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Original Article

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A Distribution Weighted Prognostic Scoring Model for Node Status in Advanced Rectal Cancer

Kwang-Hee Yeo, MD[1]
Ho Hyun Kim, MD[2]
Dong-Yi Kim, MD, PhD[1]
Young-Jin Kim, MD, PhD[1]
Jae-Kyun Ju, MD, PhD[1]

[1]*Department of Surgery, Chonnam National University Medical School, Gwangju,*
[2]*Trauma Center of Pusan National University Hospital, Busan, Korea*

Correspondence: Jae-Kyun Ju, MD, PhD
Division of Colorectal Surgery,
Department of Surgery,
Chonnam National University Hospital,
Chonnam National University Medical School,
42 Jebong-ro, Dong-gu, Gwangju
501-757, Korea
Tel: 82-62-220-6456
Fax: 82-62-227-1635
E-mail : cnuhcrs@gmail.com
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Purpose
There are various lymph node-based staging systems. Nevertheless, there is debate over the use of parameters such as the number of involved lymph nodes and the lymph node ratio. As a possible option, the distribution of metastatic lymph nodes may have a prognostic significance in rectal cancer. This study is designed to evaluate the impact of distribution-weighted nodal staging on oncologic outcome in rectal cancer.

Materials and Methods
From a prospectively maintained colorectal cancer database of our institution, a total of 435 patients who underwent a curative low anterior resection for mid and upper rectal cancer between 1995 and 2004 were enrolled. Patients were divided into 3 groups according to the location of apical metastatic nodes. A location-weighted prognostic score was calculated by a scoring model using a logistic regression test for location based-statistical weight to number of lymph nodes. All cases were categorized in quartiles from lymph node I to lymph node IV using this protocol.

Results
The location of lymph node metastasis was an independent factor that was associated with a poor prognostic outcome ($p < 0.001$). Based on this result, the location-weighted-nodal prognostic scoring model did not show lesser significant results ($p < 0.0001$) in both overall survival and cancer-free survival analyses.

Conclusion
The location of apical nodes among the metastatic nodes does not have a lesser significant impact on oncologic result in patients with advanced rectal cancer. A location-weighted prognostic scoring model, which considered the numbers of involved lymph nodes as the rate of significance according to the location, may more precisely predict the survival outcome in patients with lymph node metastasis.

Key words
Rectal neoplasms, Prognostic scoring model, Lymph nodes, Neoplasm staging

Introduction

The importance of nodal staging as a prognostic factor in oncology and as an accuracy indicator for resection in colorectal cancer has been demonstrated in many studies. The current nodal staging in the 7th American Joint Committee on Cancer (AJCC) staging system is based on the number of metastatic lymph nodes [1], while the concept of lymph node ratio to compensate for the limitation of number of lymph nodes retrieved and to evaluate the adequacy of the resection has been introduced recently [2-4]. In addition, the distribution of lymph node metastasis and high ligation of the inferior mesenteric artery is a subject of intense debate [5-8].

After Grinnell [9] reported the concept of lymphatic spread

of colorectal cancer, surgical treatment for rectal cancer has involved en bloc resection of the involved segment of rectum and the accompanying draining lymph nodes up to the level of the origin of primary blood supply [9]. Lymphatic drainage of the rectum occurs in the downward, lateral, and upward directions. The upward spread is through lymphatic vessels along the superior rectal and inferior mesenteric artery to the central lymphatic drainage, whereas lymphatic spread in the lateral and downward directions does not occur through the inferior mesenteric nodes [10]. Although lateral and downward spread are the possible routes for tumor metastasis, the upward spread is regarded as the main route of lymphatic metastasis. Based on these findings, Hermanek and Altendorf [11] and Hojo et al. [12] reported poor oncologic outcomes in patients with lymph node involvement along the trunks of the vessels compared to those in patients with lymph node involvement only at the branches of the vessels. Although there have been several studies that demonstrated the impact of the distribution of metastatic nodes, the current TNM staging system does not incorporate the location of involved lymph nodes as a prognostic indicator.

This study is designed to evaluate the difference in oncologic impact according to the level of involved lymph nodes and to promote incorporation of the value of the level of nodal involvement in the current TNM staging system.

Materials and Methods

1. Patient selection

A total of 577 consecutive patients, who underwent a low anterior resection for treatment of mid and upper rectal cancer at the Department of Surgery, Chonnam University Hospital, between 1995 and 2004, were identified from a prospectively maintained colorectal cancer database. After excluding the patients who were treated with palliative surgery, a total of 435 patients were enrolled.

