Impact of near-infrared fluorescent lymphography guided lymphadenectomy on survival of gastric cancer patients

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ABSTRACT

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Purpose: Near-infrared fluorescent lymphography-guided lymphadenectomy using indocyanine green is gaining popularity with its potential of thorough lymphadenectomy, more lymph node (LN) harvests, and high sensitivity in detecting metastatic LNs. However, it is not known whether fluorescent lymphadenectomy affects the prognosis. This study1 aims to assess the prognostic impact of NIR lymphadenectomy on patients with gastric cancer.

Method: From 2013 to 2017, 3348 patients who underwent minimally invasive gastrectomy were retrospectively analyzed. Minimally invasive gastrectomy with systemic lymphadenectomy and retrieval of lymph nodes with or without near-infrared fluorescent lymphography after indocyanine green injection 1 day before surgery. NIR lymphadenectomy and conventional lymphadenectomy groups were analyzed after a 1:1 propensity score matching. The long-term prognostic impact of NIR lymphadenectomy was assessed by comparing overall survival between the two groups.

Result: After propensity score matching, 1066 patients in each group were similar in patients' demographics and clinicopathologic characteristics. Patients

in the fluorescent lymphadenectomy group (NIR group) showed significantly more LNs retrieved in all patients (56.0 vs. 43.3, $p<0.001$) as well as in both LN negative and positive patients (54.1 vs. 42.6, $p<0.001$ and 62.7 vs. 46.6, $p<0.001$, respectively) than those in conventional lymphadenectomy group (non-NIR group). The NIR group revealed significantly higher proportion of LN involvement ($p=0.038$) and resulted in significantly less proportion of stage I ($p=0.023$) than the non-NIR group by upstaging nodal classification. The NIR group showed better survival than the non-NIR group, although it was not statistically significant ($p=0.09$). However, the NIR group showed better survival ($p=0.04$) than the non-NIR group in stage I ($p=0.04$) and stage III ($p=0.26$) while there was no difference between the two groups in stage II ($p=0.67$).

Conclusion: Fluorescent lymphadenectomy demonstrated stage migration effect through more thorough LNs evaluation by retrieving more LNs and resulted in reduction of stage I patients' proportion through decreasing LN negative patients. The stage migration effect of fluorescent lymphadenectomy leads to better survival in stage I patients by classifying stage II patients who were staged as stage I with conventional lymphadenectomy.

Key words : gastric cancer, fluorescent lymphography, prognosis

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I. INTRODUCTION

Gastric cancer is a leading cause of cancer mortality worldwide.[1] Gastrectomy with systemic lymphadenectomy offers the best opportunity to cure for patients with localized gastric cancer.[2,3] It is known that sufficient lymphadenectomy enables adequate lymph node (LN) staging in the current TNM staging system and is also related to better oncologic outcomes.[4] Recent advances in lymphatic imaging using fluorescent have enabled easier and thorough lymphadenectomy during gastrectomy.[5-8] Fluorescent lymphography by injecting indocyanine green (ICG) under the near-infrared (NIR) imaging demonstrated more LN retrieval and detected metastatic LNs with high sensitivity with low negative predictive value.[9] However, the clinical and its oncological impact of more LN harvest and high sensitivity with the low negative predictive value of fluorescent lymphography-guided lymphadenectomy in gastric cancer patients is not explored yet.

The aim of this study was to examine the long-term oncological outcomes of fluorescent lymphography-guided lymphadenectomy in gastric cancer patients. We present the long-term oncological outcomes of fluorescent lymphography-guided lymphadenectomy in gastric cancer patients by comparing survival with conventional lymphadenectomy.

II. MATERIALS AND METHODS

Subjects and clinical analysis

A retrospective review of prospectively collected gastric cancer database identified 3348 patients who underwent robotic or laparoscopic gastrectomy between 2013 and 2017. The inclusion criteria were 1) patients with histologically proven gastric adenocarcinoma, 2) patients with a single primary lesion, and 3) patients with a clinical-stage of T1–4aN0–3M0. The exclusion criteria were 1) preoperative chemotherapy or radiation therapy for current gastric cancer, 2) R1 or R2 section, 3) open conversion, (4) incomplete information on clinical or pathologic features, or (5) surgical mortality. The following clinicopathologic characteristics were analyzed: age, sex, American Society of Anesthesiologists (ASA) score, clinical stage, resection method, the extent of dissection, histologic differentiation, tumor size, location, and pathologic information. This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System (4-2020-0082) which waived informed consent for the study because of the retrospective study nature.

