The impact of lymph node count on survival in gastric cancer

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Purpose: The purpose of this study was to determine the immunologic role of lymph node (LN) and stage migration by assessing LN count and metastatic LN count.

Methods: A total of 2,117 patients with gastric adenocarcinoma located in the body and antrum who underwent distal/subtotal gastrectomy with D2 LN dissection between January 1, 1998 and December 31, 2008 were enrolled. LN count and number of metastases were determined in the N1 tier (area of D1 dissection) and N2 tier (area of D2 dissection). The lower and upper quartiles of LN counts in the same pN stage were grouped to compare the prognosis and LN positivity according to the LN tier.

Results: Stage migration from N1 tier to N2 tier occurred in 3.2% of cases. The 5-year disease-specific survival rates of the upper and lower LN count groups within the N1 tier were 91.0% and 86.7% ($P=0.01$), respectively. LN positivity in the N2 tier of the lower LN count group was higher than that of the upper LN count group (14.1% vs. 8.2%, $P<0.01$). Stage migration in the N2 tier of the lower LN count group was also higher than that of the upper LN count group (4.6% vs. 1.8%, $P<0.01$).

Conclusion: The lower LN count group had a decreased survival rate compared to that of the upper LN count group, suggesting that perigastric LN has an immunological defense role in weakening the disseminating power of metastatic tumor cells, as indicated by the LN count.

Keywords: Stomach neoplasm, Lymph node, Stage migration

INTRODUCTION

The Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) classifies the N stage of gastric cancer based on the metastatic lymph node (LN) count [1,2]. N stage is important for determining treatment strategies and predicting prognosis along with tumor depth (pT stage), and harvesting more than 15 LNs is recommended for proper N staging. Inappropriate LN count results in an inappropriate node-negative result, leading to a lower overall stage, referred to as stage migration. Stage migration

shows a worse survival than that of appropriately assessed LN count. However, a large LN count shows better prognosis, suggesting the prognostic significance of the LN count. Most of surgeons agree on the extent of LN dissection, which minimizes stage migration, in order to compare prognosis. Experienced surgeons not only perform LN dissection but also perform LN harvest for pathological examination. In Korea and Japan, D2 LN dissection is the standard LN dissection guideline for gastric cancer, and gastric surgeries are performed by experienced surgeons at hospitals specializing in gastric cancer surgery. There is a tendency to perform LN harvest during surgery, minimizing the possibility of missing positive LNs.

Recently, suspicions have been raised that stage migration is exaggerated in meta-analysis studies, arguing that although there is evidence that fat clearance and methylene blue staining during LN harvest increases LN count [2], there is no evidence that this increases LN positivity and upstaging [3]. Some studies also reported that LN count is an indicator for host immunologic role against tumor dissemination [4]. However, there is no direct evidence, and more studies need to be conducted.

The purpose of this study was to determine the immunologic role of LN and stage migration by assessing LN count and metastatic LN count.

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METHODS

Among 3,041 patients, 2,841 received radical distal/subtotal gastrectomy with D2 LN dissection between January 1, 1998 and December 31, 2008. Patients with cancer located in the upper third, who received neoadjuvant chemotherapy, and who previously underwent surgery for other intra-abdomen cancer or gastric cancer surgery were excluded from this study. Finally, the remaining 2,117 patients were included in the present study.

The hospital in which the surgeries were performed is a center that specializes in gastric cancer surgery and in which more than 150 surgeries are performed annually. Two specialized surgeons (DHY and CYK) performed the surgeries in the present study. Depending on the location of the primary tumor, one-half or two-thirds of the stomach was eliminated, and *en bloc* was performed for LN dissection of D2 or higher. Then, the surgeon divided the soft tissue based on LN station at the operation field and placed LN based on LN station into formalin. These samples were then sent for pathological examination.

The pN stage was performed according to the UICC/AJCC TNM classifications 7th edition. Japanese Gastric Cancer Association recommendations were followed for each LN station, D1 and D2, for LN dissection. LN stations 1, 3, 4sb, 4d, 5, 6, 7 were included in the D1 area, while both the D1 area and LN stations 8a, 9, 11p, and 12a were included in the D2 area. First, the pN stage was determined based on metastatic LN count in the D1 area. LN positivity changes in LN 8a, 9, 11p, and 12a areas were observed, and finally, changes in stage migration in the D2 area were recorded. The disease-specific five-year survival rate in pN stage within the

D1 area was also calculated in order to study the relationship between LN positivity and stage migration.