2. Follow-up data collection

The stage of rectal cancer was determined by a pathologist using a surgical specimen according to the 6th edition of the AJCC TNM staging system. Follow-up was conducted every 3 months for 2 years after surgery, and then every 6 months for the next 3 years. At the time of follow-up, physical examination, including a patient interview and a digital rectal examination, was performed. The serum carcinoembryonic antigen level was assessed and a simple chest X-ray was taken at 2-3 month intervals. Abdominal computed tomography and colonoscopic examinations were performed at 1-year intervals. Recurrence and survival of patients were followed up based on outpatient medical records. The recurrence pattern was classified based on the area where the recurrence was detected for the first time, and local recurrence was defined as tumors that recurred in the pelvic cavity and the anastomotic area.

3. Lymph node retrieval

In general, all patients underwent standard total mesorectal excision and regional lymphadenectomy. After tumor removal, the surgeon identified and isolated the lymph nodes, and recorded both the number and distribution of the lymph nodes in the operating room. All regional lymph nodes were individually dissected from the adipose connective tissue of the specimen immediately by performing anatomical dissection along all the vessels. Lymph node status was confirmed by a pathologist via microscopic examination. We classified the lymph nodes according to the Japanese classification of colorectal carcinoma [13]. The location of metastatic lymph nodes was defined according to the location of the apical lymph nodes among the involved lymph nodes. We categorized the apical lymph nodes as D1 when they were located along the paracolic and/or pararectal artery (251), and as D2 when they were located along the superior rectal artery (252). D3 was defined when the apical lymph nodes were located at the root of the inferior mesenteric artery (253). All lymph nodes were categorized as D1 to D3 with this protocol.

4. Statistical analysis

An analysis of survival rate was performed using a Kaplan-Meier method with a log rank test, and a Cox regression model was used for analysis of risk factors affecting the survival rate. A multivariate logistic regression test was performed for analysis of risk factors for recurrence.

For the development of location-weighted prognostic scoring model, the lymph node status was included in the logistic regression test, while the other variables were excluded in the analysis. Using the coefficients of the estimated logistic regression model (Table 1), we built a scoring model to predict a poor oncologic outcome (Y) based on the 3 group categories: D1, D2, and D3 as follows: Y=D1×0.630+ D2×1.555 +D3×2.543–1.094. In the final model, one lymph node of the D1 category was scored as 1 (the coefficient 0.630 was re-calculated as 1), one lymph node of the D2 category was scored as 2.5 (the relatively calculated value as a ratio of

Table 1. Logistic regression for statistical weight to location of lymph node

	Coefficient	p-value	Odds ratio	95 % CI
D1	0.630	0.001	1.878	1.28-2.76
D2	1.555	<0.001	4.735	2.94-7.62
D3	2.543	<0.001	12.718	7.55-21.44

CI, confidence interval.

Table 2. Characteristics of patients in relation to lymph node with metastasis

Variable	Node negative (n=275)	Node positive (n=160)			p-value
		D1 (n=108)	D2 (n=32)	D3 (n=20)	
Age (yr)	63 (32-84)	60 (37-83)	56 (37-74)	53 (26-73)	0.014
Gender					0.872
Female	133 (48.4)	54 (50.0)	16 (50.0)	8 (40.0)	
Male	142 (51.6)	54 (50.0)	16 (50.0)	12 (60.0)	
Follow-up (mo)	56 (7-162)	44 (9-165)	37 (4-128)	20 (3-106)	<0.001
Tumor size (cm)	4.5±0.17	4.6±0.16	4.9±0.35	4.7±0.31	0.858
Distal resection margin (cm)	2.2±0.08	2.3±0.12	2.5±0.28	2.3±0.20	0.423
No. of harvest LNs	14 (2-50)	13 (7-39)	13 (6-34)	13 (5-25)	0.582
Preop-CEA level (ng/dL)	8.3±1.16	13.5±6.20	18.4±5.82	32.8±19.34	0.012
T stage					<0.001
T1	24 (8.7)	1 (0.9)	0 (0.0)	0 (0.0)	
T2	74 (26.9)	7 (6.5)	1 (3.1)	1 (5.0)	
T3	170 (61.8)	95 (88.0)	28 (87.5)	19 (95.0)	
T4	7 (2.5)	5 (4.6)	3 (9.4)	0 (0.0)	
N stage					<0.001
N0	275 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	
N1	0 (0.0)	89 (82.4)	17 (53.1)	2 (10.0)	
N2	0 (0.0)	19 (17.6)	15 (46.9)	18 (90)	
Histologic grade					0.013
Grade I, II	260 (94.5)	94 (87.0)	32 (100.0)	17 (85.0)	
Grade III, mucinous	15 (5.5)	14 (13.0)	0 (0.0)	3 (15.0)	
Tumor growth pattern					0.04
Fungating	197 (71.6)	70 (64.8)	17 (53.1)	10 (50.0)	
Infiltrative	78 (28.4)	38 (35.2)	15 (46.9)	10 (50.0)	
Recurrence					<0.001
No recurrence	241 (87.7)	73 (67.6)	21 (65.6)	6 (30.0)	
Local recurrence	13 (4.7)	16 (14.8)	4 (12.5)	4 (20.0)	
Systemic recurrence	21 (7.6)	19 (17.6)	7 (21.9)	10 (50.0)	