Endoscopic ICG injection

From 2013 the day before surgery, 1.25mg/mL of Indocyanine Green (ICG, Dongindang Pharmaceutical Co.) diluted in distilled water as a fluorescent agent was injected peritumor during routine endoscopic preoperative examination. Since 0.6 mL of a 1.25mg/mL solution of ICG was injected into the submucosal layer near four points of primary gastric cancer, the total amount of ICG used was 3mg. However, the near-infrared(NIR) fluorescent signal was strong, the amount of ICG injection was gradually reduced. From 2015, we used 0.625mg/mL diluted solution, and the total amount of ICG used was 1.5mg. Our institution reported the feasibility of the preoperative peritumor ICG injection technique and studies using this technique. [5,7-9]

Operation

When performing laparoscopic surgery, a Pinpoint endoscopic fluorescent imaging system was used, and when robotic surgery was performed using a da Vinci Si or XI surgical system, we obtained near-infrared fluorescent imaging using Firefly mode. NIR fluorescent-guided lymphadenectomy was performed by switching between the general visible-light view and the NIR fluorescent view with a simple mode change, whether it is laparoscopic surgery or robotic. Depending on the location and clinical stage of the lesion, subtotal gastrectomy, total gastrectomy, or proximal gastrectomy was also carried out. According to the Korean practice guideline for gastric cancer, the D1+ area was dissected when node metastasis was not suspected in early gastric cancer, and the D2 area was dissected in patients with suspicion of node metastasis or advanced gastric cancer. NIR imaging was visualized before and after each lymph node(LN) station dissection, and it was confirmed that there were no remaining fluorescent LNs at each station, if any, additionally removed. When a fluorescent LN exists outside the originally planned dissection area, additional dissection was performed if it belonged to the D2 area, but the area outside D2 except 14v was not dissected.

Postoperative lymph node harvest

The specimens obtained after radical gastrectomy were first separated from soft tissue containing LN as defined by the LN station based on Japanese classification. Afterward, each LN station was checked whether it includes LNs contained fluorescence components using the NIR imaging function. LNs stained with fluorescent emitted ICG were classified as "fluorescent" LNs, and LNs were not stained as "non-fluorescent" LNs. Stations containing fluorescent LNs were classified as "fluorescent stations, and the others were classified as non-fluorescent stations. LNs and stations separated and classified by the surgeon were transferred to pathologists, and reexamination was performed.

Data collection

Pathologists performed pathologic examination on specimens separated by station, and nodal staging evaluation was performed on tissues classified as "fluorescent" or "non-fluorescent". In addition to the nodal staging examined in this way, various clinicopathologic features related to the patient and tumor were prospectively collected that underwent gastrectomy for gastric cancer at this institution. Patient features, tumor characteristics, surgical information, and pathologic features were recorded using various medical records. Patients were followed up to analyze overall survival until death or December 31, 2018, while 90-day surgical mortality was excluded. In order to check the patient's survival, not only the medical records of the hospital but the survey data of the National Statistical Office of Korea were used.

Statistical analysis

The group that underwent fluorescent lymphography-guided lymphadenectomy (NIR group) and the group that underwent conventional lymphadenectomy (non-NIR group) were compared and analyzed. Statistical analysis of the study was conducted using SPSS version 25 for window (IBM Corp. NY, USA) or R packages (survival and Matchit, Version 4.0.4, R foundation for statistical Computing, Vienna, Austria). Propensity score matching was applied with clinicopathologic features to minimize selection bias. Factors that can affect pathologic stage or long-term outcome were matched, and in detail, the caliper value was set to 0.1 for 1:1 matching using the nearest method adjusting the factors as follows; patients demographics (age, sex, BMI, ASA score), perioperative tumor characteristics (clinical T stage, clinical N stage, differentiation, tumor location, tumor size) and surgical extent(resection extent, LN dissection extent). Continuous variables were expressed using the mean and standard deviation or median value and interquartile range. An appropriate statistical analysis method was applied through the student's t-test or Mann

Whitney U test. For categorical variables, chi-square or Fisher exact test was used. Overall survival was evaluated using the Kaplan-Meier method, and No. at-risk was presented together. The log-rank test was performed to compare the overall survival of the two groups.

III. RESULTS

Patients' demographics

Among 3348 patients underwent laparoscopic or robotic gastrectomy for gastric cancer, 13 patients treated preoperative chemotherapy or chemoradiotherapy, and the other 13 patients were excluded because of stage T4b or M1 or because they underwent non-curative aimed resection. Twenty-six patients who received sentinel LN biopsy, D1 Lymph node dissection, or pylorus preserving gastrectomy were also excluded. Additionally, 21 open conversions, seven 90-day surgical mortalities, and six patients with incomplete clinicopathologic data or lacking in information for nodal classification were excluded. Finally, 3262 patients were analyzed after exclusion (Fig 1). There were 1079 patients in the NIR group whereas 2183 patients in the non-NIR group. When the perioperative clinicopathologic features of the two groups were compared, there were age differences (59.0 vs 57.0, $p < 0.001$) as well as resection extent ($p<0.001$), clinical nodal stage ($p=0.007$), and differentiation ($p=0.001$) (Table 1).

