

Prognosis of pN3 stage  
gastric cancer

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# Prognosis of pN3 stage gastric cancer

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This certifies that the Master's Thesis  
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<ABSTRACT>

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The aim of this study was to determine the prognosis and the recurrence pattern of pN3 stage gastric cancer patients after the curative resection, and to identify the prognostic factors according to the clinico-pathologic features.

Between January 2000 and December 2004, I retrospectively reviewed the medical records of the patients as histological confirmed pN3 stage of gastric cancer without distant metastasis including peritoneal seeding, hepatic metastasis or para-aortic lymph node metastasis. They underwent both gastrectomy and D2 or D3 lymphadenectomy with a curative aim. I then analyzed the survival according to clinico-pathologic factors as age, sex, tumor location, the type of gastrectomy, the gross features of the tumor, tumor size, tumor differentiation, and the depth of invasion, Lauren classification, lymphatic invasion, vascular invasion, the number of dissected and metastatic lymph nodes and the proportion of metastatic lymph nodes to dissected lymph nodes, the node stage by the Japanese Classification of Gastric Cancer,



involvement of perigastric lymph nodes which subdivided by Group 1 vs. others, and adjuvant chemotherapy. And I also examined recurrence pattern in pN3 gastric cancer patients.

Out of 467 patients with stage IV gastric adenocarcinoma who received surgery, 260 patients underwent curative resection and they were pathologically staged as N3. Among these 260 patients, 179 patients were pN3 stage gastric cancer without distant metastasis. The median age was 62 years (range: 16-82 years). The most common site of gastric cancer was lower third of the stomach (48.6%). Among 179 patients, 84 patients (46.9%) were restaged as N2 stage and 18 patients (10.1%) were restaged as N1 stage by JCGC. The majority of patients were received adjuvant chemotherapy (75.4%). Among 179 patients, 123 patients (68.6%) had recurred and the majority of recurrent site of gastric cancer was peritoneal metastasis (30.9%). The 3-year and 5-year disease free survival rate were 16.2% and 9.5%, respectively. The median time to recurrence was 11.9 months (range: 0.5-108.2 months).

For all the patients, the median follow-up period was 19.6 months (range: 0.5-108.2 months) and the median overall survival time was 19.6 months (95% CI, 15.17 – 23.96). The 3-year and 5-year survival rate of the pN3 gastric cancer patients were 27.9% and 12.8%, respectively. The identified predictors for a worse prognosis were Borrmann type III and IV group (HR: 1.79, 95% CI, 1.12 – 2.86,  $p = 0.020$ ), the group without adjuvant chemotherapy (HR: 6.23, 95% CI,

3.08 – 12.62,  $P < 0.0001$ ), the number of dissected lymph nodes more than 65 (HR: 2.06, 95% CI, 1.31 – 3.26,  $p = 0.002$ ) and the ratio of metastatic lymph nodes between 66 and 100 (HR: 2.01, 95% CI, 1.15-3.53,  $p = 0.015$ ) for the pN3 patients.

I suggested that gastric cancer patients staged as pN3 only without distant metastasis had a different prognosis by clinico-pathologic features, especially by metastatic lymph node ratio and adjuvant chemotherapy. These pN3 gastric cancer patients needed aggressive adjuvant chemotherapy after curative gastrectomy for better prognosis.

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Key words: advanced gastric cancer, pN3, prognostic factor, survival

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## I. INTRODUCTION

Gastric cancer is the fourth most common cancer worldwide.<sup>1</sup> According to the global estimation-GLOBOCAN 2002, gastric cancer ranks the second and the fourth mortality rate in men and women.<sup>2</sup> The prognosis of gastric cancer patients is poor with a 5-year survival rate of approximately 20%.<sup>1, 3</sup> Surgical resection with a curative aim is the principal of treatment for gastric cancer and the indications for surgical resection had been decided based on the stage.<sup>4</sup> The fifth edition of American Joint Committee on Cancer (AJCC) cancer staging system has been modified with the main change of nodal staging which was based on the number of metastatic lymph nodes.<sup>5</sup> When applying the fifth AJCC system, some studies reported 23% of the patients who migrated to another stage including stage IV.<sup>5</sup> Thus, there are variations in the survival rates even among the patients within the same stage IV gastric cancer. It is controversial that these heterogeneous groups of patients are being treated with the same

strategies according to the stage.

For stage IV patients who cannot be cured, several studies have shown that resection may be beneficial in terms of survival.<sup>4</sup> It has been reported that the survival of patients with stage IV gastric cancer was significantly better with resection than bypass procedures or laparotomy alone.<sup>6</sup> In addition, the patients with pN3M0 gastric cancer showed a higher survival rate among the stage IV patients with other pathologic characteristics.<sup>7</sup> It has been observed that the 5-year survival rate of pN3M0 gastric cancer was 8.7%, which was slightly better than that of other stage IV gastric cancers with about 4.1% ( $p = 0.039$ ).<sup>7</sup> There, I hypothesize that the prognosis may be different among stage IV patients, radically resected pN3 stage patients whose tumors were removed by gastrectomy with no gross residual tumor and without distant metastasis might have a different prognosis compare to others. Hence, the aim of this study was to determine whether the pN3 stage gastric cancer patients are a heterogeneous group with different prognoses. I also determined the prognostic factors of pN3 stage patients according to the clinico-pathologic features.

## II. MATERIALS AND METHODS

### **Patients**

Between January 2000 and December 2004, among 467 gastric cancer patients with histopathologically diagnosed as stage IV adenocarcinoma and who received surgical treatment at the Yonsei Cancer Center, Yonsei University Health System, I reviewed 260 patients who were staged as the pN3 stage after the resection. Then I enrolled 179 patients who were staged at the pN3 stage only without distant metastasis including peritoneal seeding, hepatic metastasis or para-aortic lymph node metastasis. The last follow-up date was December 31, 2008.

