BMC Cancer

RESEARCH Open Access

Refining gastric cancer staging: examining the interplay between number and anatomical location of metastatic lymph nodes - a retrospective multi-institutional study

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Abstract

Background The current gastric cancer staging system relies on the number of metastatic lymph nodes (MLNs) for nodal stage determination. However, incorporating additional information such as topographic status may help address uncertainties. This study evaluated the appropriateness of the current staging system and relative significance of MLNs based on their anatomical location.

Methods Patients who underwent curative gastrectomy for gastric cancer between 2000 and 2019 at six Catholic Medical Center-affiliated hospitals were included. Lymph node-positive patients were classified into the perigastric (stations 1–6, group P) or extragastric (stations 7–12) groups. The extragastric group was further subdivided into the near-extragastric (stations 7–9, group NE) and far-extragastric (stations 10–12, group FE) groups.

Results We analyzed the data of 3,591 patients with positive lymph node metastases. No significant survival differences were found between group P and the extragastric group in each N stage. However, in N1 and N2, group FE showed significantly worse survival than the other groups ($p = 0.013$ for N1, $p < 0.001$ for N2), but not in N3. In the subgroup analysis, group FE had a significantly lower overall survival in N2, regardless of the cancer location.

Conclusions Our large-scale multi-institutional big data analysis confirmed the superiority of the current numerical nodal staging system for gastric cancer. Nonetheless, in N1 and N2 in which there is an upper limit on metastatic nodes, attention should be paid to the potential significance of topographic information for specific nodal stations.

Keywords TNM, Staging system, Gastric cancer, Nodal stage, Metastatic lymph nodes stomach neoplasms, Gastrectomy, Lymph node excision

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Introduction

Gastric cancer (GC) remains a significant public health problem worldwide as it is ranked fifth for incidence and fourth for mortality worldwide. GC accounted for over one million new cases and 769,000 deaths in 2020 [1]. In Korea, there is a marked decline in the incidence of GC and an increasing prevalence in early GC [2]. Nevertheless, curative gastrectomy and postoperative adjuvant chemotherapy are considered the mainstay of treatment for GC [3].

The Tumor–Node–Metastasis (TNM) staging system is used to evaluate the prognosis of patients with GC and to determine optimal treatment options based on disease severity [4]. Particularly, the intelligibility and conciseness of the numeric N stage have been improved to provide a more convenient means of predicting prognosis and making objective comparisons with previous anatomical-based classifications [5–8]. Although previous studies have reported the prognostic superiority of the numeric N system over the topographical system in GC [9], it has some limitations: uncertain cut-offs for the optimal N stage, insufficient anatomical information regarding the extent of lymph node metastasis (LNM), and the surgical extent of lymphadenectomy. Additionally, the current system proves disadvantageous as it does not reflect the complexity and multidirectional structure of the perigastric lymphatic drainage pathways [10].

Therefore, using a large-scale dataset, we investigated the appropriateness of the current nodal staging system based on the number of metastatic lymph nodes (MLNs). Moreover, by considering the relative significance of MLNs according to location, we aimed to identify ways to address the limitations of the current staging system and enhance the prognostic performance through a comprehensive big data analysis.

Materials and methods

Patient population and data collection

In total, 13,860 patients who underwent curative gastrectomy with lymphadenectomy for GC between January 2000 and December 2019 at six hospitals affiliated to the Catholic Medical Center in Korea were recruited: Seoul St. Mary's Hospital (n=6,591), St. Vincent's Hospital (n=1,524), Incheon St. Mary's Hospital (n=1,437), Bucheon St. Mary's Hospital (n=956), Yeouido St. Mary's Hospital (n=764), and Uijeongbu St. Mary's Hospital (n=634). The inclusion criteria were as follows: primary GC, no other malignancy, no preoperative chemotherapy, no distant metastasis, R0 resection (no residual macroscopic or microscopic tumor), regular outpatient follow-up without disease, and complete data. Patients with missing operative and/or follow-up data were excluded. Finally, 10,772 patients were enrolled. The enrollment process is shown in Fig. 1.

Surgical details and follow-up

Surgeons specializing in GC performed all surgeries based on the Korean and Japanese guidelines for Gastric Cancer [11, 12]. Patient demographic data were also collected. Preoperative clinical characteristics and postoperative complications were classified using the Eastern Cooperative Oncology Group [13] and Clavien–Dindo criteria [14]. Histological staging was performed according to the 8th American Joint Committee on Cancer TNM guidelines [15]. Histological types were categorized as differentiated or undifferentiated. Poorly differentiated tubular and signet ring cells and mucinous adenocarcinomas were considered undifferentiated. Regular follow-ups were scheduled at 3- and 6-month intervals for patients with advanced and early GC, respectively, for the first 3 years, and every 12 months thereafter. At each follow-up, tumor marker levels were measured, and abdominal computed tomography and endoscopy were performed. The observation period was defined as the time from the date of surgery to the time of death or loss to follow-up, whichever occurred first. Overall survival (OS) was calculated from the date of primary gastrectomy to the date of death from any cause or at the time of the last follow-up.

Histopathological analysis and categorization of metastatic lymph nodes according to anatomical regions

The specimens were removed via en bloc dissection. Each lymph node (LN) was accurately mapped and harvested either intraoperatively or immediately after surgery via back-table dissection. Histological evaluation was performed by gastrointestinal neoplasia specialists; they providing detailed pathological results according to LN stations.

The pathological findings were used to classify the MLNs. The MLNs were first categorized into the perigastric (group P) and extragastric groups. The extragastric groups were further divided into the near-extragastric (NE) and far-extragastric (FE) groups, altering the previous classification of LN tiers [16, 17] (Fig. 2). Group P had LNMs in the perigastric region (station No. 1, 2, 3, 4, 5, and 6). Group NE included LNMs near the celiac axis (No. 7, 8a, and 9). Finally, group FE comprised stations 10, 11, and 12.