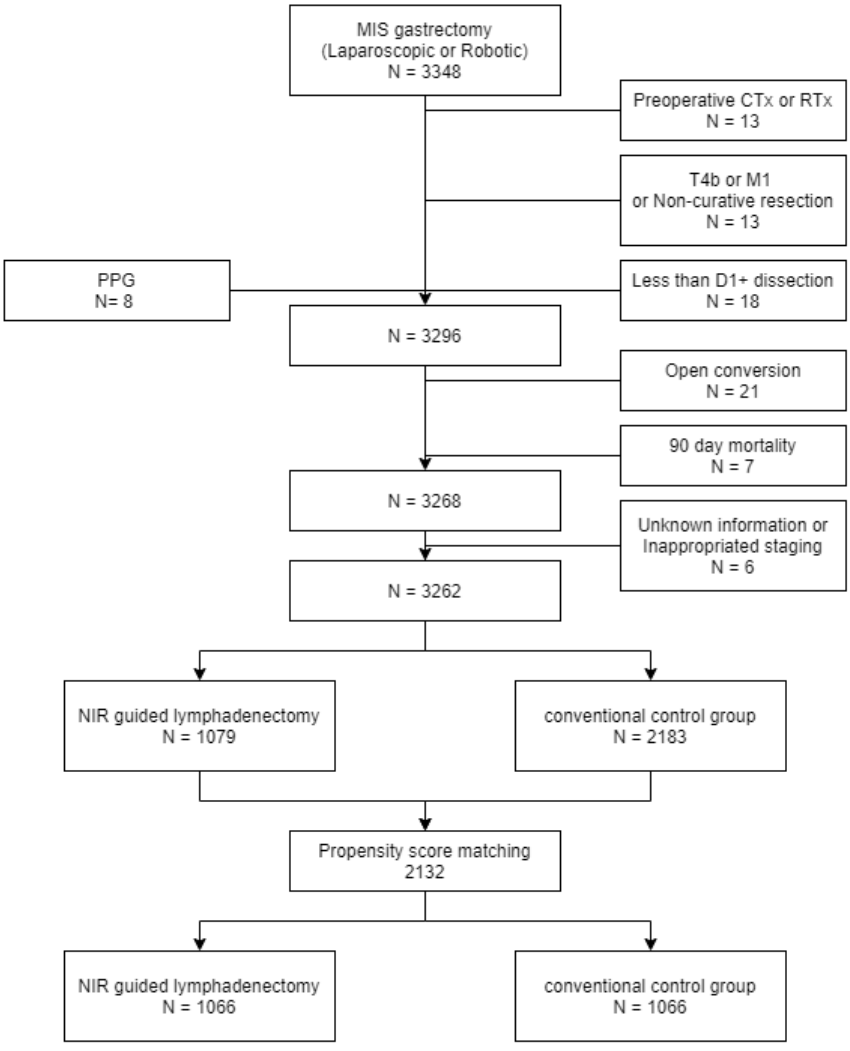

Figure 1. Study profile

Table 1. Clinico-pathologic feature between fluorescent guided lymphadenectomy group (NIR group) and conventional lymphadenectomy group(non-NIR group) before matching

	Unmatched		
	No. (%)		
Variable	Non-NIR group (n = 2183)	NIR group (n = 1079)	P value
Age, mean(SD), y	59.0 (12.2)	57.0 (12.4)	<.001
Sex			.34
Male	1312 (60.1)	629 (58.3)	
Female	871 (39.9)	450 (41.7)	
BMI, mean (SD), kg/m2	23.6 (3.1)	23.5 (3.1)	.29
ASA score			.34
1	459 (21.2)	255 (23.6)	
2	1203 (55.6)	594 (55.0)	
3	471 (21.8)	220 (20.4)	
4	30 (1.4)	11 (1.)	
cT			.12
cT1	1578 (72.3)	742 (68.8)	
cT2	428 (19.6)	251 (23.3)	
cT3	151 (6.9)	74 (6.9)	
cT4a	26 (1.2)	12 (1.1)	
cN			.007
cN0	1992 (88.0)	909 (84.2)	
cN1	232 (10.6)	146 (13.5)	
cN2	29 (1.3)	24 (2.2)	