The pathology was confirmed as gastric adenocarcinoma according to endoscopic biopsy. Preoperative computed tomography was done to evaluate for possible metastases in the abdominal organs or lymph nodes. All the enrolled patients had received the following operative procedures for curative aim: 1) total or subtotal gastrectomy depending on the location, 2) D2 or D3 lymphadenectomy. Curative resection was defined as having no grossly remaining visible tumor tissues and microscopically negative surgical margins with the sufficient resection margins.<sup>8</sup> Lymph node dissection was followed by the guideline of the Japanese Research Society for Gastric Cancer (JRS GC).<sup>9</sup> The D2 lymphadenectomy was performed for all the Group 1 and Group 2 lymph nodes and the D3 lymphadenectomy was performed for all the Group 1,

Group2 and Group 3. Retrieved lymph nodes were classified by surgeons in operative rooms and all lymph nodes were inspected by light microscopy for metastasis. Then, the pN3 stage was defined with metastases in more than 15 lymph nodes according to the sixth edition of UICC TNM classification.<sup>10</sup>

The clinical and pathological features of the pN3 patients were retrospectively reviewed. I then analyzed the survival according to clinico-pathologic factors as age, sex, tumor location, the type of gastrectomy, the gross features of the tumor, tumor size, tumor differentiation, and the depth of invasion, Lauren classification, lymphatic invasion, vascular invasion, the number of dissected and metastatic lymph nodes and the proportion of metastatic lymph nodes to dissected lymph nodes (metastatic LN ratio), the node stage by the Japanese Classification of Gastric Cancer (JCGC), involvement of perigastric lymph nodes which subdivided by Group 1 vs. others, and adjuvant chemotherapy.

The recurrence rate and the recur pattern were evaluated. To confirm the locoregional recurrence of gastric bed or anastomotic site, endoscopy with biopsy was performed. Otherwise, the recurrence was mainly documented radiologically. Recurrences were categorized as locoregional, hematogenous, peritoneal, distant lymph node or mixed.<sup>11</sup> Locoregional recurrence included tumor in gastric bed, anastomotic site, or regional lymph node (perigastric, left gastric, common hepatic, celiac, hepatoduodenal, retropancreatic, mesenteric, or

para-aortic). Hematogenous recurrence included metastases to in liver, bone, lung, brain, CSF, or other distant sites. Peritoneal recurrence included peritoneal seeding or Krukenburg's tumor. Recurrence in distant lymph node was defined as extra-abdominal lymph nodes. Mixed pattern of recurrence included more than one other category of recurrence pattern at the time of recurrence was confirmed.

To elucidate the subgroup among pN3 based on the nodal status, the number of dissected lymph nodes, metastatic lymph nodes, or metastatic lymph node ratio were evaluated. As I needed to determine the cutoff level, the number of metastatic lymph nodes was compared at each interval of 5 or 10 lymph nodes. Then, I divided into three groups by the number of metastatic lymph nodes according to their differences of survival time. For analysis of the metastatic lymph node ratio, I divided into several groups: (1) 2 groups by the median metastatic lymph node ratio, (2) 3 groups by equal division, or (3) 4 groups divided into quarters.

### **Statistical Analysis**

The primary end point, overall survival was defined as the time from operation to death or to the data of last follow-up date. And disease free survival was defined as the time from operation to recurrence. I compared overall survival of pN3 by clinic-pathological factors. The probability of survival was

calculated using the Kaplan-Meier method. Differences between survival curves were compared by the log-rank test. The multivariate analysis was done using the Cox proportional hazards model, which calculated a hazard ratio. A p-value of  $< 0.05$  was considered significant.



### III. RESULTS

#### **Characteristics of Patients**

One hundred and seventy nine gastric cancer patients who underwent gastrectomy and who were finally confirmed as pN3 stage without distant metastasis were enrolled. The clinico-pathologic features of the patients are shown in table 1 and table 2. There were 117 (65.4%) males and 62 (34.6%) females. The median age was 62 years (range: 16-82 years). The most common site of gastric cancer was lower third of the stomach (48.6%) followed by the middle third (33.5%) and the upper third (15.6%). The median tumor size of all the patients was 7cm (range: 2 – 20cm). For the depth of invasion, no cases of T1 stage existed, while the number of T2, T3, and T4 stages was 7 (3.9%), 161 (89.9%) and 11 (6.2%), respectively. Poorly differentiated type of histology (59.8%) and diffuse type by Lauren classification (24.6%) were the most common type in pN3 gastric cancer patients. The node stage by JCGC showed the migration of node stage compared with the sixth UICC TNM classification. Among 179 patients, 84 patients (46.9%) were restaged as N2 stage and 18 patients (10.1%) were restaged as N1 stage by JCGC (Table2). The majority of patients were received adjuvant chemotherapy (75.4%). Among these patients, Adriamycin based combination was the most common (43%) followed by Cisplatin-based (29.6%), monotherapy with 5-fluorouracil analogues (14.8%) and Taxane-based combination (10.4%). Thirty four patients were unavailable

to analyze due to transfer to the other hospital (Table 1).

**Table 1. Patients characteristics**

<b>Characteristics</b>	<b>Number of patients (%)</b>
<b>Age (yr)</b>	
<b>Median (range)</b>	<b>62 (16-82)</b>
<b>Sex</b>	
<b>Male</b>	<b>117 (65.4)</b>
<b>Female</b>	<b>62 (34.6)</b>
<b>Type of gastrectomy</b>	
<b>Total</b>	<b>106 (59.2)</b>
<b>Subtotal</b>	<b>73 (40.8)</b>
<b>Location</b>	
<b>Upper</b>	<b>28 (15.6)</b>
<b>Middle</b>	<b>60 (33.5)</b>
<b>Lower</b>	<b>87 (48.6)</b>
<b>Diffuse</b>	<b>3 (1.7)</b>
<b>unknown</b>	<b>1 (0.6)</b>
<b>Borrmann type</b>	
<b>I</b>	<b>3 (1.7)</b>
<b>II</b>	<b>33 (18.4)</b>
<b>III</b>	<b>82 (45.8)</b>
<b>IV</b>	<b>60 (33.5)</b>
<b>unknown</b>	<b>1 (0.6)</b>
<b>Tumor size (cm)</b>	
<b>Median (range)</b>	<b>7 (2-20)</b>
<b>Depth of invasion</b>	
<b>T2</b>	<b>7 (3.9)</b>
<b>T3</b>	<b>161 (89.9)</b>
<b>T4</b>	<b>11 (6.2)</b>
<b>Adjuvant chemotherapy</b>	
<b>Yes</b>	<b>135 (75.4)</b>
<b>5-fluorouracil analogue*</b>	<b>20 (14.8)</b>
<b>Adriamycin-based</b>	<b>58 (43.0)</b>
<b>Cisplatin-based</b>	<b>40 (29.6)</b>
<b>Taxane-based</b>	<b>14 (10.4)</b>
<b>Unknown</b>	<b>3 (2.2)</b>
<b>No</b>	<b>10 (5.6)</b>
<b>Unavailable</b>	<b>34 (19.0)</b>

\*5-fluorouracil analogue, monotherapy of 5-fluorouracil analogue including UFT, furtulon, xeloda.