Values are presented as median (range), number (%), or mean±SE. LN, lymph node; CEA, carcinoembryonic anigen.

the coefficient [D2]/the coefficient [D1]), and one lymph node of the D3 category was scored as 4. The final scoring model was as follows: Prognostic score (PS)=Number of D1×1+Number of D2×2.5+Number of D3×4. All patients were classified into 4 groups according to the quartile scores as follows: lymph node I (LN I) (PS<2), lymph node II (LN II) (2≤PS<3), lymph node III (LN III) (3≤PS<6), lymph node IV (LN IV) (PS≥6).

Results

1. Clinical characteristics of patients and distribution of lymph node metastases

The median age of the study population was 60 years (range, 26 to 84 years) without gender predominance.

Table 3. The distribution of nodes and the number of harvested nodes according to as whether patients underwent preoperative CRT

	Preoperative CRT		p-value
	No (n=414)	Yes (n=21)	
Node negative	258 (62.3)	15 (71.4)	-
D1	101 (24.4)	4 (19.0)	-
D2	33 (8.0)	2 (9.5)	0.642
D3	22 (5.3)	0 (0.0)	-
No. of harvested nodes	13.87±0.34	11.19±1.11	0.087

CRT, chemoradiation therapy.

Table 4. Disease-free survival rate according to location weighted prognostic scoring model (p=0.011)

			Node stage	Median (95% CI, range, mo)	Survival rate		
					3 yr	5 yr	10 yr
N1	1a	LN I	PS<2 (n=42)	77 (55-88)	75.6	73.0	62.6
	1b	LN II	2≤PS<3 (n=27)	67 (51-81)	68.5	64.3	36.8
N2	2a	LN III	3≤PS<6 (n=52)	52 (45-79)	67.3	51.3	40.3
	2b	LN IV	PS≥6 (n=39)	26 (26-50)	39.2	30.3	23.4

CI, confidence interval; LN, lymph node.

Patients with positive proximal lymph nodes were significantly younger than elder patients (p=0.014). The median length of follow-up of overall patients was 49.5 months (range, 3 to 165 months). Among the 435 rectal cancer patients who underwent a curative low anterior resection, 160 patients had pathologically proven positive nodes. Of these 160 patients with positive nodes, lymph nodes in 108 patients were categorized as D1, those in 32 patients as D2, and those in 20 patients were categorized as D3 according to the protocol of this study. Tumors showed an infiltrative growth pattern in patients with proximal lymph node metastases (p=0.04). Patient characteristics are summarized in Table 2.

2. Treatment modalities

Of the 435 patients, 21 patients underwent preoperative chemoradiation therapy. In cases that received preoperative chemotherapy, there was a trend for a smaller number of harvested lymph nodes; however, it was not statistically significant. The distribution of metastatic lymph nodes was not significantly different between the group that underwent preoperative chemoradiation and the groups that did not undergo preoperative chemoradiation, although the patient volume was small (Table 3).

3. Oncologic outcome according to the location of lymph node metastases

After a median 49.5 months of follow-up, the 5-year overall survival rate was 84.1% in patients without lymph node metastasis, 65.2% in patients with N1, and 45.0% in patients with N2. In survival analysis according to our distribution-weighted nodal staging, the 5-year overall/disease-free survival rate was 72.2%/69.0% in patients with metastatic lymph nodes categorized as D1, 40.6%/35.7% in patients with metastatic lymph nodes categorized as D2, and 22.7%/0.0% in patients with metastatic lymph nodes categorized as D3. Fig. 1 shows significantly different results for the overall and disease-free survival analyses according to the level of metastatic lymph nodes.