Tumor size, mean (SD), mm	27.9 (19.5)	29.4 (20.8)	.04
Location			.08
LC	845 (38.7)	365 (33.8)	
GC	381(17.5)	205 (19.0)	
AW	429 (19.7)	222 (20.6)	
PW	516 (23.6)	283 (26.2)	
Circumferential	12 (0.5)	4 (0.4)	
Differentiation			.001
Differentiated	940 (43.1)	394 (36.5)	
Undifferentiated	1169 (53.6)	650 (60.2)	
Other	74 (3.4)	35 (3.2)	
Resection			<.001
STG	1799 (82.4)	865 (80.2)	
TG	296 (13.6)	136 (12.6)	
PG	88 (4.0)	78 (7.2)	
Dissection			.24
D1+	1496 (68.5)	717 (66.5)	
D2	687 (31.5)	362 (33.5)	
No. retrieved LN, median (IQR), No	40 (30-53)	53 (42-67)	<.001
Mean(SD), No	42.7 (17.2)	56.2 (20.1)	<.001
pT			<.001
pT1a	966 (44.3)	439 (40.6)	
pT1b	775 (35.5)	359 (33.2)	
pT2	191 (8.7)	102 (9.4)	
pT3	141 (6.5)	112 (10.4)	
pT4	110 (5.)	68 (6.3)	

pN			.001
pN0	1805 (82.7)	837 (77.6)	
pN1	199 (9.1)	111 (10.3)	
pN2	104 (4.8)	65 (6.0)	
pN3	75 (3.4)	67 (6.2)	
Stage(AJCC 8th)			<.001
Stage I	1822 (83.5)	831 (77.0)	
Stage II	221 (10.1)	141 (13.1)	
Stage III	140 (6.4)	107 (9.9)	

Abbreviations: NIR, near-infrared; SD, standard deviation; BMI, body mass index; ASA, American Society of Anesthesiologists; LC, lesser curvature; GC, greater curvature; AW, anterior wall; PW, posterior wall; STG, subtotal gastrectomy; TG, total gastrectomy; PG, proximal gastrectomy; LN, lymph node; IQR, interquartile rage; AJCC, American Joint Committee on Cancer.

$\chi 2$ tests were used to evaluate for categorical variables, and Mann Whitney U test was used for continuous variables.

propensity score matching

After 1:1 propensity score matching, 1066 patients in each group were included in the final analysis (Fig 1). There was no significant difference between the two groups in terms of the patient's basic characteristics (Table 2). The two groups were well balanced in preoperative tumor characteristics, clinical stage, and the extent of surgical resection and lymphadenectomy.

Table2. Clinical feature between NIR group and non-NIR group after propensity score matching

	Propensity score matched		
	No. (%)		
Variable*	Non-NIR group (n = 1066)	NIR group (n = 1066)	P value
Age*, mean(SD), y	57.2 (12.4)	57.1 (12.3)	.99
Sex*			.90
Male	627 (58.8)	623 (58.4)	
Female	439 (41.2)	443 (41.6)	
BMI*, mean (SD), kg/m2	23.5 (3.1)	23.5 (3.1)	.71
ASA score*			.83
1	237 (22.2)	251 (23.5)	
2	607 (56.9)	586 (55.0)	
3	212 (19.9)	219 (20.5)	
4	10 (0.9)	11 (1.0)	
cT*			.23
cT1	758 (71.1)	739 (69.3)	
cT2	213 (20.0)	245 (23.0)	
cT3	80 (7.5)	73 (6.8)	
cT4a	15 (1.4)	9 (0.8)	
cN*			.89
cN0	909 (85.3)	9.7 (85.1)	
cN1	138 (12.9)	137 (12.9)	
cN2	19 (1.8)	22 (2.1)	

Tumor size*, mean (SD), mm	28.3 (19.7)	28.9 (19.5)	.48
Location*			.44
LC	378 (35.5)	362 (34.0)	
GC	185 (17.4)	205 (19.2)	
AW	207 (19.4)	221 (20.7)	
PW	289 (27.1)	275 (25.8)	
Circumferential	7 (0.7)	3 (0.3)	
Differentiation*			.31
Differentiated	420 (39.4)	394 (37.0)	
Undifferentiated	606 (56.8)	639 (59.9)	
Other	40 (3.8)	33 (3.1)	
Resection*			.06
STG	838 (78.6)	862 (80.9)	
TG	165 (56.8)	129 (12.1)	
PG	63 (5.9)	75 (7.0)	
Dissection*			.96
D1+	716 (67.2)	714 (67.0)	
D2	350 (32.8)	352 (33.)	