**Table 2. Patients characteristics by histology**

<b>Characteristics</b>	<b>Number of patients (%)</b>
<b>Histological type</b>	
Well/moderate differentiated	33 (18.4)
Poorly differentiated	107 (59.8)
Signet ring cell	29 (16.2)
Mucinous	10 (5.6)
<b>Lauren classification</b>	
Intestinal	26 (14.5)
Diffuse	44 (24.6)
Mixed	9 (5.0)
Unknown	100 (55.9)
<b>Lymphatic invasion</b>	
Negative	2 (1.1)
Positive	125 (69.8)
Unknown	52 (29.1)
<b>Vascular invasion</b>	
Negative	15 (8.4)
Positive	106 (59.2)
Unknown	58 (32.4)
<b>JCGC* node stage</b>	
N1	18 (10.1)
N2	84 (46.9)
N3	44 (24.6)
M	33 (18.4)
<b>Perigastric lymph nodes†</b>	
Yes	24 (13.4)
No	155 (86.6)
<b>Dissected lymph nodes</b>	
Median (range)	51.5 (26-108)
<b>Metastatic lymph nodes</b>	
Median (range)	22 (16-61)
<b>Metastatic lymph node ratio (%)</b>	
Median (range)	48.1 (19.4-98.3)

\*JCGC, Japanese Classification of Gastric Cancer

†Perigastric lymph nodes, includes Group 1 lymph nodes by JCGC

### **Evaluation for recurrence**

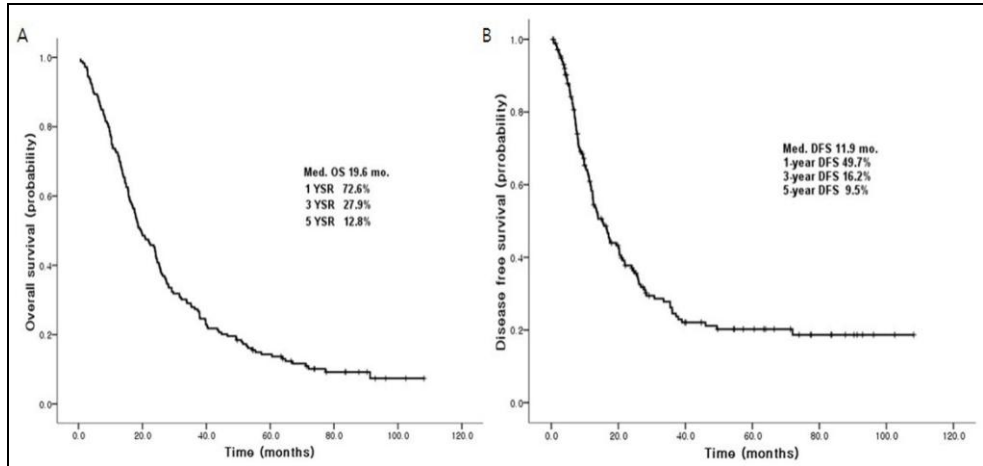
I investigated 179 patients to determine the recurrence rate and the pattern of recurrence. Among 179 patients, 123 patients (68.6%) had recurred. When I calculated the site of recurrence, the peritoneal recurrence (30.9%) was the most common. Meanwhile, when I calculated peritoneal metastasis combined with other metastases which were categorized as mixed group, peritoneal recurrence was 51% of recurrent patients. It was followed by locoregional recurrence (29.3%) and hematogenous recurrence (13%) (Table 3). Mixed pattern of recurrences had 5 subgroups. Peritoneal with locoregional recurrence and peritoneal with hematogenous recurrence were 62.5% and 15.6%, respectively. Also, locoregional with hematogenous recurrence without peritoneal recurrence was 15.6%. Only one patient (3.1%) had all type of recurrence pattern including peritoneal, hematogenous and locoregional recurrence. Then we evaluated the time to recurrence, 50.3% patients recurred within 1 year, suggesting the delayed recurrence after 5 years about 10%. Interestingly, among the patients with hematogenous recurrence, 81.2% of patients had recurred within 12 months, and all of patients had recurred within 24 months. Locoregional and peritoneal recurrences were occurred in less than 48 months. Patients with mixed pattern of recurrence had a similar pattern compare to peritoneal recurrence (Figure 2). Among 135 patients who received adjuvant chemotherapy, 103 patients (76.3%) had recurrence, while 5 patients (50%) out of 10 patients

without adjuvant chemotherapy had recurred. The overall 1-year, 3-year and 5-year disease free survival rate were 49.7%, 16.2% and 9.5%, respectively (Figure 1). The median time to recurrence, the time from operation to recurrence, was 11.9 months (range: 0.5 – 108.2 months). At last follow-up, 161 patients (89.9%) were dead of disease. When I calculated the time from recurrence to death, the median time was 6.5 months (range: 0.1 – 61.2 months). Sixty four percents of patients were dead within 1 year and 80.5% were dead within 2 years.