LN counts were divided into lower and upper groups according to quartile. Because LN count was in proportion to metastatic LN count, as shown in Fig. 1A, when LN count was divided into quartiles, more metastatic LN counts were included in the upper quartile, causing a selection error, LN count that was applied to the number of metastatic LN was divided into lower LN count group (< 25 percentile) and upper LN count group (> 75 percentile).

Differences in LN positivity and stage migration were observed between the lower and upper LN count groups. In order to compare disease-specific 5-year survival rates in the D1 and D2 areas, the lower and upper LN counts were calculated for both areas. The lower and upper LN count groups in D1 area included 570 and 575 patients, respectively. The lower and upper LN count groups in D2 area included 566 and 570 patients, respectively. Differences in clinicopathologic features were assessed between the lower and upper LN count groups for patient age, sex, body mass index (BMI), tumor size, extent of lymphadenectomy, tumor differentiation, Lauren classification, presence of lymphatic invasion, pT stage, pN stage, and TNM stage.

In patients with multiple synchronous gastric cancers, the lesion with the deepest infiltration of the gastric wall was regarded as the main lesion. The clinicopathological characteristics of the main lesion were used for the analysis. Resections were deemed radical when no gross residual disease was evident at the time of operation, with tumor-free resection margins on histological examination.

Not all patients were administered postoperative chemotherapy. Patients with advanced gastric cancer more than TNM stage II

Fig. 1. Lymph node counts (LNCs) were divided into lower and upper groups according to quartile. (A) LNC increased in proportion to metastatic LNC (Pearson coefficient=0.30, $P<0.01$). In order to eliminate selection error, we marked the upper and lower LNC group through making a quartile for each number of the metastatic lymph node (LN). (B) LNCs within the LN 8a, 9, 11p, and 12a were proportionate with LNC within the D1 area, having a Pearson coefficient of 0.27 ($P<0.01$).

were administered 5-fluorouracil-based postoperative chemotherapy starting within three weeks after surgery. No patients were administered postoperative or preoperative radiotherapy.

In general, the follow-up consisted of abdominopelvic computed tomogram every 6 months for 5 years after surgery and esophag-

gastro-duodenoscopy annually for 5 years after surgery. Follow-up of patients was completed until the cutoff date of 31 December, 2013. The median follow-up interval at the cutoff date was 50 months (range, 0–232 months). At the time of the last follow-up, 334 patients (11.8%) had been lost to follow-up.

Table 1. Clinicopathologic characteristic of the lower and upper quartile group of lymph node count in the D1 and D2 dissection area

Characteristic	LNC quartile of D1 dissection area			LNC quartile of D2 dissection area		
	Lower (n = 570)	Upper (n = 575)	P-value	Lower (n = 566)	Upper (n = 570)	P-value
Sex			0.23			0.89
Male	396 (69.5)	380 (66.1)		393 (69.4)	398 (69.8)	
Female	174 (30.5)	195 (33.9)		173 (30.6)	172 (30.2)	
Age (yr)			< 0.01			0.01
< 60	256 (44.9)	324 (56.3)		262 (46.3)	322 (56.5)	
≥ 60	314 (55.1)	251 (43.7)		304 (53.7)	248 (43.5)	
BMI (kg/m ²)			< 0.01			< 0.01
< 20	73 (12.8)	122 (21.3)		66 (11.7)	133 (23.4)	
20–25	289 (50.7)	297 (58.0)		279 (49.4)	335 (58.9)	
> 25	208 (36.5)	110 (20.7)		220 (38.9)	101 (17.7)	
Tumor size (cm)			0.04			< 0.01
≤ 3	348 (61.7)	315 (55.7)		353 (62.9)	287 (51.2)	
> 3	216 (38.3)	251 (44.3)		208 (37.1)	274 (48.8)	
Extent of lymphadenectomy			0.85			< 0.01
D2	184 (32.3)	189 (32.9)		229 (40.5)	157 (27.5)	
Over D2	386 (67.7)	386 (67.1)		337 (59.5)	413 (72.5)	
Differentiated			0.01			0.01
Well	325 (57.0)	287 (49.9)		330 (58.3)	295 (51.8)	
Poorly	245 (43.0)	288 (50.1)		236 (41.7)	275 (48.2)	
Lauren			0.02			0.04
Intestinal	265 (60.0)	228 (52.2)		276 (61.6)	227 (54.8)	
Diffuse	177 (40.0)	209 (47.8)		172 (38.4)	187 (45.2)	
Lymphatic invasion			0.15			0.29
Negative	287 (69.2)	327 (73.6)		286 (67.5)	293 (70.9)	
Positive	128 (30.8)	117 (26.4)		138 (32.5)	120 (29.1)	
pT stage			0.44			0.01
pT1	352 (61.8)	326 (56.7)		356 (64.5)	301 (52.8)	
pT2	67 (11.8)	72 (12.5)		65 (11.5)	82 (14.4)	
pT3	65 (11.4)	72 (12.5)		59 (10.4)	70 (12.3)	
pT4	86 (15.0)	92 (16.0)		77 (13.6)	117 (20.5)	
pN stage ^{a)}			0.58			0.51
pN0	382 (67.0)	395 (68.7)		384 (67.8)	378 (66.3)	
pN1	63 (11.1)	59 (10.3)		63 (11.1)	57 (10.0)	
pN2	49 (8.6)	56 (9.7)		49 (8.7)	65 (11.4)	
pN3a	35 (6.1)	36 (6.3)		34 (6.0)	39 (6.8)	
pN3b	41 (7.2)	29 (5.0)		36 (6.4)	31 (5.4)	
TNM stage ^{a)}			0.83			0.12
Ia	313 (54.9)	300 (52.2)		323 (57.1)	277 (48.6)	
Ib	58 (10.2)	62 (10.8)		56 (9.9)	62 (10.9)	
IIa	38 (6.7)	45 (7.8)		39 (6.9)	49 (8.6)	
IIb	46 (8.1)	51 (8.9)		44 (7.8)	55 (9.6)	
IIIa	37 (6.5)	29 (5.0)		34 (6.0)	33 (5.8)	
IIIb	39 (6.8)	43 (7.5)		33 (5.8)	40 (7.0)	
IIIc	39 (6.8)	45 (7.8)		37 (6.5)	54 (9.5)	