*Matched variables

Stage migration

Table 3 shows the pathologic distribution between two groups after propensity score matching.NIR group showed significantly more LNs in all patients (56.0 vs. 43.3, p<0.001) as well as in both LN negative and positive patients (54.1 vs. 42.6, p<0.001 and 62.7 vs 46.6, p<0.001, respectively). The pathologic nodal stage distribution differed when the pathologic examination results between the two groups were compared. The nodal stage of the NIR group tended to be more advanced, and the proportion of node-negative patients was smaller than the non-NIR group (Figure 1). There were 829 (77.8%) node-negative patients and 237 (22.2%) node-positive in NIR group. In the non -NIR, there were 871 (81.7%) node-negative patients and 195(18.3%) node-positive patients. In addition, as the node stage distribution changed, the pathological stage distribution according to the AJCC 8th edition also showed stage migration effect that the NIR group showed a more progressive tendency than the non-NIR group. The proportion of Stage I decreased (77.5% vs 82.2%) in the NIR group compared to the non-NIR group, and the proportion of Stage III increased (9.6% vs 7.1%). Figure 2 shows described stage migration effect (Fig 2.)

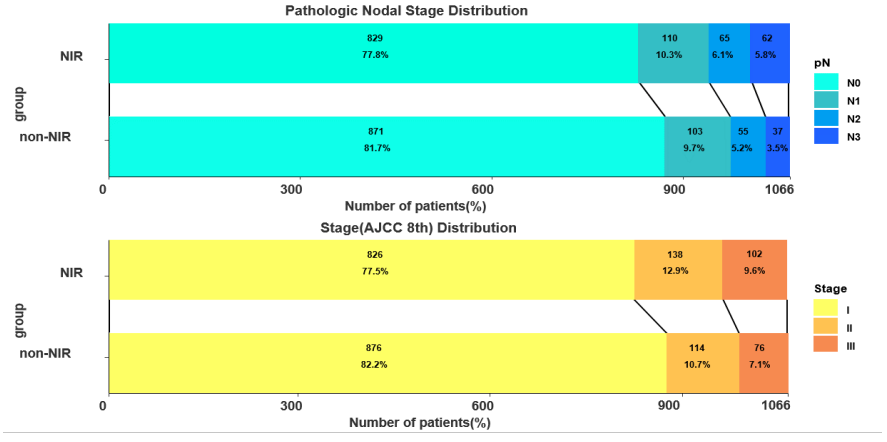

Figure 2. Pathologic nodal stage and AJCC 8th stage distribution between NIR group and non-NIR group

Table 3. Pathologic distribution between NIR and non-NIR group after propensity score matching

	Propensity score matched		
	No. (%)		
Variable	Non-NIR group (n = 1066)	NIR group (n = 1066)	P value
No. retrieved LN, median (IQR), No	41 (31-53)	53 (42-67)	<0.001
pT			.10
pT1a	441 (41.4)	438 (41.1)	
pT1b	391 (36.7)	354 (33.2)	
pT2	94 (8.8)	102 (9.6)	
pT3	74 (6.9)	106 (9.9)	
pT4	66 (6.2)	66 (6.2)	
pN			
pN0	871 (81.7)	829 (77.8)	.04
pN1	103 (9.7)	110 (10.3)	
pN2	55 (5.2)	65 (6.1)	
pN3	37 (3.5)	62 (5.8)	
Stage(AJCC 8th)			.02
Stage I	876 (82.2)	826 (77.5)	
Stage II	114 (10.7)	138 (12.9)	
Stage III	76 (7.1)	102 (9.6)	

Survival

When comparing the survival between two groups in all patients (Fig 3), the NIR group showed a better survival although there was no statistical significance (p=0.09). When survival was compared after stratification of the pathologic stages to investigate the stage migration effect of the fluorescent lymphadenectomy, stage I (Fig 4) patients in the NIR group showed a better survival (p=0.04) than those in the non-NIR group. In stage III (Fig 6), a better survival was demonstrated in the NIR group than in the non-NIR group, although it was not statistically significant (p=0.26). There was no survival difference between the two groups in stage II (p=0.67) (Fig 5).

