8±2.9	0.04
Short axis (mm)	6.6±3.7	4.6±1.8	0.03
Area (mm^2)	55.5±58.2	26.6±20.4	0.03

*mean±SD.

Conclusion

The effects of chemoradiotherapy on LNs in patients with rectal adenocarcinoma differed inside and outside the radiation field. LNs should be separately evaluated inside and outside the irradiation field in studies assessing the relations between the numbers of LNs and oncological outcomes.

Conflicts of Interest

The Authors indicated no potential conflicts of interest. None of the Authors received any funding support for this work.

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