

Contributing Factors on Lymph Node Yield after Surgery for Mid-Low Rectal Cancer

Young Jae Ahn,¹ Hye Youn Kwon,¹ Yoon Ah Park,² Seung-Kook Sohn,¹ and Kang Young Lee¹

¹Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul;

²Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

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Corresponding author: Dr. Kang Young Lee,
Department of Surgery,
Yonsei University College of Medicine,
211 Eonju-ro, Gangnam-gu,
Seoul 135-720, Korea.
Tel: 82-2-2019-3378, Fax: 82-2-3462-5994
E-mail: kylee117@yuhs.ac

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Purpose: The purpose of the present study was to evaluate the contributing factors to the lymph node status as well as to define the impact of preoperative concurrent chemoradiotherapy (CCRT) on the number of lymph nodes retrieved in mid-low rectal cancer. **Materials and Methods:** We retrospectively analyzed 277 patients who underwent curative surgical resection for mid-low rectal cancer between 1998 and 2007. Eighty-two patients received long course preoperative CCRT followed by surgery. **Results:** A mean of 13.12±9.28 lymph nodes was retrieved. In a univariate analysis, distance from the anal verge, pT stage, pN stage, lymphovascular invasion, preoperative CCRT had significant influence on the number of lymph nodes retrieved. In a multivariate model, patients in the CCRT group had fewer retrieved lymph nodes than the non-CCRT group ($p<0.001$). Both univariate and multivariate analyses showed that the ypN0 group had fewer retrieved lymph nodes than the ypN1-2 group ($p=0.027$) in the CCRT group. **Conclusion:** Preoperative CCRT was an independent risk factor for failure to harvest an appropriate number of lymph nodes, and node-negative patients who received CCRT had fewer lymph nodes harvested.

Key Words: Rectal neoplasm, lymph node, neoadjuvant therapy

INTRODUCTION

Metastatic lymph nodes are the most potent prognostic factor after curative resection of rectal cancer.¹ Whether the tumor metastasizes to regional lymph nodes is the key consideration not only for the prognosis,² but also for applying adjuvant therapy. For accurate nodal staging after surgery, the number of lymph nodes examined is clinically important.^{3,4} In particular, in patients with no metastatic lymph nodes, the number of lymph nodes identified in surgical specimens is critical for an accurate diagnosis. Inadequate lymph node assessment may affect survival, since it could be associated with understaging the disease. For this reason, the College of American Pathologists recommends examining a minimum of 12 lymph nodes to accurately stage node-negative rectal cancer⁵ and the Tumor-Node-Metastasis staging of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) suggest obtaining at least 7-14 lymph

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nodes in radical resections.⁶ The number of lymph nodes retrieved could be affected by several factors. The extent of surgery and the examining pathologist could influence the number of lymph nodes.⁷⁻⁹ Even in similar surgical specimens, the number of lymph nodes retrieved could be affected by age, body mass index, tumor location, tumor size, depth of tumor invasion,^{8,10-12} lymph node metastasis,^{13,14} and preoperative concurrent chemoradiotherapy (CCRT).^{3,10,15} Identifying high risk factors that could decrease lymph node retrieval would be valuable for accurate nodal staging, since other techniques could be used to harvest lymph nodes for high-risk patients.

The aim of this study was to identify risk factors associated with a failure to harvest adequate lymph nodes for accurate nodal staging and to define the impact of CCRT on the number of lymph nodes retrieved in patients who underwent curative radical surgery for mid-low rectal cancer.

MATERIALS AND METHODS

Data from 277 patients who underwent radical surgery with curative intention for mid-low rectal cancer between January 1998 and December 2007 were retrospectively analyzed. All patients had histologically proven adenocarcinoma located on the mid to low rectum, within 10 cm from the anal verge. The retrospective review of each patient's medical records yielded clinicopathologic information. The number of lymph nodes harvested was derived from the pathologic report. Distant metastasis was diagnosed by clinical, radiologic examination (abdominopelvic computed tomography, chest computed tomography, pelvic magnetic resonance imaging, positron emission tomography or positron emission tomography-computed tomography), or intraoperative observation and pathologic confirmation. The tumors were categorized according to AJCC 7th edition. Patients with synchronous distant metastasis were included in the analysis if radical surgery with curative intention was performed.