Values are presented as number (%).

LNC, lymph node count; BMI, body mass index.

^{a)}Final stage including D2 and over D2 lymph node dissection patients.

All statistical analyses were performed using SPSS 15.0 (SPSS, Inc., Chicago, IL, USA). Categorical variables were compared by chi-square tests. Correlation analysis was performed with two-tailed test, and Pearson coefficients were calculated. Disease-specific survival rates were determined using the Kaplan-Meier method and compared using log-rank tests. For all analyses, P-values of <0.05 were considered statistically significant.

All information was obtained with appropriate Institutional Review Board waivers, and data were collected without revealing any personal information. The study was approved by the Ethical Review Board at the Chonbuk National University, Jeonju, Korea (2012-01-003).

RESULTS

The mean age of patients was 59 years (median, 60; standard deviation [SD], 11.3; range, 22–91 years), with a male-to-female ratio of 2.1:1. The clinicopathologic characteristics of the lower and upper LN count groups in the D1 and D2 areas are shown in Table 1. The characteristics that showed differences between the lower and upper groups for the D1 area included age, BMI, tumor size, adenocarcinoma differentiation, and Lauren classification, while the extent of lymphadenectomy and pT stage differed in the D2 area.

There were 677 patients with D2 LN dissection (32.5%), and 1,430 patients were diagnosed with over D2 LN dissection (67.5%). The TNM stage for the patient group was as follows: Ia, 1,465 (55.2%); Ib, 221 (10.4%); IIa, 161 (7.6%); IIb, 178 (8.4%); IIIa, 109 (5.1%); IIIb, 141 (6.7%); and IIIc, 139 (6.6%). The median LN count for the total patient group was 45 (mean, 48.0; SD, 20.2; range,

6–168). The median LN count for the D1 area was 25 (mean, 26.6; SD, 12.6; range, 2–112). The median for the LN 8a, 9, 11p, and 12a areas were 17 (mean, 18.2; SD, 8.9; range, 0–72). The median LN count for the D2 area was 42 (mean, 44.8; SD, 17.4; range, 6–149). Fig. 1A is a graph of the total metastatic and total LN counts, which are proportionate ($P < 0.01$). Fig. 1B shows that the LN count of D1 area and the LN 8a, 9, 11p, and 12a areas were also proportionate.

The median positive LN count in the D1 area was 4.0 (mean, 5.8; SD, 7.5; range, 1–43) and 639 patients (30.2%) showed LN positivity. The median positive LN count for the LN 8a, 9, 11p, and 12a areas was 2.0 (mean, 2.9; SD, 4.4; range, 1–33), with 223 patients (10.5%) showing LN positivity. Two hundred and twelve patients showed LN positivity in both areas. Only 11 patients (0.5%) showed negative results in the D1 area but positive in the D2 area. The median positive LN count in the D2 area was 4.0 (mean, 6.7; SD, 9.7; range, 1–73) and 650 patients (30.7%) showed LN positivity in the LN 8a, 9, 11p, and 12a area, which included 11 patients with LN positivity.