Statistical analysis

Kaplan–Meier analysis was performed to evaluate OS. Survival data are presented as mean patient survival, as it was not always possible to calculate the median survival. Continuous values are presented as means with standard deviations; they were compared using the Student's t-test. Categorical variables were compared using the chi-square or Fisher's exact test (as appropriate). Statistical significance was set at $p<0.05$. 3. All analyses were

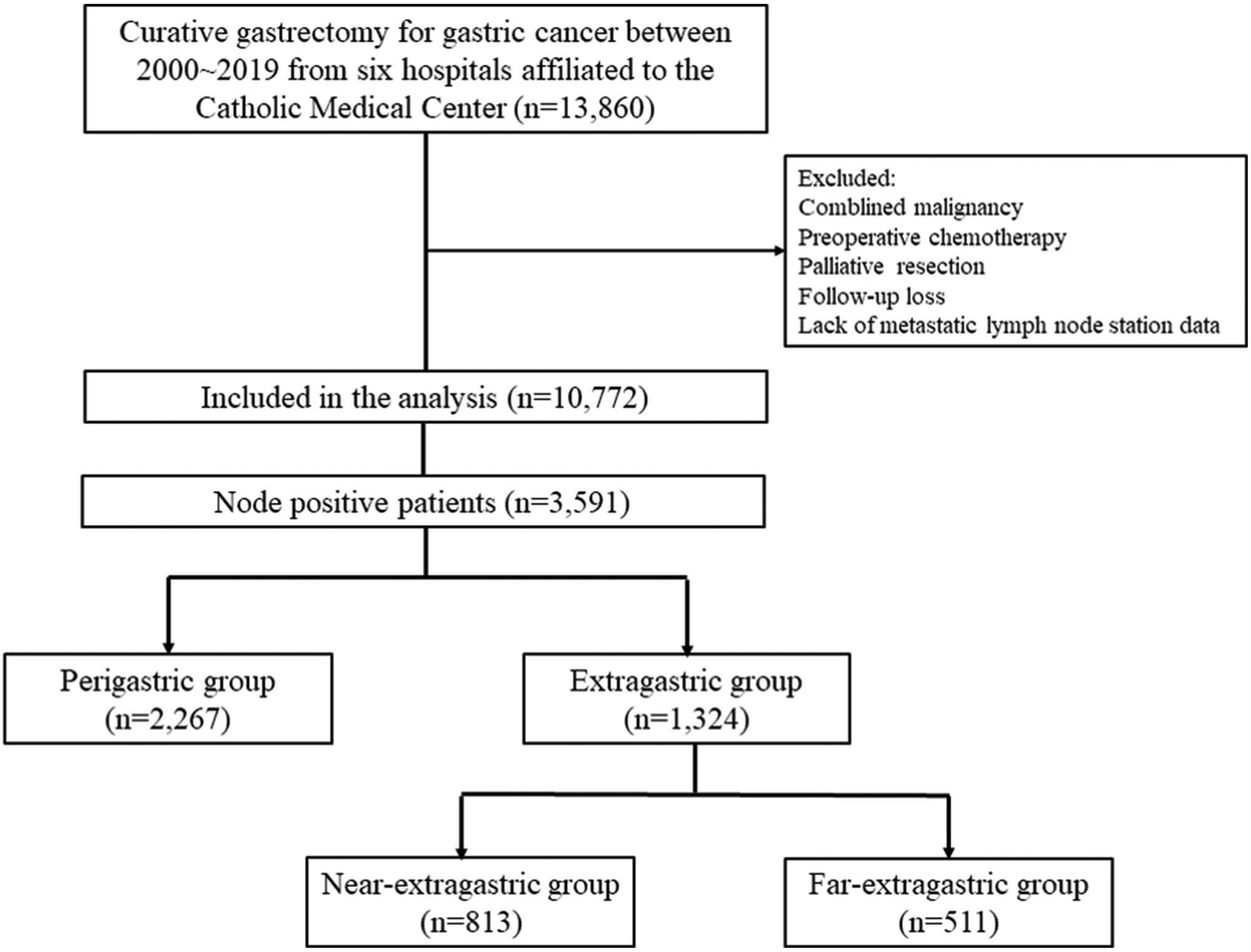

Fig. 1 Flowchart depicting the patient enrollment process of the study cohort

performed using SPSS ver. 24.0 for Windows (IBM Corp., Armonk, NY, USA).

Results

Patient demographic and clinicopathological characteristics

The patients' clinicopathological characteristics are shown in Table 1. The total cohort consisted of 7,181 (66.7%) male individuals, with a mean age of 61.16±11.95 years, and a mean body mass index (BMI) of 23.68±3.31 kg/m^2. Of the 10,772 patients, 2,449 (22.7%) underwent total gastrectomy, 6,880 (63.9%) underwent D2 or higher lymphadenectomy, and 3,591 (33.3%) had with node-positive disease. OS was compared according to pathological stage and revealed a decline in survival with increasing disease severity (Supplementary Fig. 1).

Compared with the total patient group, node-positive patients had a higher proportion of individuals aged 65 years or older, a greater prevalence of patients with a poor performance status, and a lower average BMI. Additionally, these patients underwent more invasive surgeries and radical lymphadenectomies (beyond D2), and had a higher proportion of total gastrectomy cases than in the total cohort. Notably, the node-positive subgroup exhibited a significantly higher disease severity. The sex distribution was comparable between the groups (Table 1).