All patients underwent curative radical surgery based on standardized technique and principle, which did not change significantly during the study period. In all patients, surgery included total mesorectal excision with adequate resection margin and regional lymph node dissection with ligation of the inferior mesenteric artery at its origin. For surgery, low anterior resection was normally done. However, in cases where the distal resection margin was not secure, ultra low

anterior resection with coloanal anastomosis or abdominoperineal resection was performed instead. Resected specimens were evaluated for depth of tumor invasion, lymph node involvement, histologic type, lymphovascular invasion and resection margins according to standard pathologic evaluation. A careful manual lymph node dissection technique was used to harvest regional lymph nodes. Mesenteric fat clearance technique using chemicals was not used in this study.

Of the 277 patients, 195 (70.4%) underwent radical surgery without preoperative CCRT, and 82 (29.6%) underwent radical surgery after preoperative CCRT. Patients with tumor invasion to mesorectal fascia or adjacent organ and lymph node metastasis on preoperative staging studies or with tumors within 5 cm of the anal verge received preoperative CCRT. The schedule and technique at our institute was as follows. A total of 5040 cGy radiation was delivered in 25 fractions of 180 cGy/day over 5 weeks. Concurrent chemotherapy was administered with intravenous or oral fluorouracil in all the patients. Intravenous 5-FU (425 mg/m²) and leukovorin (20 mg/m²) was administered for 5 days in a continuous manner during the first and fifth weeks of radiotherapy. Otherwise, oral doxifluridine (900 mg/m², Furtulon, Roche, Seoul, Korea) and leukovorin (30 mg/day) were administered during the entire course of radiotherapy. Radical surgery was performed around 6-8 weeks after completing radiation therapy.

Statistical analysis was performed with the statistical package SPSS for Windows (version 12.0 SPSS Inc., Chicago, IL, USA). The Student's t-test was used to analyze the statistical differences in lymph node retrieval between the surgery alone and preoperative CCRT groups, and applied to continuous variables. The χ^2 -test was used for categorical variables. Multivariate analysis using a multiple linear regression model was used to identify independent variables influencing lymph node retrieval. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Clinicopathologic characteristics

The clinicopathologic characteristics are described in Table 1. The median age was 60 (range; 24-85) years. The mean BMI was 23.59±3.02 kg/m². The mean distance from the anal verge to the low edge of the tumor was 6.28±2.53 cm. The mean length of the resected specimen was 20.35±8.98

Table 1. Factors Contributing to Lymph Node Yield

Variables	No. of patients (n=277)	Retrieved lymph nodes	<i>p</i> value
Age			0.882
≤60	147	13.04±9.37	
>60	130	13.21±9.20	
Gender			0.319
Male	173	12.69±9.37	
Female	104	13.84±9.11	
Body mass index			0.463
≤25	196	13.38±9.37	
>25	81	12.48±9.06	
Distance from the anal verge (cm)			<0.001
≤6	154	11.05±8.43	
>6	123	15.71±9.66	
Specimen length (cm)			0.069
≤20	181	13.86±8.67	
>20	96	11.73±10.23	
pT stage			<0.001
pT0-2	86	9.77±8.59	
pT3-4	191	14.63±9.20	
pN stage			<0.001
pN0	157	11.36±9.26	
pN1-2	120	15.42±8.82	
Distant metastasis			0.656
No	255	13.19±9.22	
Yes	22	12.27±10.20	
Tumor differentiation*			0.499
Low grade	244	13.37±9.38	
High grade	29	12.14±8.49	
Lymphovascular invasion			0.017
No	243	12.62±9.09	
Yes	34	16.68±9.98	
Preoperative CCRT			<0.001
No	195	15.30±9.23	
Yes	82	7.94±7.12	

CCRT, concurrent chemoradiotherapy.

*4 patients were omitted from the pathologic report.

cm. In patients receiving preoperative CCRT, the specimen was longer than in patients who received surgery alone (27.64±9.86 cm vs. 17.28±6.50 cm, $p<0.001$) (Table 2).

Preoperative CCRT was performed in 82 patients (29.6%). The median number of lymph nodes retrieved was 12 (range; 1-52). Metastatic lymph nodes were detected in 119 (43.0%) patients, 80 of whom had up to three metastatic nodes (pN1) and 39 patients had four or more (pN2).

Factors contributing to lymph node retrieval

By univariate analysis, distance from the anal verge ($p<0.001$), pT stage ($p<0.001$), pN stage ($p<0.001$), lymphovascular invasion (0.017), preoperative CCRT ($p<0.001$) signif-

icantly contributed to lymph node retrieval. Age, gender, BMI, specimen length, distant metastasis and tumor differentiation had no significant influence (Table 1).