Sixty-eight patients (3.2%) showed stage migration between the D1 and D2 areas. Subdividing according to pN stage within the D1 area in order to observe the changes in LN positivity and stage migration in the LN 8a, 9, 11p, and 12a areas revealed LN positivity and stage migration of 0.7% and 0.7%, respectively, for pN0; 13.7% and 7.7%, respectively, for pN1; 26.5% and 10.5%, respectively, for pN2; 48.4% and 14.3%, respectively, for pN3a; pN3b had an LN positivity of 83.5%, showing an increase with increased pN stage (Fig. 2).

One minus the cumulative 10-year disease-specific survival rates for pN stage within the D1 area were 0.8%, 15.8%, 17.3%, 46.7%, and 81.0% for pN0, pN1, pN2, pN3a, and pN3b, respectively, which were similar to the LN positivity rates of 0.7%, 13.7%, 26.5%, 48.4%, and 83.5% for pN0, pN1, pN2, pN3a, and pN3b, re-

Fig. 2. The pN stage and stage migration. Subdividing according to pN stage within the D1 area shows the ratio between the lymph node (LN) positivity in the LN 8a, 9, 11p, 12a area and the pN stage within the D1 area shows the frequency of stage migration in the D2 area. LN positivity and stage migration increased with pN stage.

Fig. 3. The 10-year disease-specific survival rate for pN stage within D1 are 1– the cumulative 10-year disease-specific survival rate similar to the lymph node (LN) positivity rate in LN 8a, 9, 11p, 12a area.

Fig. 4. The lymph node (LN) positivity and stage migration. (A) The ratio of LN positivity within LN 8a, 9, 11p, 12a area is shown through pN stage within the D1 area. While LN positivity increases with pN stage, there was more in the lower group of lymph node count (LNC) than the upper group ($P=0.01$). (B) pN stage within the D1 area shows the frequency of stage migration in the D2 area. While the stage migration increases with pN stage, there was a higher frequency in group of LNC ($P=0.01$).

spectively (Fig. 3).

Analysis of the differences in LN positivity within the LN 8a, 9, 11p, and 12a areas in the lower and upper LN count groups within the D1 area revealed that the total positivity rate in the lower group was 14.0% compared to 8.2% in the upper group and was also higher for each pN stage ($P=0.01$) (Fig. 4A). The rates of stage migration in the lower and upper LN count groups were 4.4% and 1.7%, respectively, with a significantly higher stage migration in the lower LN count group ($P=0.01$) (Fig. 4B).

The disease-specific five-year survival rates in the lower and upper LN count groups for the D1 area were 86.7% and 91.0%, respectively ($P=0.01$) (Fig. 5). The rates for the D2 area were 88.5% and 91.5%, respectively ($P=0.04$). The survival rate for the lower LN count group was low for each pN stage from pN1 to pN3a, with the exception of pN0.

DISCUSSION

The important initial event by which solid tumors spread occurs through the lymphatic system. Since metastatic regional LN is considered a prognostic indicator, it is important to avoid missing positive LNs. To obtain sufficient LN count is not only by the range of LN dissection but the motivation of the pathologist as well. While the national guidelines suggest harvesting more than 15 LNs, up to three times this number is required to approach the Japanese standard. Therefore, there is an increased risk for stage migration with inappropriate LN dissection or when the pathologist is passive at finding LNs [5-8]. However, some authors argue that stage migration could be over-exaggerated. In a multicenter randomized trial, Degiuli et al. [9] reported that the LN positivity

rates for D1 and D2 dissection (51.5% and 55.2%, respectively), as well as the range of pN stage, did not differ significantly. In another study comparing D2 and D1 dissection, the mean LN counts were 37.2 and 19.2, respectively, but the node positivity rates did not differ significantly, at 3.9% and 3.4%, respectively. Our results were similar to these previous findings. The median LN count of the D1 and D2 areas were 25 and 42, respectively, but the median number of positive LNs was the same (4.0) and the LN positivity rates were 30.2% and 30.7%, respectively. While patients with stage migration showed an increasing pattern for pN with D1 area, overall only 68 patients (3.2%) had stage migration. In assessing the relationship between LN count and metastatic LN count in Fig. 1A, simply interpreting that in order for LN count to increase, metastatic LN count has to increase, with a corresponding increased potential for up-staging is not correct. LN count and metastatic LN count are not in a cause-and-effect relationship. Metastatic LN count is an indicator for the disseminating power of the primary tumor and is direct related to survival. As shown in Fig. 2, the LN positivity rate for the LN 8a, 9, 11p, and 12a areas was 0.7% for pN0 within the D1 area while the rate for pN3b within the D1 area increased to 83%. Interestingly, this is almost the same as 1 - disease-specific cumulative survival rate, which could be explained based on the close relationship between the disseminating power of metastatic LN count and survival (Fig. 3). While there was no large difference in pN0 within D1, the upper LN count group showed low LN positivity from pN1 through pN3 within D1; the survival graph in Fig. 4 also showed the same trend in LN positivity rate. As suggested in previous reports on the significance of LN count, the reason for the low survival rate in the lower LN count group could be that the lower LN count is in a more distant area than that of the upper LN