Comparison of survival according to anatomic location of lymph node metastases

Comparison of survival between the perigastric and extragastric lymph node metastasis groups across nodal stages

OS was compared between group P and the extragastric groups according to the N stage; there was no significant difference in 5-year survival rates (5YOS) at different nodal stages. In N1, the 5YOS in group P and extragastric groups was 82.4% and 75.5%, respectively, with no significant disparity (*P=0.091*). Similar findings were observed in N2 (65.0 vs. 64.3, *P=0.162*), N3a (55.0 vs. 49.4, *P=0.136*) and N3b (33.9 vs. 25.9, *P=0.690*). Therefore, in each N stage, there was no significant difference

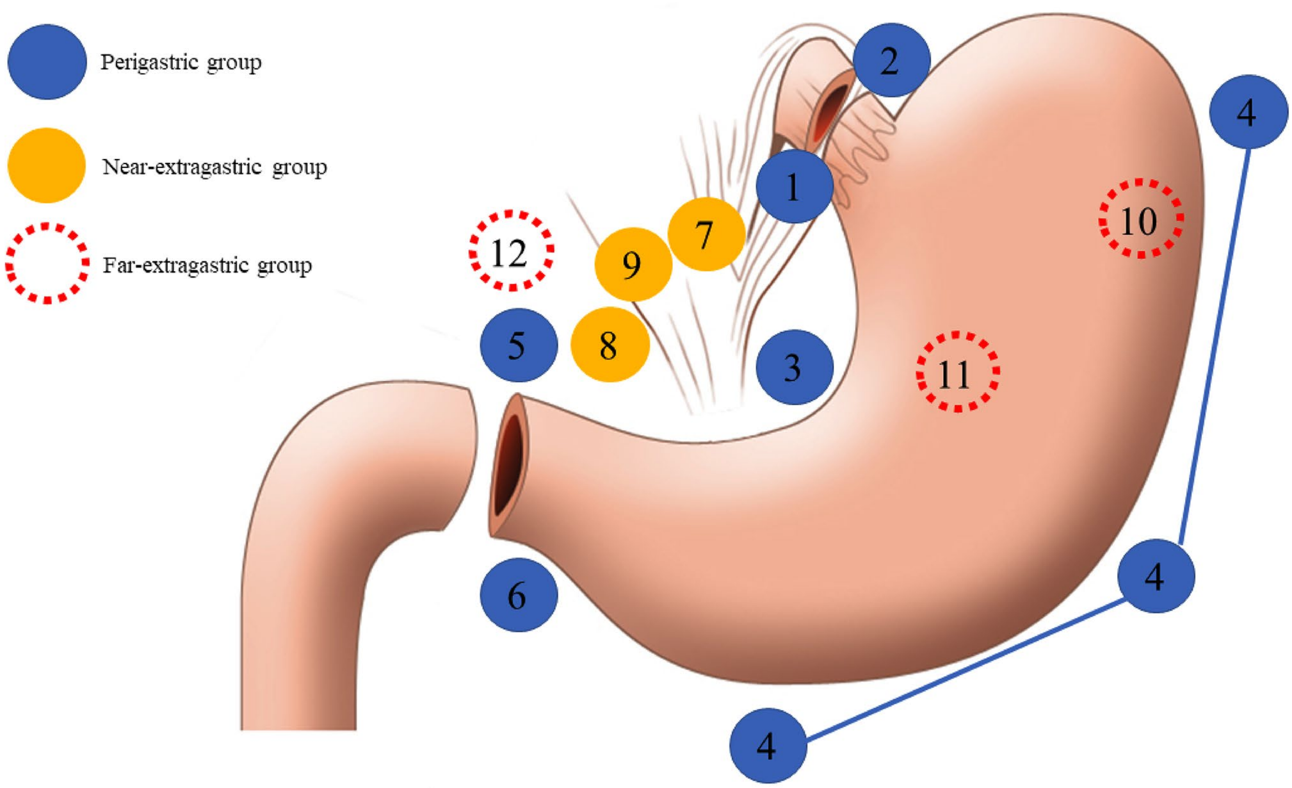

Fig. 2 Schematic diagram of the metastatic lymph nodes. The perigastric group had lymph node metastasis (LNMs) in the perigastric region (stations No. 1, 2, 3, 4, 5, and 6). The near-extragastric group included LNMs near the celiac axis (stations No. 7, 8a, and 9). The far-extragastric group comprised stations No. 10, 11, and 12

in patient survival between group P and the extragastric group (Supplementary Fig. 2).

Comparison of overall survival between three lymph node metastasis groups

The characteristics of the Three LNM groups were compared. There were no significant differences in baseline characteristics such as age, sex, and ECOG. Group FE had a significantly higher rate of open approach and total gastrectomy, and was confirmed to have performed more lymphadenectomy of D2 or higher. Additionally, compared to group P, it was confirmed that the disease severity of groups NE and FE was relatively advanced disease (Supplementary Table 1).

The OS of the three LNM groups (P, NE, and FE) was analyzed according to the N stage. In N1, the 5YOS was 82.4% for group P, 77.9% for group NE, and 63.8% for group FE; the difference was significant ($P=0.013$). Similarly, in N2, the 5YOS was 65.0%, 71.0%, and 46.8%, respectively ($P<0.001$). However, the difference in OS in N3 between the three groups was not significant. These findings demonstrated that patients in group FE had significantly lower survival rates in N1 and N2 (Fig. 3).

Univariate and multivariate analysis of factors related to survival including three lymph node Metastasis groups

In the univariate analysis for the N1 stage, significant factors included age, sex, ECOG, BMI, approach method, lymphadenectomy extent, T stage, TNM stage, and LNM group. Through multivariate analysis, it was confirmed that the hazard ratio (HR) of group FE compared to group P was 2.457, surpassing other significant baseline variables such as age, sex, ECOG, and BMI. In the multivariate analysis of the N2 stage, group FE was established as a statistically significant factor, along with age, ECOG, and TNM stage. However, it did not exhibit significance in N3a and N3b stages (HR, CI, p-value; 1.024, 0.767–1.366, 0.873 / 1.153, 0.884–1.506, 0.293), respectively (Table 2-1, 2-2, 2-3, 2-4).