**Table 3. Recurrence pattern**

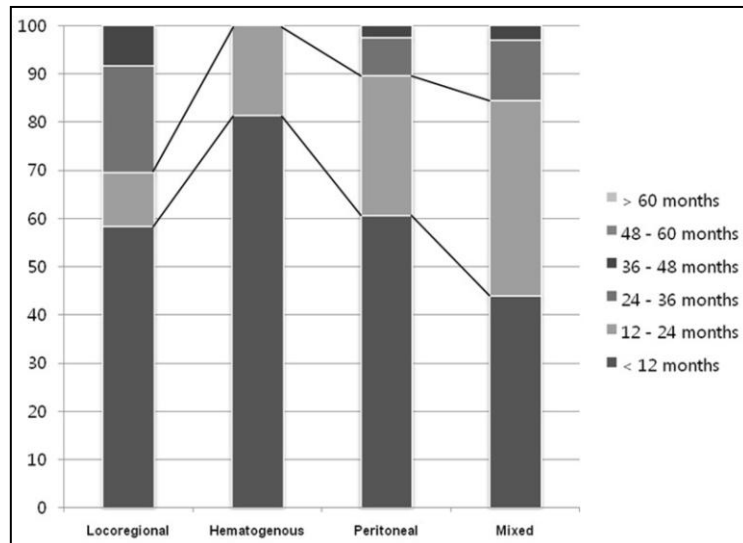
<b>Recurrence pattern</b>	<b>Number of patients (%)</b>
<b>Locoregional</b>	<b>36 (29.3)</b>
<b>Hematogenous</b>	<b>16 (13.0)</b>
<b>Peritoneal</b>	<b>38 (30.9)</b>
<b>Distant lymph node</b>	<b>1 (0.8)</b>
<b>Mixed</b>	<b>32 (26.0)</b>
<b>peritoneal + locoregional</b>	<b>20 (62.5)</b>
<b>peritoneal + hematogenous</b>	<b>5 (15.6)</b>
<b>peritoneal + distant LN</b>	<b>1 (3.1)</b>
<b>peritoneal + locoregional +           hematogenous</b>	<b>1 (3.1)</b>
<b>locoregional + hematogenous</b>	<b>5 (15.6)</b>

**Figure 1. Overall survival and disease free survival of pN3 gastric cancer patients**



**A. Overall survival of pN3 gastric cancer patients. Med. OS, median overall survival. mo., months. YSR, year overall survival rate. B. Disease free survival rate of pN3 gastric cancer patients. Med. DFS, median disease free survival. DFS, disease free survival rate.**

**Figure 2. Proportion of the time to recurrence by recur site**

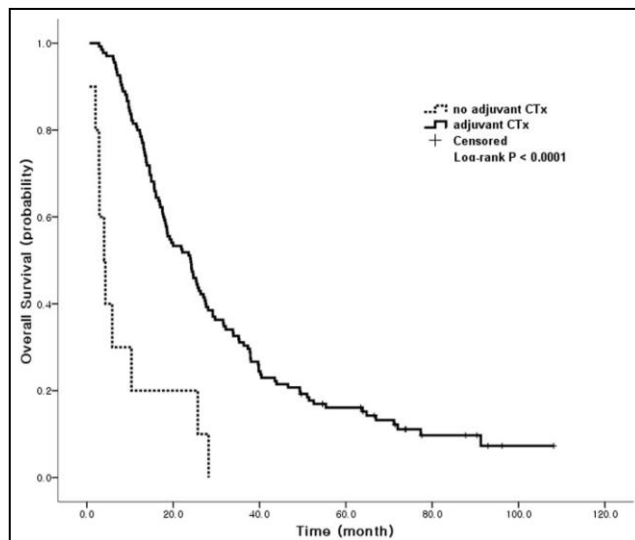


### **Survival analysis of pN3 stage gastric cancer patients**

With a median follow-up period of 19.6 months (range: 0.5 – 108.2 months), the median overall survival of all patients was 19.6 months (95% CI, 15.17 - 23.96). The 1-year, 3- year and 5-year overall survival rate were 72.6%, 27.9% and 12.8%, respectively. For the Borrmann type, advanced type including III and IV had a worse prognosis ( $p = 0.006$ ) and the median survival times for Borrmann type I, II and Borrmann type III, IV were 25.7 months (95% CI, 19.74 – 31.60) and 17.7 months (95% CI, 14.66 – 20.74), respectively. The patients who received adjuvant chemotherapy had a better prognosis ( $p < 0.0001$ ) compared to who didn't (Figure 3). The median survival time was 24.1 months (95% CI, 18.96 – 29.18) in the group with adjuvant chemotherapy. However, the median survival time in the group without adjuvant chemotherapy was 4 months (95% CI, 1.83 – 6.17).

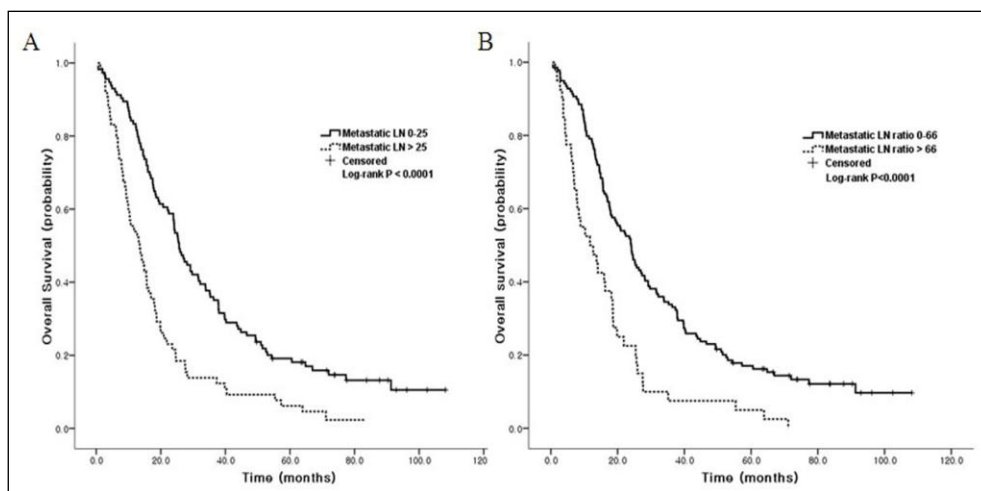
In order to determine the appropriate cutoff point of the number of metastatic lymph nodes, the log-rank test was performed to compare the differences in survival curves (Figure 4). There was a significant difference in surviving using a cutoff point of 25% (Table 4). For the metastatic lymph node ratio, a cutoff point was 66 (Figure 4, Table5).