Fig. 5. The 5-year disease-specific survival rate. (A) Five-year disease-specific survival rates in the upper and lower lymph node count (LNC) group for the D1 dissection area was 91.0% and 86.7% ($P=0.01$) while the 5-year disease-specific survival rates for the LNC group for the D2 dissection area was 91.5% and 88.5% ($P=0.04$). (B-F) Five-year disease-specific survival rate of pN0 through pN3b is shown as well as the survival rate for the D1 and D2 dissection areas were calculated. There was not a large difference in the pN0 5-year disease-specific survival rates from pN1 through pN3 were low in the lower LNC group.

count, with more disseminated tumor cells rather than low quality surgery, resulting in missing positive LN caused by under-staging. The difference in survival between the lower and upper LN count groups in not only the D1 but also the D2 areas, as shown in Fig. 5, could be due to differences in dissemination in D2. From Fig. 1 we could hypothesize that metastatic LN count is an indicator of the disseminating power of the primary tumor and that the LN count is the indicator of the immunologic defense power of the host, which weakens the disseminating power. Also, these two trends are in proportion, in which cancer immunologic reaction causes local LN hyperplasia, resulting in larger LN size and higher detectability.

The role of LNs in cancer progression is still not fully understood. Multiple steps are necessary to successfully seed from tumor cells passing the lymphatic vessel to the draining LN that causes lymphatic metastasis, which is different from previous hypotheses. Therefore, successful LN metastasis requires that both tumor and host factors be fulfilled. The presence of a few LN metastases in solid tumors suggests that other clones from metastatic cells from the primary cancer site have escaped in large numbers. However, before the LN count can increase throughout the body, the LN count of the host may act as an immunologic defense barrier. There is no doubt that the immune system has an important role in patient prognosis. For example, tumor-infiltrating lymphocytes are linked to a favorable prognosis, in which the immune system plays an important role. However, to the authors' knowledge, few reports have shown a direct relationship between LN count and immunologic response. Kim et al. [10] and George et al. [11] recently reported tumor infiltration by lymphocytes and LN count to be related in colon cancer; in addition, while microsatellite instability is an immunologic factor and a well-known predictor for favorable prognosis in colon cancer, it has also been reported to be related to the LN count [12,13].

While LN count and metastatic LN count are in proportion, the reason for differences between individuals and the direct parameter for immunologic response is unknown. Previous reports suggest that younger patients have higher LN counts, that Asians and non-Hispanic blacks have an increased frequency of higher LN count compared to that of non-Hispanic whites, and that patients diagnosed with higher stage and operated on have a higher LN count. The significant factors in our study included age under 60 years, low BMI, tumor size > 3 cm, poorly-differentiated adenocarcinoma, diffuse-type Lauren classification, more extensive lymphadenectomy, and advanced pT and pN stage.

With low motivation during LN harvest along with inappropriate LN dissection, the possibility of stage migration due to missing positive LN does not disappear. In other cases, LN count does not

need to be reflected in the patient's survival as an immunologic indicator [14]. However, as previous reports suggest, the LN ratio combined with LN count may better predict prognosis than UICC/AJCC pN stage. This is because the prediction accounts for stage migration; however, the results of the present study suggest that the host immune system may also play a role in the control of metastatic LN count, which is the disseminating force in tumor cells [8].

In conclusion, LN positivity and stage migration in the D1 and D2 LN dissection areas showed a trend for increasing pN stage; however, the overall trend was not statistically significant. The lower LN count group had a worse survival rate compared to that of the upper LN count group, suggesting that perigastric LN has an immunological defense role in weakening the disseminating power of metastatic tumor cells, as indicated by the LN count.

This study has some limitations. First, our long-term retrospective study design in a single Eastern institution could cause selection bias. Second, there may be treatment biases due to the progression of surgical skill, including LN dissection, and chemotherapy. Third, while cancer-related survival was the study end-point, the reported cause of death report was not always accurate.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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