Comparison of survival according to cancer location

We conducted an analysis according to the primary cancer location. The lesions were classified as upper, middle, or lower lesions. Subsequently, we compared the survival outcomes among the three groups. Irrespective of the cancer location, group FE had significantly lower OS rates, specifically in N2. However, for the remaining N stages except N2, there were no significant difference in

Table 1 Patient characteristics according to lymph node metastasis

Variables, *n*(%)	Node (+) (*N* = 3591, 100%)	Total (*N* = 10,772, 100%)	*P*-value
Age (years)			< 0.001
< 65	1940 (54.0%)	6268 (58.2%)	
≥ 65	1651 (46.0%)	4504 (41.8%)	
Sex			0.371
Male	2423 (67.5%)	7181 (66.7%)	
Female	1168 (32.5%)	3591 (33.3%)	
ECOG			< 0.001
0–1	3396 (94.6%)	10,359 (96.2%)	
≥ 2	166 (4.6%)	347 (3.2%)	
N/A	29 (0.8%)	66 (0.6%)	
Preoperative BMI (kg/m^2)			< 0.001
< 23	1303 (47.5%)	3611 (42.8%)	
≥ 23	1439 (52.5%)	4834 (57.2%)	
Approach			< 0.001
MIS	1222 (34.0%)	5556 (51.6%)	
Open	2254 (62.8%)	4946 (45.9%)	
N/A	115 (3.2%)	270 (2.5%)	
Resection			< 0.001
STG	2427 (67.6%)	8261 (76.7%)	
TG	1134 (31.6%)	2449 (22.7%)	
Others	30 (0.8%)	62 (0.6%)	
Lymphadenectomy			< 0.001
D1+ ↓	806 (22.4%)	3828 (35.5%)	
D2 ↑	2727 (75.9%)	6780 (62.9%)	
N/A	58 (1.6%)	164 (1.5%)	
Reconstruction			< 0.001
B-I	381 (10.6%)	1704 (15.8%)	
B-II	1899 (52.9%)	5758 (53.5%)	
RY	1093 (30.4%)	2752 (25.5%)	
Others	218 (6.1%)	558 5.2%)	
pT stage			< 0.001
T1	735 (20.5%)	6448 (59.9%)	
T2	487 (13.6%)	1094 (10.2%)	
T3	1022 (28.5%)	1596 (14.8%)	
T4	1347 (37.5%)	1634 (15.2%)	
pN stage			< 0.001
N0	0 (0.0%)	7181 (66.7%)	
N1	1277 (35.6%)	1277 (11.9%)	
N2	972 (27.1%)	972 (9.0%)	
N3a	778 (21.7%)	778 (7.2%)	
N3b	564 (15.7%)	564 (5.2%)	
pTMN stage			< 0.001
I	684 (19.0%)	6776 (62.9%)	
II	887 (24.7%)	1796 (16.7%)	
III	2020 (56.3%)	2200 (20.4%)	

Abbreviations: *ECOG* Eastern Cooperative Oncology Group performance status, *N/A* not applicable, *BMI* body mass index, *MIS* minimal invasive surgery, *STG* subtotal gastrectomy, *TG* total gastrectomy

survival based on the specific cancer location in relation to the MLN groups (Figs. 4 and 5).

Comparison of survival according to extent of Surgery

We also conducted an analysis based on the extent of surgery and lymph node dissection range. Firstly, when total gastrectomy was performed, the 5YOS for group P, group NE, and group FE were as follows (N1: 75.6 vs. 66.9 vs. 61.7), (N2: 59.9 vs. 68.6 vs. 36.2), and (N3a: 67.9 vs. 61.4 vs. 23.4). These results confirmed the notably lower survival rates in group FE. For patients who underwent subtotal gastrectomy, a statistically significant outcome was observed (N3a: 40.4 vs. 29.9 vs. 28.4) (Supplementary Figs. 3 and 4). Similarly, an analysis was conducted based on the extent of lymph node dissection, revealing significantly lower OS rates in group FE exclusively in the N2 stage. This trend was observed both in the range below D1 plus (N2: 71.7 vs. 62.6 vs. 31.7) and in the range above D2 (N2: 57.7 vs. 53.8 vs. 45.7) (Supplementary Figs. 5 and 6).

Discussion

The current TNM staging system focuses on the absolute number of MLNs and does not consider the anatomical location of LNM when predicting the prognosis of gastric cancer [18, 19]. In this study, using large-scale multi-institutional big data, we aimed to evaluate the topographical characteristics of MLNs to remedy the shortcomings of current TNM staging, especially the pathological N stage. Our findings suggest that MLN location can be used as a tool for prognosis measurement that can supplement the current TNM staging of GC. As mentioned earlier, the number of MLNs influences the prognosis of patients with GC in most circumstances. However, in cases where the number of MLNs is relatively small but located far from the tumor, the anatomical location of metastasis may also impact the prognosis.

In previous studies, many authors focused on the different classifications of LNM rather than the number or topographical nodal stages of GC [20–23]. The ratio of MLNs to harvested LNs is a good alternative, as it can be used in cases of an inadequate number of harvested LNs, thus providing valuable prognostic stratification [20]. Some researchers have suggested using the logarithmic odds ratio of positive to negative LNs as a functional, up-to-date classification of LNM [24, 25]. However, these suggested novel systems cannot overcome limitations of the current TNM system because the primary background of these systems is the same numeric-based N staging. Currently, no adequate N staging system integrates the number and anatomical regions of MLNs.