**Figure 3. Overall survival in pN3 gastric patients by adjuvant chemotherapy**



CTx, chemotherapy

**Figure 4. Overall survival in pN3 gastric cancer patients by lymph node related parameters**



**(A) Overall survival by the number of metastatic lymph nodes, (B) Overall survival by the metastatic lymph node ratio (%)**



**Table 4. Overall survival by the numbers of metastatic lymph node**

Characteristics	Median survival time months (CI)	p-value*
<b>Metastatic lymph nodes</b>		<b>&lt; 0.0001</b>
16 - 20	25.3 (21.7 - 28.9)	
20 - 25	26.4 (19.8 - 32.9)	
25 - 30	15.7 (12.5 - 18.9)	
30 - 35	14.9 (11.1 - 11.8)	
> 35	9.7 (7.5 - 11.8)	
<b>Metastatic lymph nodes</b>		<b>&lt; 0.0001</b>
16 - 20	25.3 (21.7 - 28.9)	
20 - 30	22.1 (16.0 - 28.2)	
30 - 40	14.9 (10.2 - 19.6)	
> 40	8.4 (5.6 - 11.2)	
<b>Metastatic lymph nodes</b>		<b>&lt; 0.0001</b>
16 - 20	25.3 (21.7 - 28.9)	
20 - 25	26.4 (19.8 - 32.9)	
25 - 30	15.7 (12.5 - 18.9)	
30 - 40	14.9 (10.2 - 19.6)	
> 40	8.4 (5.6 - 24.0)	
<b>Metastatic lymph nodes</b>		<b>&lt; 0.0001</b>
16 - 25	25.7 (22.2 - 29.1)	
25 - 40	15.6 (12.0 - 19.3)	
> 40	8.4 (5.6 - 11.2)	
<b>Metastatic lymph nodes</b>		<b>&lt; 0.0001</b>
16 - 25	25.7 (22.2 - 29.1)	
> 25	13.5 (9.0 - 17.9)	

\*p-value calculated by log-rank test

**Table 5. Overall survival by the metastatic lymph node ratio**

Characteristics	Median survival time months (CI)	p-value*
Metastatic LN ratio (%)		< 0.0001
0 - 30	23.9 (6.5 - 41.4)	
30 - 50	24.3 (18.0 - 30.7)	
50 - 70	17.9 (13.6 - 22.3)	
70 - 100	11.7 (5.9 - 17.5)	
Metastatic LN ratio (%)		< 0.0001
0-30	23.9 (6.5 - 41.4)	
30-60	24.2 (20.4 - 28.0)	
60-100	12.7 (9.3 - 24.0)	
Metastatic LN ratio (%)		< 0.0001
0 - 33	29.7 (14.6 - 44.8)	
33 - 66	22.4 (16.8 - 28.1)	
66 - 100	11.7 (4.3 - 19.1)	
Metastatic LN ratio (%)		< 0.0001
0 - 66	24.1 (20.0 - 28.2)	
66 - 100	11.7 (4.3 - 19.1)	

\*p-value calculated by log-rank test

### **Prognostic factors for survival in patients with pN3 stage gastric cancer**

The median survival time according to the clinico-pathologic factors that were analyzed are summarized in table 6 and table 7. Also, the results of the multivariate analysis are shown in table 8. The factors influencing survival for the patients with pN3 stage disease were Bormann type ( $p=0.02$ ), adjuvant chemotherapy ( $p < 0.0001$ ) (Figure 3), the number of dissected lymph nodes ( $p=0.002$ ) and the ratio of metastatic lymph nodes ( $p=0.015$ ) (Figure 4). For all the patients, a multivariate analysis that including seven factors (age, sex,

Borrmann type, adjuvant chemotherapy, the number of dissected lymph nodes, the number of metastatic lymph nodes, and the metastatic lymph node ratio) from the univariate analysis showed that Borrmann type III and IV, the group without adjuvant chemotherapy after gastrectomy, the number of dissected lymph nodes, and the metastatic lymph node ratio were independent prognostic factors for survival (Table 8). Borrmann type III and IV had a higher hazard ratio than the Borrmann type I and II (hazard ratio: 1.79, 95 % CI, 1.12-2.86,  $p < 0.0001$ ). The hazard ratio for the group without adjuvant chemotherapy was 6.23 (95% CI, 3.08-12.62,  $p < 0.0001$ ). The patients who had the metastatic lymph node ratio between 66 and 100 showed a hazard ratio as 2.01 (95% CI, 1.15-3.53,  $p = 0.015$ ).

**Table 6. Univariate analysis for overall survival of pN3 gastric cancer patients**

Characteristics	Number of patients (%)	median survival time (months)	95% CI	p-value
Age (yr)				0.528
≤ 60	86 (48.0)	24.1	17.80 - 30.34	
> 60	93 (52.0)	17.9	14.24 - 21.63	
Sex				0.112
Male	117 (65.4)	22.1	17.51 - 26.69	
Female	62 (34.6)	16.6	13.16 - 20.04	
Type of gastrectomy				0.168
Total	106 (59.2)	17.5	14.36 - 20.64	
Subtotal	73 (40.8)	24.1	19.38 - 28.75	
Location				0.179
Upper	28 (15.6)	15.6	13.69 - 17.58	
Middle	60 (33.5)	24.6	14.10 - 35.10	
Lower	87 (48.6)	20.7	13.80 - 27.67	
Diffuse	3 (1.7)	24.2	5.76 - 42.57	
Borrmann type				0.006
I + II	36 (20.1)	25.7	19.74 - 31.60	
III + IV	142 (79.3)	17.7	14.66 - 20.74	
Tumor size (cm)				0.707
≤ 10	135 (75.4)	19.2	14.14 - 24.26	
> 10	44 (24.6)	19.6	12.60 - 26.54	
Depth of invasion				0.073
T2	7 (3.9)	39.8	39.54 - 40.06	
T3	161 (89.9)	19.6	14.89 - 24.25	
T4	11 (6.2)	18.5	12.74 - 24.32	
Adjuvant CTx†				< 0.0001
Yes	135 (75.4)	24.1	18.96 - 29.18	
No	10 (5.6)	4.0	1.83 - 6.17	