4. Predictability of location-weighted prognostic scoring model for oncologic outcome

According to our scoring model, 42 patients was classified into the LN I group and their median survival period was 77 months, 27 patients were classified into the LN II group and their median survival period was 67 months, 52 patients were classified into the LN III group and their median survival period was 52 months, and 39 patients were classified into the LN IV group and their median survival

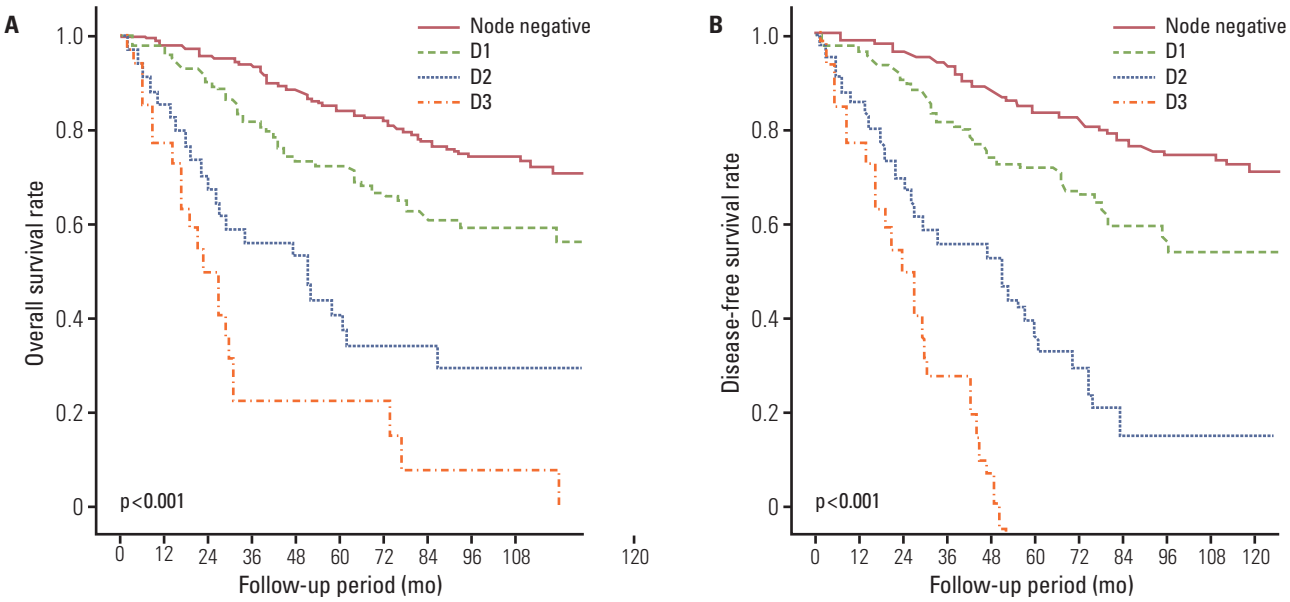

Fig. 1. Overall survival (A) and disease-free survival (B) curves according to a location of lymph node metastases ($p < 0.001$ and $p < 0.001$, respectively).

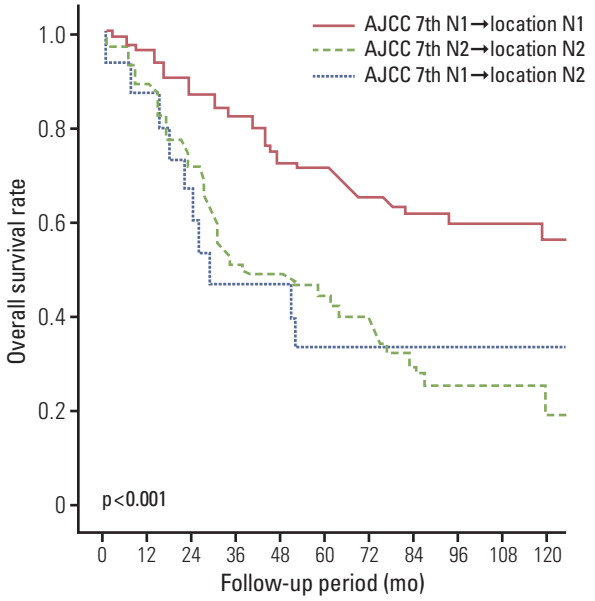

Fig. 2. Overall survival curve according to a location weighted model with nodal staging of Americal Joint Committee on Cancer (AJCC) 7th edition ($p < 0.001$).

period was 26 months (p=0.011) (Table 4). Survival analysis showed significant differences between groups ($p < 0.001$).