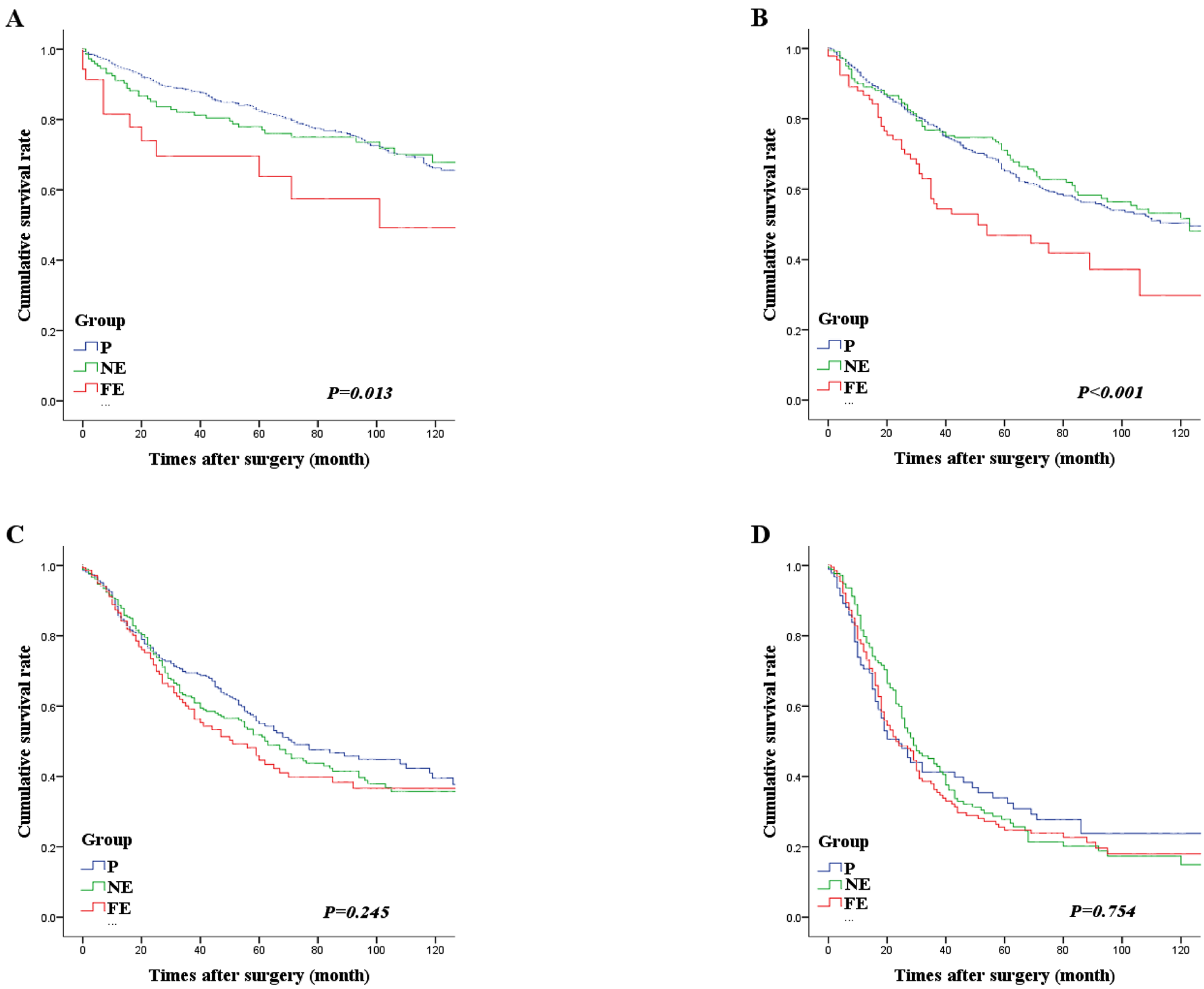

Fig. 3 Analysis of the overall survival of the three lymph node metastasis groups according to the N stage. **A**: N1 stage, **B**: N2 stage, **C**: N3a stage, **D**: N3b stage. Patients in the far-extragastric group (group FE) had significantly lower survival rates in N1 and N2 stages

The stomach is an organ in which blood is supplied by five main vessels (the right and left gastroepiploic arteries, right and left gastric arteries, and short gastric artery). The lymphatic drainage route for GC is generally multidirectional and complicated. Therefore, compared with other malignant neoplasms, it may be difficult to consider lymphatic drainage of the stomach when incorporating the anatomical location of MLNs into an adequate N staging system [10, 26]. However, the anatomical location of MLNs could be essential to compensate for the limitations of the current N-staging system, which uses only the absolute counts of metastatic nodes [19].

The current numeric N stage has gained an overwhelming advantage in terms of utility and versatility owing to its simple and objective nature. However, there are still challenges such as the lack of clear cut-offs, insufficient anatomical information regarding the extent of LNM, and variability in the surgical extent of lymph node dissection. In our study, anatomical differences in MLNs had a limited significance in advanced nodal stages, where the number of MLNs was relatively large without restrictions. However, in N1 and N2, which are characterized by a moderate number of MLNs (1–6), the anatomical location of the MLN was a significant factor. This tendency was consistently observed across various analyses, including those stratified by tumor location, extent of surgery, and lymphadenectomy, in this study. Based on this theoretical framework, excluding the prognostic value of the far-extragastric group in nodal stages characterized by a limited number of MLNs seems unwarranted.