\*LN, lymph nodes

†CTx, chemotherapy

**Table 7. Univariate analysis for overall survival of pN3 gastric cancer patients (continued)**

Characteristics	Number of patients (%)	median survival time (months)	95% CI	p-value
<b>Histological type</b>				<b>0.075</b>
well, moderate differentiated	33 (18.4)	28.2	19.46 - 36.94	
others	146 (81.6)	17.9	14.28 - 21.59	
<b>Lauren classification</b>				<b>0.806</b>
intestinal	26 (14.5)	18.5	12.45 - 24.61	
diffuse	44 (24.6)	18.2	10.84 - 25.50	
mixed	9 (5.0)	16.9	16.02 - 17.78	
<b>Lymphatic invasion</b>				<b>0.153</b>
negative	2 (1.1)	27.6	.	
positive	125 (69.8)	17.9	14.61 - 21.13	
<b>Vascular invasion</b>				<b>0.624</b>
negative	15 (8.4)	25.4	11.33 - 39.53	
positive	106 (59.2)	17.5	14.03 - 21.04	
<b>JCGC* node stage</b>				<b>0.428</b>
N1	18 (10.1)	19.2	8.04 - 30.36	
N2	84 (46.9)	23.6	19.14 - 28.00	
N3	44 (24.6)	17.5	14.8 - 20.21	
M	33 (18.4)	14.9	9.72 - 20.08	
<b>Perigastric LN†</b>				<b>0.181</b>
Yes	23 (12.8)	24.1	9.20 - 38.94	
No	156 (87.2)	18.6	14.83 - 22.37	
<b>Metastatic LN‡</b>				<b>&lt; 0.0001</b>
16 - 25	114 (63.7)	25.7	22.24 - 29.10	
> 25	65 (36.3)	13.5	9.03 - 17.91	
<b>Dissected LN</b>				<b>0.024</b>
≤ 65	144 (80.4)	21.9	17.46 - 26.28	
> 65	35 (19.6)	14.5	11.09 - 17.97	
<b>Metastatic LN ratio (%)</b>				<b>&lt; 0.0001</b>
0 – 66	139 (77.7)	24.1	19.96 – 28.18	
66 - 100	40 (22.3)	11.7	4.26 - 19.14	

\*JCGC, Japanese Classification of Gastric Cancer

†Perigastric LN, perigastric lymph nodes included Group 1 lymph nodes by JCGC

‡LN, lymph nodes

**Table 8. Multivariate analysis for overall survival of pN3 gastric cancer patients**

<b>Variables</b>	<b>Hazard ratio</b>	<b>95% CI</b>	<b>p-value</b>
<b>Age</b>			<b>0.41</b>
≤ 60	<b>1.00</b>		
> 65	<b>1.19</b>	<b>0.79 - 1.79</b>	
<b>Sex</b>			<b>0.51</b>
Male	<b>1.00</b>		
Female	<b>1.13</b>	<b>0.78 - 1.66</b>	
<b>Borrmann type</b>			<b>0.02</b>
I + II	<b>1.00</b>		
III + IV	<b>1.79</b>	<b>1.12 - 2.86</b>	
<b>Adjuvant chemotherapy</b>			<b>&lt; 0.0001</b>
Yes	<b>1.00</b>		
No	<b>6.23</b>	<b>3.08 - 12.62</b>	
<b>Dissected LN*</b>			<b>0.002</b>
≤ 65	<b>1.00</b>		
> 65	<b>2.06</b>	<b>1.31- 3.26</b>	
<b>Metastatic LN</b>			<b>0.227</b>
16 - 25	<b>1.00</b>		
> 25	<b>1.32</b>	<b>0.84 - 2.07</b>	
<b>Metastatic LN ratio (%)</b>			<b>0.015</b>
0 - 66	<b>1.00</b>		
66 - 100	<b>2.01</b>	<b>1.15 - 3.53</b>	

\*LN, lymph nodes

#### IV. DISCUSSION

The prognosis of stage IV gastric cancer has been thought to be poor. The standard treatment of stage IV gastric cancer is systemic chemotherapy<sup>12</sup> and the benefits of surgery are controversial. Some study reported longer survival for patients with resected stage IV gastric cancer,<sup>13</sup> and the selected patients with acceptable risk should be considered for surgical resection even in stage IV gastric cancer.<sup>14</sup> In addition, Medina-Franco et al. have reported low surgical mortality and low morbidity rates when patients with stage IV gastric cancer undergo surgical resection.<sup>6</sup> As a radical resection is the standard of care for gastric cancer, most of gastric cancer patients who are resectable in the preoperative imaging studies undergo radical gastrectomy with a curative aim. However, some are classified into pathologic stage IV after the surgery due to their pN3 with or without distant metastasis, according to the sixth AJCC staging system.

The fifth edition of AJCC cancer staging system for gastric cancer is generally thought to be a good predictor for the prognosis. Compared to the fourth edition, the N3 stage is based on the number of positive metastatic lymph nodes, and TanyN3M0 and T4N1M0 are defined as stage IV in fifth edition. As a result of change, stage migration has been detected. Klein et al. reported that some of the node-positive patients changed to another N stage including a higher stage, as compared to the fourth edition.<sup>5</sup> In this study, fifth edition's of node stage was

suggested to be the most significant variable. Some studies have also reported the fifth edition of new classification for node stage showed more homogenous survival than the old classification.<sup>15</sup>

Some researchers have suggested that stage IV has heterogeneous prognoses for several groups of patients. Lin et al. reported that the patients with the N3 stage and who underwent palliative gastrectomy had much higher 1-year, 2-year survival rates than the patients who underwent operation without resection of stomach (by-pass or laparotomy exploration only). In Lin et al's study, the 1-year survival rate of the patients with N3 lymph node metastasis was 66.7%, which was comparable to my study of 72.6%.<sup>16</sup> Park et al. suggested sub-classifying stage IV gastric cancer into IVa (T1-3N3M0, T4N1-2M0) and IVb (T4N3M0, TanyNanyM1) for better prediction of survival.<sup>7</sup> Park et al. showed that the survival of the patients with T1-3N3M0 and T4N1-2M0 stage disease was significantly longer than that of patients with stage T4N3M0 and stage M1 disease. Li et al. divided stage IV gastric cancer into four groups in the same way.<sup>17</sup> In addition, An et al. reported on 1056 patients who were divided into three groups: T4N1M0, T1-3N3M0, and TanyNanyM1 stage group.<sup>18</sup> The patients with the T1-3N3M0 stage showed a better prognosis than the patients with T4N1-3M0 or TanyNanyM1 stage. These studies showed that the N3 stage without distant metastasis has a better prognosis than M1 stage.