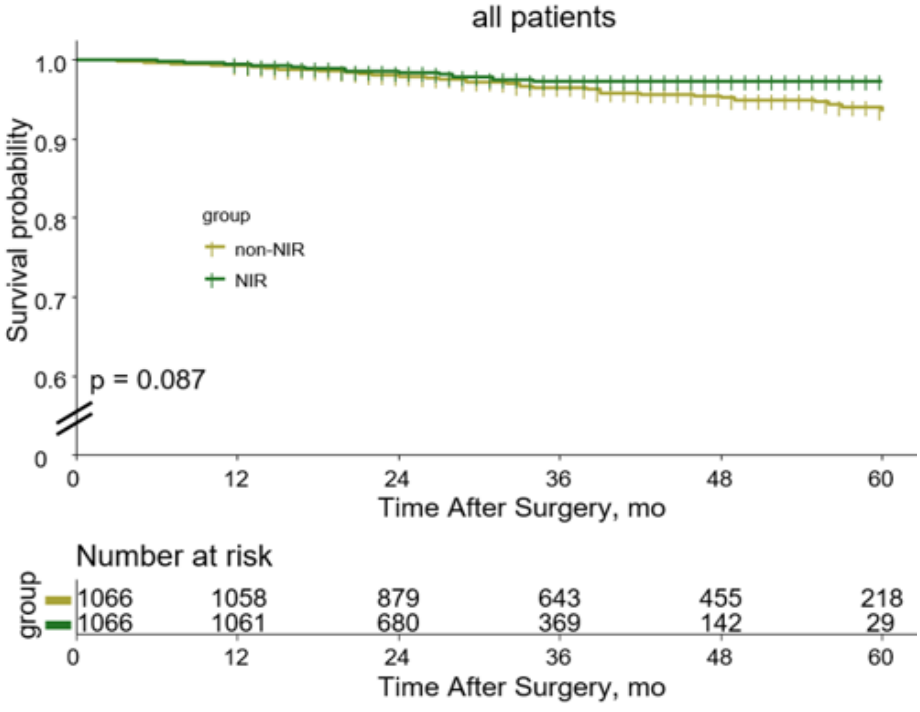

Figure 3. Kaplan-Meier survival curve between NIR group and non-NIR group

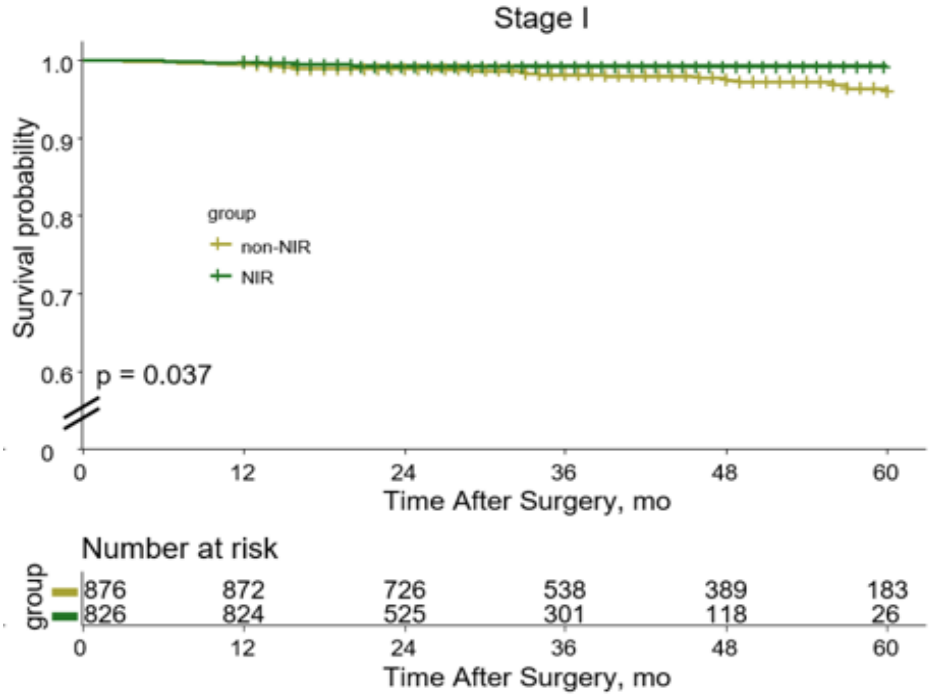

Figure 4. Kaplan-Meier survival curve between NIR group and non-NIR group in Stage I patients