Although the anatomical location of MLNs cannot replace the current staging system as a tool for prognostic

Table 2-1 Multivariate analysis of factors contributing to OS of N1 case

Variables	Univariate			Multivariate		
	HR	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Older age (vs. < 65)	2.067	1.632–2.618	< 0.001*	1.545	1.147–2.082	0.004*
Female sex (vs. male)	0.554	0.424–0.726	< 0.001*	0.586	0.414–0.827	0.002*
ECOG 2–4 (vs. 0–1)	6.932	1.624–29.586	< 0.001*	2.372	1.428–3.940	0.001*
Higher BMI (vs. <23)	0.653	0.492–0.865	0.003*	0.734	0.551–0.979	0.035*
Approach (vs. open)	0.739	0.584–0.935	0.012*	794.021		0.833
TG (vs. STG)	0.430	0.158–1.173	0.099			
Lymphadenectomy (vs. D1+ ↓)	0.303	0.160–0.573	< 0.001*	0.445	0.229–0.864	0.017*
T stage						
T1	Ref			Ref		
T2	1.845	1.229–2.772	0.003*	0.651	0.232–1.825	0.414
T3	3.087	2.216-4.300	< 0.001*	0.954	0.349–2.607	0.927
T4	4.417	3.135–6.222	< 0.001*	0.644	0.277–1.499	0.308
p TNM stage						
I	Ref			Ref		
II	2.917	2.116–4.021	< 0.001*	3.435	1.246–9.474	0.017*
III	5.488	3.890–7.742	< 0.001*	8.872	3.723–21.144	< 0.001*
Group						
Group P	Ref			Ref		
Group NE	1.144	0.821–1.594	0.428	1.070	0.692–1.653	0.762
Group FE	2.297	1.285–4.106	0.005*	2.457	1.278–4.725	0.007*

Abbreviations: *OS* overall survival, *HR* hazards ratio, *CI* confidence interval, *ECOG* Eastern Cooperative Oncology Group performance status, *BMI* body mass index, *TG* total gastrectomy, *STG* subtotal gastrectomy

Table 2-2 Multivariate analysis of factors contributing to OS of N2 case

Variables	Univariate			Multivariate		
	HR	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Older age (vs. < 65)	1.991	1.615–2.455	< 0.001*	1.676	1.291–2.176	< 0.001*
Female sex (vs. male)	0.068	0.640–1.016	0.806			
ECOG 2–4 (vs. 0–1)	4.703	1.612–13.721	0.005*	0.513	0.308–0.853	0.010*
Higher BMI (vs. <23)	0.776	0.605–0.994	0.045*	0.942	0.731–1.215	0.648
Approach (vs. open)	1.005	0.586–1.721	0.987			
TG (vs. STG)	0.660	0.244–1.790	0.415			
Lymphadenectomy (vs. D1+ ↓)	0.379	0.187–0.766	0.007*	1.029	0.741–1.431	0.863
T stage						
T1	Ref			Ref		
T2	0.970	0.625–1.508	0.894	0.907	0.296–2.778	0.864
T3	1.571	1.110–2.224	0.011*	0.978	0.306–3.125	0.970
T4	3.067	2.196–4.283	< 0.001*	1.757	1.307–2.364	< 0.001*
p TNM stage						
II	Ref			Ref		
III	2.282	1.387–71.778	0.002*	7.154	2.947–18.399	0.002*
Group						
Group P	Ref			Ref		
Group NE	0.989	0.773–1.265	0.930	1.399	0.981–1.996	0.063
Group FE	1.775	1.288–2.445	< 0.001*	1.724	1.138–2.611	0.010*

Abbreviations: *OS* overall survival, *HR* hazards ratio, *CI* confidence interval, *ECOG* Eastern Cooperative Oncology Group performance status, *BMI* body mass index, *TG* total gastrectomy, *STG* subtotal gastrectomy

measurement, it is worth noting that anatomical location may influence the limited MLN stage.

This study has some limitations. First, the unavoidable biases associated with longer observation periods may have resulted in changes in treatment strategies such as changes in chemotherapy regimens and surgical guidelines. However, our data was from a multi-institutional database and compensated for this discrimination. Second, the outcomes were obtained from multiple

Table 2-3 Multivariate analysis of factors contributing to OS of N3a case

Variables	Univariate			Multivariate		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Older age (vs. < 65)	1.538	1.247–1.895	< 0.001*	1.435	1.158–1.778	0.001*
Female sex (vs. male)	0.767	0.605–0.972	0.028*	1.190	0.935–1.515	0.158
ECOG 2–4 (vs. 0–1)	1.202	0.406–3.560	0.740			
Higher BMI (vs. <23)	0.828	0.642–1.069	0.147			
Approach (vs. open)	1.292	0.802–2.083	0.292			
TG (vs. STG)	0.700	0.327–1.497	0.358			
Lymphadenectomy (vs. D1+ ↓)	0.883	0.469–1.660	0.699			
T stage						
T1	Ref					
T2	1.368	0.787–2.380	0.267			
T3	1.071	0.661–1.734	0.870			
T4	1.908	1.204–3.022	0.006*			
p TNM stage						
II	Ref					
III	1.952	1.179–22.146	0.001*	29.442	6.623-264.308	< 0.001*
Group						
Group P	Ref			Ref		
Group NE	1.130	0.896–1.426	0.301	1.043	0.824–1.323	0.720
Group FE	1.260	0.950–1.670	0.109	1.024	0.767–1.366	0.873

Abbreviations: *OS* overall survival, *HR* hazards ratio, *CI* confidence interval, *ECOG* Eastern Cooperative Oncology Group performance status, *BMI* body mass index, *TG* total gastrectomy, *STG* subtotal gastrectomy