Since these studies included all subgroups of stage IV, the current study was



focused on the pN3 gastric cancer patients without other systemic metastases. First of all, clinico-pathologic parameters and the survival of pN3 stage patients were evaluated. Then, the prognostic factors were evaluated. When I compared the clinico-pathologic parameters of pN3 only (pN3/M0) with pN3 combined with distant metastases (pN3/M1) in previous study, there was no differences.<sup>19</sup> However, the result showed that pN3 stage without distant metastasis showed the better survival with median survival time 19.2 months (95% CI, 14.9~23.4) compared to pN3 stage with M1 stage (10.7 months, 95% CI, 8.5~12.8), which is confirming that stage IV consists of heterogeneous groups. Therefore, I reviewed pN3 stage gastric patients in detail.

I started to analyze the recurrence pattern. It is similar to the results of a previous report. In D'Angelica et al. study, 68% of the patients had a recurrence involving a single area.<sup>11</sup> Of the 496 patients (42.3%) of whom had a recurrence, 28.1% involved distant sites, 25.9% involved locoregional sites, and 13.6% involved peritoneum. In my study, 74% had a recurrence in a single area. The peritoneal recurrence was the majority of the patients in my study. Although, there were differences in recurrence site, the majority of recurrence occurred within two years both in my study and in previous study, 72.1% and 79%, respectively. Especially, all of the hematogenous recurrence occurred within 2 years in current study. Also, some recurred after 5 years from the time of gastrectomy, suggesting that I should continuously follow the patients after

gastrectomy more than 5 years. Also, the results of the current study showed that the time from the recurrence to the death mainly occurred within 2 years after recurrence (80.5%). D'Angelica et al. reported that the median time from recurrence to death was 6 months which is about the same in our study.<sup>20</sup> So, it is important that the patients should need regular and consistent methods to detect the recurrence early, especially during six months after gastrectomy.

As I confirmed that the patients of pN3 stage gastric cancer had a heterogeneous pattern of recurrence, I considered that I need more specific predictors for poor prognoses among pN3 patients. Previous studies reported that node stage is the most significant prognostic factor.<sup>21, 22</sup> Since all of the patients in my study were diagnosed as same node stage, I was concerned about new prognostic factors which were related with detailed status of lymph nodes in same pN3 stage. Hence, I evaluated the number of dissected lymph nodes, the number of metastatic lymph nodes, and the metastatic lymph node ratio in order to evaluate their prognostic role. Kim et al. suggested that the metastatic lymph node ratio was the only valuable predictors for the long-term prognosis.<sup>23</sup> As Kim et al. reported, I also found that the metastatic lymph node ratio was a significant predictive factor for overall survival.

On the year of 2007, Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) reported the results that S-1 is effective adjuvant chemotherapy after radically gastrectomy for locally advanced gastric cancer.<sup>24</sup> A recent

meta-analysis reported that tegafur-based (mainly UFT) adjuvant chemotherapy for patients with curative aim of gastrectomy was significantly prolonged overall survival (HR: 0.75, 95% CI, 0.58 – 0.98,  $p = 0.037$ ).<sup>25</sup> The dissected lymph nodes also showed that the patients had a significantly different prognosis. I could consider that the extension of lymphadenectomy could effect on survival which is still controversial.<sup>24, 25</sup> I included adjuvant chemotherapy after curative resection as a predictive factor, although the majority of patients received adjuvant chemotherapy after gastrectomy due to being diagnosed as pN3 stage. The result of this study also showed that patients who received postoperative adjuvant chemotherapy had a prolongation of survival. But, I couldn't analyze by regimen of chemotherapy individually due to variability of regimen, so I only separate by the main regimen for description.

## V. CONCLUSION

In this current study, I suggested that gastric cancer patients staged as pN3 only without distant metastasis had a different prognosis by clinico-pathologic features, especially by metastatic lymph node ratio and adjuvant chemotherapy. These pN3 gastric cancer patients needed aggressive adjuvant chemotherapy after curative gastrectomy for better prognosis.

## REFERENCES

1. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol*. 2006;24:2137-50.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin*. 2005;55:74-108.
3. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin*. 2008;58:71-96.
4. Hartgrink HH, Putter H, Klein Kranenbarg E, Bonenkamp JJ, van de Velde CJ. Value of palliative resection in gastric cancer. *Br J Surg*. 2002;89:1438-43.
5. Klein Kranenbarg E, Hermans J, van Krieken JH, van de Velde CJ. Evaluation of the 5th edition of the TNM classification for gastric cancer: improved prognostic value. *Br J Cancer*. 2001;84:64-71.
6. Medina-Franco H, Contreras-Saldívar A, Ramos-De La Medina A, Palacios-Sanchez P, Cortés-González R, Ugarte JA-T. Surgery for stage IV gastric cancer. *Am J Surg*. 2004;187:543-6.
7. Park JM, Park SS, Mok YJ, Kim CS. pN3M0 gastric cancer: the category that allows the sub-classification of stage-IV gastric cancer (IVa and IVb). *Ann Surg Oncol*. 2007;14:2535-42.

8. Catalano V, Labianca R, Beretta GD, Gatta G, de Braud F, Van Cutsem E. Gastric cancer. *Crit Rev Oncol Hematol*. 2009;1287:1-38.
9. Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma - 2nd English Edition. *Gastric Cancer*. 1998;1:10-24.
10. Greene FL, Compton, CC, Fritz, AG, Shah, J, Winchester, DP (Eds). *AJCC cancer staging atlas*. Springer. 2006;9:352.
11. D'Angelica M, Gonen M, Brennan MF, Turnbull AD, Bains M, Karpeh MS. Patterns of initial recurrence in completely resected gastric adenocarcinoma. *Ann Surg*. 2004;240:808-16.
12. Wagner AD, Schneider PM, Fleig WE. The role of chemotherapy in patients with established gastric cancer. *Best Pract Res Clin Gastroenterol*. 2006;20:789-99.
13. Takeno S, Noguchi T, Kikuchi R, Sato T, Uchida Y, Yokoyama S. Analysis of the survival period in resectable stage IV gastric cancer. *Ann Surg Oncol*. 2001;8:215-21.
14. Lim S, Muhs BE, Marcus SG, Newman E, Berman RS, Hiotis SP. Results following resection for stage IV gastric cancer; are better outcomes observed in selected patient subgroups? *J Surg Oncol*. 2007;95:118-22.
15. Yoo CH, Noh SH, Kim YI, Min JS. Comparison of prognostic significance of nodal staging between old (4th edition) and new (5th edition) UICC TNM classification for gastric carcinoma. *International Union Against*

Cancer. World J Surg. 1999;23:492-7.