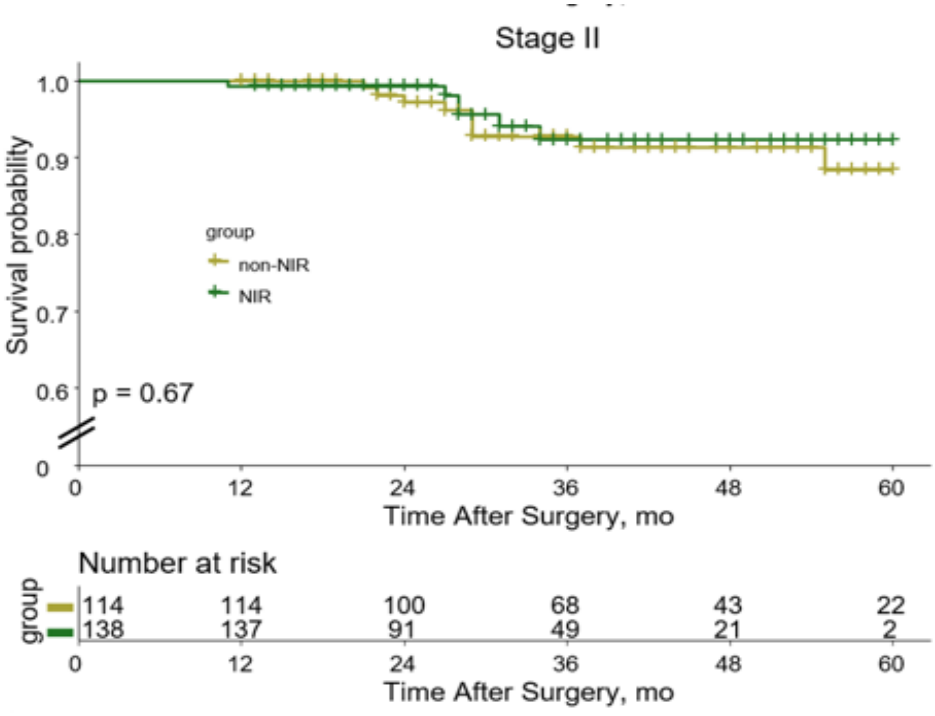

Figure 5. Kaplan-Meier survival curve between NIR group and non-NIR group in Stage II patients

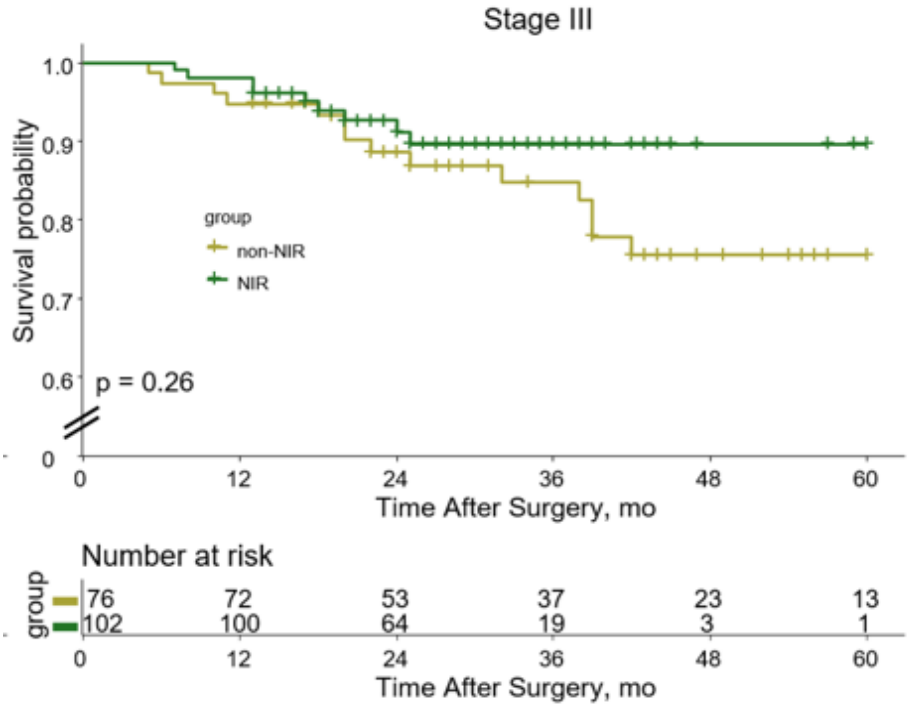

Figure 6. Kaplan-Meier survival curve between NIR group and non-NIR group in Stage III patients

IV. DISCUSSION

Compared to the non-NIR group, the NIR group showed more retrieved LNs regardless of node positivity. In addition, the NIR group reported a lower proportion of node-negative patients and Stage I patients and a larger ratio of node-positive patients and Stage III patients than the non-NIR group. In terms of survival analysis, the Nir group showed significantly better long-term outcomes in Stage I patients. Besides, in stage 3 patients also resulted in better long-term survival follow-up despite marginal p-value.

These data demonstrated the stage migration effect of NIR lymphadenectomy in comparison with conventional lymphadenectomy. Thorough lymphadenectomy and examination with high metastatic LN detection sensitivity enable not only to retrieve the larger number of LNs but to result in nodal stage migration. The NIR group revealed a more progressive nodal stage and significantly less proportion of N0 and stage 1 patient than in the non-NIR group by upstaging nodal classification. This result implies that some proportion of node-negative patients who carried out conventional lymphadenectomy could become node-positive patients if they had undergone fluorescent lymphadenectomy Similar to the AJCC stage, some Stage I patients in the non-NIR group would have been diagnosed as Stage II if patients had carried out fluorescent lymphadenectomy. Considering that the NIR group shows a higher proportion of Stage III in the NIR group, we could presume that stage migration occurred between Stage II and Stage III with a similar mechanism.