Table 2-4 Multivariate analysis of factors contributing to OS of N3b case

Variables	Univariate			Multivariate		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Older age (vs. < 65)	1.410	1.113–1.786	0.004*	1.146	0.892–1.471	0.286
Female sex (vs. male)	1.156	0.901–1.483	0.256			
ECOG 2–4 (vs. 0–1)	1.205	0.278–5.220	0.804			
Higher BMI (vs. <23)	0.911	0.687–1.208	0.518			
Approach (vs. open)	0.804	0.578–1.117	0.194			
TG (vs. STG)	1.285	1.019–1.622	0.034*	0.778	0.617–0.982	0.034*
Lymphadenectomy (vs. D1+ ↓)	1.041	0.462–2.342	0.923			
T stage						
T1	Ref					
T2	1.012	0.379–2.699	0.982			
T3	0.953	0.386–2.354	0.917			
T4	1.176	0.483–2.862	0.721			
p TNM stage						
III	Ref					
Group						
Group P	Ref			Ref		
Group NE	0.982	0.709–1.362	0.914	1.135	0.830–1.555	0.428
Group FE	1.168	0.854–1.598	0.330	1.153	0.884–1.506	0.293

Abbreviations: *OS* overall survival, *HR* hazards ratio, *CI* confidence interval, *ECOG* Eastern Cooperative Oncology Group performance status, *BMI* body mass index, *TG* total gastrectomy, *STG* subtotal gastrectomy

institutions in Korea. Validation in other Eastern and Western countries may be essential to generalize these results.

Despite these limitations, our study has notable strengths that distinguish it from previous studies. First, this is one of the largest studies to date to examine the impact of the number and anatomical location of LNMs on the survival of patients with GC. Conducting prospective studies on the loopholes identified in this study has numerous challenges. Of note, the current staging system was developed based on retrospective data. Second, our study is the first to use a large-scale cohort to elucidate

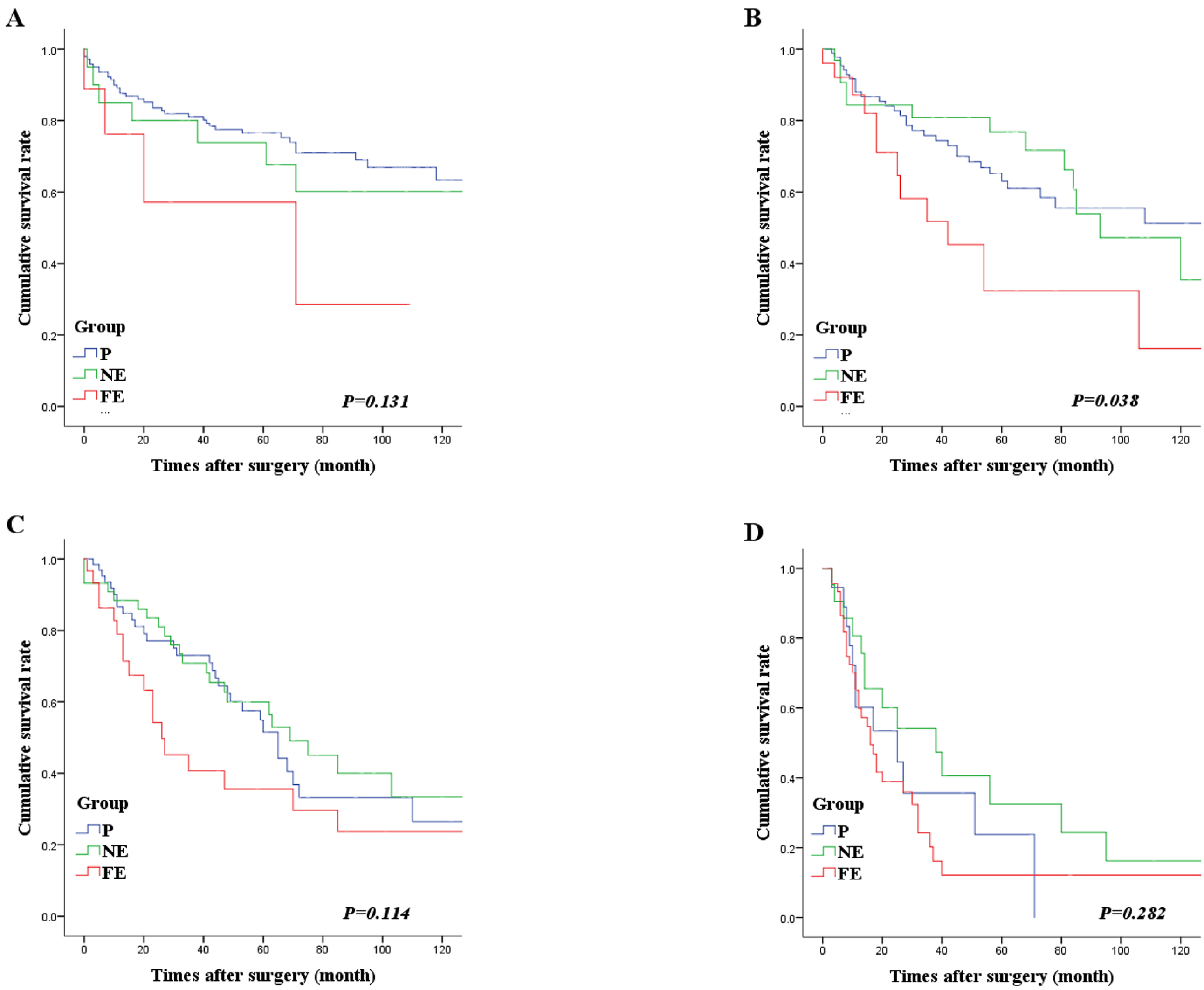

Fig. 4 Comparison of survival according to the primary cancer location: Primary lesion at upper location. **A**: N1 stage, **B**: N2 stage, **C**: N3a stage, **D**: N3b stage. The far-extragastric group (group FE) had significantly lower overall survival, specifically in the N2 stage

the significance of the anatomical location of MLNs in the survival of patients with GC with a limited number of nodal metastases.