16. Lin SZ, Tong HF, You T, Yu YJ, Wu WJ, Chen C, et al. Palliative gastrectomy and chemotherapy for stage IV gastric cancer. J Cancer Res Clin Oncol. 2008;134:187-92.

17. Li C, Yan M, Chen J, Xiang M, Zuh ZG, Lin YZ. Prognostic influence of sub-stages according to pTNM categories in patients with stage IV gastric cancer. J Surg Oncol. 2009;99:324-8.

18. An JY, Ha TK, Noh JH, Sohn TS, Kim S. Proposal to subclassify stage IV gastric cancer into IVA, IVB, and IVM. Arch Surg. 2009;144:38-45

19. Ahn JR, Kim C, Hong MH, Chon HJ, Kim HR, Rha SY et al. Prognosis of pN3 stage gastric cancer. Cancer Res Treat. 2009;041(02):73-9.

20. Shiraishi N, Inomata M, Osawa N, Yasuda K, Adachi Y, Kitano S. Early and late recurrence after gastrectomy for gastric carcinoma. Univariate and multivariate analyses. Cancer. 2000;89:255-61.

21. Karpeh MS, Leon L, Klimstra D, Brennan MF. Lymph node staging in gastric cancer: is location more important than Number? An analysis of 1,038 patients. Ann Surg. 2000;232:362-71.

22. Aurello P, D'Angelo F, Rossi S, Bellagamba R, Cicchini C, Nigri G, et al. Classification of lymph node metastases from gastric cancer: comparison between N-site and N-number systems. Our experience and review of the literature. Am Surg. 2007;73:359-66.

23. Kim J, Cheong JH, Hyung WJ, Shen J, Choi SH, Noh SH. Predictors of long-term survival in pN3 gastric cancer patients. *J Surg Oncol.* 2004;88:9-13.
24. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto T, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med.* 2007;357:1810-20.
25. Oba K. Efficacy of adjuvant chemotherapy using tegafur-based regimen for curatively resected gastric cancer: update of a meta-analysis. *Int J Clin Oncol.* 2009;14:85-9.



< ABSTRACT(IN KOREAN)>

병리학적 N3 병기로 진단받은 위암 환자의 예후

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안정련

진행성 위암으로 4기를 진단 받은 환자들 중, 원격전이가 없고 N3 병기로 진단받은 환자들의 예후는 원격전이가 있는 환자들과 비교하여 예후가 다르다. 따라서, 위선암으로 진단받고 위 절제술을 시행한 환자군 중 병리학적 N3 병기로 진단받은 위암 환자들의 임상양상 및 예후를 평가하고, 임상병리학적 요인들에 따른 예후 인자를 찾아내고자 하였다.

연세의료원에서 2000년 1월부터 2004년 12월까지 병리학적으로 N3 병기로 진단받은 환자들을 후향적으로 분석하였다. 환자들의 의무기록을 재검토하여 이들 중 완치를 목적으로 위암 절제술과 D2/D3 림프절 절제술을 받았고, 복강내 전이, 간전이나 대동맥 림프절로의 전이를 포함한 원격전이가 없는 환자들을 대상으로 하였다. 연령, 성별, 종양의 위치, 위 절제술의 종류, 종양의 육안적

소견, 종양의 크기, 분화도, 침범의 깊이, Lauren 분류, 림프선 침범, 혈관 침범, 절제된 림프절의 수와 전이된 림프절, 그리고 절제된 림프절에 대한 전이된 림프절의 비(ratio), Japanese Classification of Gastric Cancer (JCGC)에 따른 림프절의 병기, 위 주변으로의 림프절 전이, 보조항암요법 등의 임상병리학적 요인을 분석하였고, 재발의 유무, 재발의 위치, 재발 시기 및 생존율을 확인하여 생존율과 관련이 있는 예후인자를 조사하였다.

위암 절제술을 받고 4기로 진단받은 환자들 467명 중 260명의 환자들이 완치 목적의 수술을 받았으며, 병리학적으로 N3 병기를 진단받았다. 이들 260명 중에서 179명이 원격전이가 없는 병리학적 N3 병기 환자들이었다. 연령은 16세부터 82세까지였고, 가장 호발한 부위는 위 하부였다(48.6%). 179명의 N3 병기 환자들 중에서 84명(46.9%)이 JCGC에 따라 N2 병기로 진단되었고, 18명(10.1%)이 N1 병기로 재분류되었다. 대다수의 환자들은 보조항암요법을 시행 받았고(75.4%), 재발은 123명(68.6%)의 환자들에게 있었으며, 가장 재발이 호발한 부위는 복강내 전이였다(30.9%). 수술 후 재발하기까지의 중앙 재발기간은 11.9개월(0.5-108.2개월)이었다. 3년 무병생존율과 5년 무병생존율은 각각 16.2%, 9.5%였으며, 중앙 생존기간은 19.6개월(0.5-108.2개월)이었으며, 3년 생존율과 5년

생존율은 각각 27.9%와 12.8%였다. 단변량 분석 결과에 따라 다변량 분석을 시행하여, Borrmann 형, 보조항암요법, 절제된 림프절의 수, 전이된 림프절에 대한 절제된 림프절의 비(ratio)가 의미 있는 예측인자임을 확인하였다.

결론적으로 위암 환자에서 원격전이가 없는 병리학적 N3 환자는 4기의 환자들 중에서도 임상병리학적 요인에 따른 다양한 예후를 가지고 있음을 확인하였다. 4기에 포함되는 환자들일지라도 원격전이가 없는 병리학적 N3 환자의 경우, 수술 후 보조항암요법의 치료를 진행함으로써 생존율을 높이는데 도움이 될 것이다.

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핵심되는 말 : 위암, pN3, 예후인자, 생존