Fig. 2 shows a comparison of a location-weighted model with AJCC 7th edition nodal stage. Seventeen patients were classified as N2 according to our model; however, their stage was N1 according to the AJCC 7th edition, and the survival course of these patients was similar to that of patients in the N2 by both the staging systems.

Discussion

Our study showed that the distribution of involved lymph nodes may be an independent factor for the prediction of oncologic outcome in curatively treated patients with mid and upper rectal cancer. The distribution-weighted nodal staging model used in the present study showed that the modified nodal staging more precisely reflected the natural oncologic course in patients with rectal cancer.

In the current AJCC nodal staging system, the prediction of oncologic outcome is based on the number of involved lymph nodes and the topographical distribution of lymph nodes is not taken into consideration [1]. Although this study underscores the prognostic significance of proximal lymph node involvement, Hermanek and Altendorf [11] reported that colorectal cancer patients with proximal lymph node involvement usually have at least four or more metastatic nodes. Lymph nodes along the inferior mesenteric artery are defined as regional lymph nodes in the recent edition of AJCC. However, Kang et al. [5] and Kim et al. [14] reported the prognostic significance of lymph nodes along the inferior mesenteric artery (IMA) in their study. The presence of proximal lymph node metastasis not only has a prognostic impact, but it is also an independent prognostic factor [5,14].

After comparing with some studies that reported the significance of the distribution of involved lymph nodes after categorizing them into proximal or distal lymph nodes, we could demonstrate a more precise grouping according to the lymphatic drainage from D1 to D3, and we could estimate the relative value of each groups. One lymph node of the D1 category was scored as 1, one lymph node of the D2 category was scored as 2.5, and one lymph node of the D3 category was scored as 4. This significance value was used to calculate the statistical weight of the involved nodes, and the prognostic score was finally calculated. In this study, there may some concerns regarding the use of the location-weighted prognostic scoring model, such as small volume, and no consensus about lymph node harvesting; nevertheless, the significance of distribution of lymph nodes seems to differ according to their location.

Location based nodal scoring model was essentially based on the extent of dissection and the level of the IMA ligation. Although several reports, including our study report, have demonstrated the significance of IMA lymph node metastasis as a prognostic factor, the oncologic benefit of complete removal of lymph nodes including those along the IMA is still under debate [15]. Survival benefit of removal of IMA lymph nodes by high ligation has been observed in some studies, and it appeared to be due to the stage migration effect. Most studies found no significant difference in survival between high ligation of the IMA and low ligation of the IMA. Hence, the current evidence appears to demonstrate a preference for low ligation of the IMA because the oncologic benefit is insufficient, while high ligation of the IMA causes a significant reduction in perfusion and disruption of autonomic innervation. In our study, there were 20 patients (4.6%) with lymph node involvement along the IMA; this proportion of patients was not different from the reported range of proportion of patients with lymph node involvement along the IMA, between 0.3% and 8.6% [16]. Nevertheless, our study suggested that the D2 category of lymph nodes had a significant impact on oncologic outcome; however, not as much as the D3 category of lymph nodes (the coefficient, 1.555 vs. 2.543; odds ratio, 1.878 vs. 4.735).

Recently, there have been several studies that used the lymph node ratio, of the involved lymph nodes to the harvested lymph nodes, as an option to estimate the effect on the oncologic outcome in rectal cancer. Some studies have implicated that the neoadjuvant chemoradiation therapy used for treatment of mid and lower rectal cancer leads to limited lymph node harvest [3-6]. This study did not include patients with lower rectal cancer to avoid the effect of lateral pelvic node involvement and neoadjuvant chemotherapy; and according to this point of view, non-inclusion of these patients could be the major limitation of our study. Nevertheless, we tried to estimate the pure impact of the location of involved lymph nodes on oncologic outcome.

This study confirms that the location of metastatic lymph nodes was significantly and independently associated with a poor oncologic outcome. The location-weighted prognostic scoring model may help to overcome the limitations associated with the use of number of involved nodes, lymph node ratio of involved nodes to harvested nodes, and high ligation of the IMA. A larger scale, multi-center study should be performed to confirm the impact of involved lymph nodes oncologic outcome in rectal cancer.

Conclusion

The distribution of involved lymph nodes had a significant impact on prediction of the survival outcome. Our location-weighted prognostic scoring model, a prediction system that includes both the number and location of lymph node metastasis, may help to overcome the limitations of the current lymph node-related prognostic prediction system. A large scale study should be initiated and the significance of the distribution of metastatic lymph nodes may be included in the next TNM staging system.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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