Subsequent multivariate analysis using a multiple linear regression model showed that preoperative CCRT ($p<0.001$) was an independent variable influencing the number of lymph nodes retrieved (Table 3).

Factors contributing to lymph node retrieval after preoperative CCRT

In patients receiving CCRT before surgery, regional lymph node metastasis was a significant factor influencing lymph node retrieval by univariate analysis ($p=0.005$) (Table 4).

Table 2. Comparison between the Non-CCRT and CCRT Groups

Variables	Non-CCRT (n=195)	CCRT (n=82)	<i>p</i> value
Age	60.83±11.09	56.41±10.66	0.002
Gender	1.47 : 1	2.28 : 1	0.116
Body mass index	23.64±2.95	23.46±3.20	0.635
Distance from the anal verge (cm)	7.35±2.13	3.73±1.25	<0.001
Specimen length (cm)	17.28±6.50	27.64±9.86	<0.001
pT stage			<0.001
pT0-2	44	42	
pT3-4	151	40	
pN stage			<0.001
pN0	93	64	
pN1-2	102	18	
Distant metastasis			0.090
No	183	72	
Yes	12	10	
Tumor differentiation*			0.456
Low grade	176	68	
High grade	19	10	
Lymphovascular invasion			0.015
No	165	78	
Yes	30	4	
Retrieved lymph nodes	15.30±9.23	7.94±7.12	<0.001
Metastatic lymph nodes	2.07±3.56	0.40±0.89	<0.001

CCRT, concurrent chemoradiotherapy.

*4 patients were omitted from the pathologic report.

Table 3. Independent Variables Influencing Lymph Node Retrieval

Variables	Regression coefficient	95% CI	<i>p</i> value
Distance from the anal verge (≤6 cm vs. >6 cm)	1.428	-1.082; 3.938	0.264
Specimen length (≤20 cm vs. >20 cm)	1.465	-0.953; 3.883	0.234
Depth of invasion (pT0-2 vs. pT3-4)	2.388	-0.061; 4.836	0.056
Lymph node metastasis (pN0 vs. pN1-2)	1.233	-1.120; 3.585	0.303
Lymphovascular invasion (high grade vs. low grade)	1.788	-1.455; 5.031	0.279
Preoperative CCRT	-5.937	-9.054; -2.819	<0.001

CCRT, concurrent chemoradiotherapy; CI, confidence intervals.

There was no significant difference in lymph node retrieval by age, gender, BMI, distance from the anal verge, specimen length, ypT stage, distant metastasis, tumor differentiation or lymphovascular invasion.

Likewise, by multivariate analysis using a multiple regression model, BMI ($p=0.032$) and regional lymph node metastasis ($p=0.027$) were independent variables influencing the number of lymph nodes retrieved (Table 5).

DISCUSSION

The number of lymph nodes retrieved is one reference point to estimate the diagnostic accuracy of nodal staging after

curative resection of rectal cancer. In the current study, preoperative CCRT was independently associated with the number of lymph nodes retrieved. In addition, BMI and regional lymph node metastasis were independent contributing factors for the number of lymph nodes retrieved in patients who received preoperative CCRT.

An adequate number of examined lymph nodes is crucial for accurate staging, especially in patients without regional lymph node metastasis.^{3,4,14,16} Moreover, not examining enough lymph nodes could be associated with poor prognosis because of the chance of understaging the tumor.¹² For this reason, the AJCC and UICC recommend harvesting at least 12 negative nodes in the surgical specimen of node negative patients to confirm adequate nodal staging. How-

Table 4. Factors Contributing to Lymph Node Yield in the Preoperative CCRT Group

Variables	No. of patients (n=82)	Retrieved lymph nodes	<i>p</i> value
Age			0.503
≤60	51	8.35±7.78	
>60	31	7.26±5.94	
Gender			0.473
Male	57	8.32±7.62	
Female	25	7.08±5.90	
Body mass index			0.059
≤25	59	8.86±7.96	
>25	23	5.57±3.42	
Distance from the anal verge (cm)			-
≤6	82	7.94±7.12	
>6	0	-	
Specimen length (cm)			0.154
≤20	25	6.24±4.22	
>20	57	8.68±8.00	
ypT stage			0.201
ypT0-2	42	6.95±6.84	
ypT3-4	40	8.98±7.35	
ypN stage			0.005
ypN0	64	7.02±6.81	
ypN1-2	18	11.22±7.44	
Distant metastasis			0.261
No	72	8.14±7.01	
Yes	10	6.50±8.14	
Tumor differentiation*			0.538
Low grade	68	8.04±7.39	
High grade	10	8.50±6.40	
Lymphovascular invasion			0.686
No	78	8.04±7.24	
Yes	4	6.00±4.24	

CCRT, concurrent chemoradiotherapy.