In patients with a limited number of MLNs, the location of nodal metastases should be considered when choosing the appropriate treatment approach. For example, adjuvant chemotherapy, such as the XELOX doublet, which is applied to patients with N2 or higher disease through the CLASSIC TRIAL, can be applied to N1 patients in group FE, where the OS is expected to deteriorate. Moreover, patients with a lower T stage but N2 stage, including one or more metastatic stations 10 to 12, may require more intensive treatment and intervention to improve their survival prospects.

In conclusion, the current numerical nodal staging system is the most effective for treating gastric cancer. However, it is crucial to recognize that in the N1 and N2 stages, where there is an upper limit to the number of metastatic nodes, the specific topographic characteristics of a particular lymph node station may have significant implications.

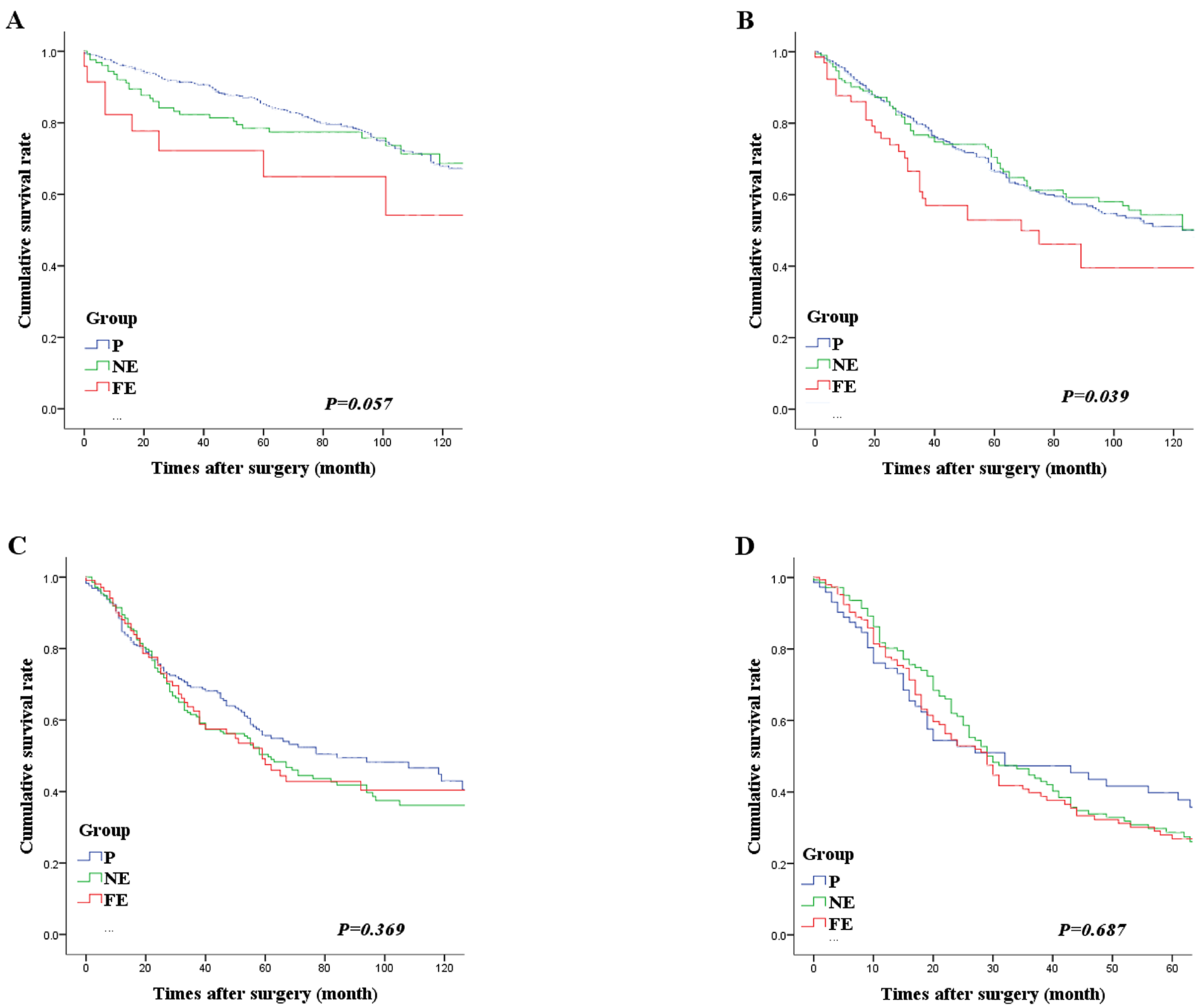

Fig. 5 Comparison of survival according to the primary cancer location: Primary lesion at middle and/or lower location. **A**: N1 stage, **B**: N2 stage, **C**: N3a stage, **D**: N3b stage. The far-extragastric group (group FE) had significantly lower overall survival, specifically in the N2 stage

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-023-11653-0.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Acknowledgements

Not applicable.

Author Contributions

All authors contributed to the study conception and design. Material preparation and data collection and analysis were performed by C.H.J., K.B.P., H.L., D.J.K and H.S.S. The first draft of the manuscript was written by C.H.J., and all authors commented on previous versions of the manuscript. Supervision was performed by J.L., K.Y.J., J.J.K., H.H.L. All authors read and approved the final manuscript.

Funding

This study was financially supported by the National Research Foundation of Korea (grant no. 2020R1A2C1012007).

Data Availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate

This study was approved by the Institutional Review Board of the College of Medicine, Catholic University of Korea (XC21RIDI0092), in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. All procedures followed the ethical standards of the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration of 1964 and later versions. Informed consent or an appropriate substitute was obtained from all the patients included in the study.

Consent for publication
NA.

Competing interests
The authors declare no competing interests.

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Received: 28 August 2023 / Accepted: 18 November 2023
Published online: 05 December 2023

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