The stage migration effect of fluorescent lymphadenectomy may lead to better survival in stage I patients by classifying stage II patients staged as stage I with conventional lymphadenectomy. In Stage III, on the contrary, we can explain that better survival in the NIR group may include patients who would have been stage II.

Limitation

This study has limitations in addition to the retrospective study nature. Although ICG fluorescent imaging technique has high sensitivity and negative predictive value for metastatic LN detection, but low specificity. Since ICG is not tumor-specific, if a tumor-specific tracer is developed, it is expected that the imaging-guided technique will bring better oncologic outcomes for radical cancer surgery. Secondly, we did not evaluate micrometastasis using immunohistochemistry for confirming node metastasis. As a future study, we plan to re-examine micrometastasis in the fluorescent enhancement status.

V. CONCLUSION

Fluorescent lymphadenectomy retrieved more LNs, showing a stage migration effect with a more thorough LN dissection and examination, and reduced the proportion of stage I patients by reducing LN-negative patients. The stage migration effect of fluorescent lymphadenectomy results in better survival in stage I patients by classifying stage II patients diagnosed as stage I with conventional lymphadenectomy.

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ABSTRACT(IN KOREAN)

근적외선 형광 림프조영술 유도 림프절절제술이 위암 환자 예후에 미치는 영향

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목적: 인도시아닌그린(ICG)를 이용한 근적외선 형광 림프 조영술 보조 림프절절제술은 철저한 림프절절제술을 가능하게 하고, 더 많은 림프절을 구득할 수 있게 하며, 전이 림프절을 찾는데 있어 높은 민감도를 가지므로 점점 많이 이용되고 있다. 하지만 형광 보조 림프절절제술이 예후에 어떤 영향을 미치는지는 알려진 바가 없다. 본 연구의 목적은 근적외선 형광 보조 림프절절제술이 위암 환자의 예후에 어떤 영향을 미치는지 알아 보는 것이다.

방법: 2013년부터 2017년까지 최소침습위절제술을 받은 3348명의 환자를 후향적으로 분석하였다. 근적외선 형광 보조 림프절절제술을 사용한 경우 수술 1일전 내시경적으로 인도시아닌그린(ICG)을 종양 주위 점막하조직에 주입하였다. 근적외선 형광 보조 림프절절제술을 시행한 환자와 그렇지 않은 대조군을 1:1 성향 점수 매칭 후 비교 분석하였다. 전체생존기간을 두 그룹에서 비교하여 근적외적 형광 보조 림프절절제술의 장기간 종양학적 예후 영향을 확인하였다.

결과: 성향 점수 매칭 후, 각 그룹의 1066명의 환자에서 임상병리학적 특성을 비교하였을 때, 두 그룹의 차이는 없었다. 근적외선 형광 림프

조영술 보조 림프절절제술을 시행한 그룹(근적외선 그룹)에서 대조군에 비해서 전체 환자(56.0 vs. 43.3, p<0.001), 뿐만 아니라 림프절 전이 음성 및 양성 환자에서도 더 많은 림프절을 구득 할 수 있었다(54.1 vs. 42.6, p<0.001, 62.7 vs. 46.6, p<0.001, 각각). 근적외선 그룹에서 림프절 전이 양성 환자의 비율이 더 높았으며(p=0.038), 따라서 1기 환자의 비율은 더 적었다(p=0.023). 통계학적으로 유의미하지는 않았지만(p=0.09) 전체 환자에서 근적외선 그룹이 대조군에 비해서 더 좋은 생존률을 보였다. 1기와(p=0.04) 3기환자(p=0.26)에서 근적외선 그룹이 대조군에 비해서 높은 생존률을 보였으며, 1기에서는 통계적으로 유의미한 결과를 보였다.

결론 : 근적외선 형광 보조 림프절절제술은 철저한 림프절절제술을 통해 림프절 구득을 더 많이 할 수 있게 하며, 림프절병기에 있어 병기이동효과를 나타내었다. 형광보조 림프절절제술을 하지 않았다면 1기였을 환자를 형광보조 림프절절제술이 2기로 진단하게 하여, 같은 1기에서 형광보조 림프절절제술이 더 좋은 생존률을 보였다. 형광 보조 림프절절제술은 위암 환자를 예후 분석할 때 더 정확히 병기 분류를 하는데 도움을 줄 수 있다.

핵심되는 말 : 위암, 근적외선 형광 림프절조영술, 예후 분석