*4 patients were omitted from the pathologic report.

Table 5. Independent Variables Influencing Lymph Node Retrieval in the Preoperative CCRT Group

Variables	Regression coefficient	95% CI	<i>p</i> value
Body mass index (≤25 vs. >25)	-3.763	-7.203; -0.324	0.032
Specimen length (≤20 cm vs. >20 cm)	2.067	-1.190; 5.324	0.210
Depth of invasion (ypT0-2 vs. ypT3-4)	0.290	-2.932; 3.512	0.858
Lymph node metastasis (ypN0 vs. ypN1-2)	4.403	0.522; 8.283	0.027

CCRT, concurrent chemoradiotherapy; CI, confidence intervals.

ever, the number of lymph nodes retrieved varies in rectal cancer patients due to several factors. Using at least 12 nodes as the standard, Baxter, et al.¹⁰ found only 20% of patients who underwent preoperative CCRT had adequate lymph node staging. We found only 24.4% of patients who underwent preoperative CCRT had adequate lymph node staging, although 52.4% of total patients had adequate lymph node staging.

Preoperative CCRT has become a standard treatment in

managing advanced rectal cancer,¹⁷ since it decreases the risk of local recurrence,¹⁸ improves the prognosis of advanced rectal cancer patients, and facilitates radical excision of T4 cancer and sphincter saving surgery.¹⁹ However, one issue is that after preoperative CCRT, surgical specimens often do not contain enough lymph nodes to reach the recommended standard.^{10,15,20} In the current study, preoperative CCRT was an independent risk factor to decrease lymph node retrieval. Moreover, when we looked at tumors treated

with preoperative CCRT, lymph nodes retrieved were significantly low in node negative tumors. Thus, there is a chance of understaging, especially in node negative patients.^{21,22} However, there may be no association between lymph node retrieval in patients treated by preoperative CCRT and curative surgery with negative lymph node metastasis, and overall survival and disease-free survival.^{12,23,24} After preoperative chemoradiation, retrieved lymph nodes could also be decreased from the therapeutic effect of radiation, resulted in the sterilization of cancer cell and fibrosis in the lymph nodes. If that was the case, then the reduced number of examined lymph nodes is caused by therapeutic effect of preoperative chemoradiation and there would be no effect on patients' survival. However, the clinical impact of reduced lymph nodes after preoperative chemoradiation is still being debated and should be clarified with further study.

Manual lymph node dissection is the current standard at most institutions, and was also used in the present study. Since 1938, when the fat clearance technique was first used,²⁵ other similar methods have been developed to isolate lymph nodes in surgical specimens. Although there has been variation in consistency among the different methods regarding harvesting and processing of lymph nodes, the fat clearance technique could be used for patients at risk of understaging.^{26,27} If patients received preoperative CCRT or fewer than 12 lymph nodes were retrieved from the surgical specimens by manual lymph node dissection, the fat clearance technique could be available to increase the staging accuracy.²⁶⁻²⁸ A multivariate model of the present study revealed that in patients of the CCRT group with higher BMI, fewer lymph nodes were retrieved. For such patients, the fat clearance technique might deserve special consideration.

The current study included rectal cancer within 10 cm from the anal verge, since lymph node yield could be influenced by tumor localization or specimen length.^{8,13} Colonic bowel segments bear significantly more lymph nodes than rectal bowel segments, possibly because of a longer mesenteric radix. In the present study, specimens from patients receiving CCRT were longer than in patients who received surgery alone, since we carried out an anastomosis with unirradiated bowel by removing all the sigmoid colon to avoid adverse effects and improve bowel function.²⁹ The number of retrieved lymph nodes was significantly lower in patients who underwent preoperative CCRT despite the longer specimens. This is explained by the high radiosensitivity of lymphoid tissue; lymphocytes can die within hours of radiotherapy without cell division, whereas tumor cells need

more time.³⁰⁻³²

In conclusion, preoperative CCRT was an independent variable influencing lymph node retrieval after surgery for mid-low rectal cancer. In patients receiving CCRT before surgery, lower BMI and regional lymph node metastasis were independent variables, increasing lymph node retrieval.

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