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ORIGINAL ARTICLE

Impact of skip lymph node metastasis on the prognosis of gastric cancer patients who underwent curative gastrectomy

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Summary

Purpose: *Skip metastasis (SK) is an exceptional pattern of lymph node metastasis and the incidence of skip metastasis is not infrequent in gastric cancer (GC). In the present study, we evaluated the clinical significance of skip LN metastasis in GC patients.*

Methods: *According to the anatomical location of positive lymph nodes (LNs), the patients who underwent curative gastrectomy in our institute were classified in three groups: only perigastric involvement (PG group), only extraperigastric involvement (SK group) and both perigastric and extraperigastric involvement (PG+EP group). The clinicopathologic features and prognostic differences between the different groups were compared.*

Results: *The incidence of skip metastasis was 3.9% in all GC patients and the most common location of skip metastasis was No.7 and No.8a node station. The proportion of only one involved station accounted for 83.0% of all cases. In addition, the SK group had fewer numbers of retrieved LNs than the PG and the PG+EP group, especially in the perigastric area. There were significant differences between different groups in the baseline characteristics. After clinicopathologic factors were adjusted and matched, we found that the prognosis of skip metastasis was poorer than that of only perigastric involvement, but was similar to that of both perigastric and extraperigastric involvement.*

Conclusion: *The patients with skip metastasis had a poorer prognosis than those with only perigastric involvement. Anatomical location of metastatic LNs may be not ignored, and adequate lymphadenectomy should be indispensable for node-positive patients.*

Key words: *gastric cancer, lymph node metastasis, prognosis, skip metastasis*

Introduction

Gastric cancer (GC) is one of the most common malignancies worldwide and remains one of the main causes of cancer-related death [1]. Due to the vague clinical manifestations and signs, GC patients are usually diagnosed at advanced stages. Curative resection with adequate lymphadenectomy is regarded as primary treatment modality for these patients [2]. However, the prognosis of GC patients is still unsatisfactory due to the high rate of recurrence and metastasis [3]. The lymphatic system is a common pathway for the spread of tumor cells, and lymph node (LN) metastasis is considered as an important prognostic factor in GC patients [4,5]. In general, positive LNs should be firstly detected in the area close to the primary tumor, and then tumor cells could spread stepwise to distant areas. However, the stomach was a organ that had complicated lymphatic network and multiple blood supply. It is difficult to accurately estimate the extent of positive LNs before operation or during the operation [6,7]. According to the anatomical location of positive LNs, skip metastasis is

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defined as a metastatic pattern that involves LNs in the N2 station only (extraperigastric area) but is not detected in the N1 station (perigastric area). The exceptional pattern and complicated lymphatic drainage may limit the clinical application of sentinel lymph node biopsy in GC patients [7-9].

According to previous reports, skip metastasis in GC occurs in about 1.8-6.7% of the patients who have undergone curative gastrectomy [6,8,10-12]. For the node-positive patients, the incidence of skip metastasis is more frequent [8,10]. However, the prognostic significance of skip metastasis in GC patients remain unclear. Some studies reported that the prognosis of patients with skip metastasis was not significantly different from that of those with only N1 station involvement, but was better than that of those with stepwise N2 station involvement [6,12]. On the contrary, Choi et al. demonstrated that the prognosis of skip metastasis was poorer compared with only perigastric involvement, but was similar with extraperigastric involvement [10]. In view of limited studies and conflicting results, in the present study we investigated the impact of skip metastasis on the prognosis of GC patients. For this purpose, we reviewed GC patients who underwent curative gastrectomy in our institute. All patients were classified into three groups based on the anatomical location of positive LNs. Then, we compared the prognostic difference and clinicopathologic features between the different patient groups and evaluated the clinical significance of skip metastasis in GC.

Methods

Patients

The inclusion and exclusion criteria of this study were as follows: (1): All patients were pathologically diagnosed as primary GC after operation. (2): Curative gastrectomy with $D1^+$ or D2 ($D2^+$ if necessary) was performed, and the minimal number of retrieved LNs was 15. (3): Patients with distant metastasis were excluded, including liver metastasis, peritoneal metastasis and extraregional LN metastasis (No.13, No.14, No.15 and No.16 station). (4): Those patients who underwent neoadjuvant chemotherapy or had a history of other malignant tumors were excluded from the present study. (5): The pathological information of all patients were complete, especially for the number of positive LNs and the anatomical location of positive LNs.

According to the eligibility criteria mentioned above, this study included 1,343 GC patients who underwent curative gastrectomy at the Department of Surgical Oncology, the First Affiliated Hospital of China Medical University between January 1989 and January 2010. Our study was approved by the Ethics Committee of China Medical University, and all patients provided written informed consent prior to surgery.

Surgical procedures and postoperative treatment

Based on the tumor size, tumor location and resection margins, distal gastrectomy, proximal gastrectomy or total gastrectomy were performed. Digestive reconstruction methods included Billroth-I, Billroth-II and Roux-en-Y esophagojejunostomy. The extent of LN dissection was based on the Japanese Gastric Cancer Treatment Guidelines [13]. The surgeons defined the anatomical location of relevant LNs and dissected regional LNs in perigastric and extraperigastric area during the operation. After curative operation, the surgeons continued to retrieve as many LNs as possible from the resected specimens. The following clinicopathological information of patients was collected: gender, age, tumor location, tumor size, resection type, Lauren type, lymphovascular invasion, infiltration growth pattern (INF), the number of positive LNs, the depth of tumor invasion and adjuvant chemotherapy. The depth of tumor invasion and metastatic status of retrieved LNs were reviewed and assessed independently by two pathologists, and the disagreements were resolved by discussion with a third expert. According to the Japanese Classification of Gastric Cancer (JCGC), the growth pattern of tumor cells infiltration into the surrounding tissue could be classified in 3 categories: INFα, INFβ, and INFγ. The INFα pattern indicated that the tumor showed an expanding growth and distinct border could be observed in the surrounding tissue. The INFγ pattern was described as the infiltrating growth and indistinct border with the surrounding tissue. The intermediate pattern between INFα and INFγ was defined as INFβ pattern [14]. In our institute, infiltration growth pattern was routinely evaluated by hematoxylin-eosin staining and was regarded as a pathological feature of the resected specimens.

According to the anatomical location of positive LNs, perigastric (PG) area included No.1, No.2, No.3, No.4, No.5 and No.6 LN stations, and extraperigastric (EP) area included No.7, No.8, No.9, No.10, No.11 and No.12 LN stations [15]. For the purpose of this study, GC patients were classified into PG group, PG+EP group and skip metastasis (SK) group. The PG group indicated that positive LNs were confined to perigastric area (No.1-6 stations), and PG+EP group indicated that positive LNs were distributed in both perigastric and extraperigastric areas. Skip metastasis group ment that involved LNs were detected only in the EP area but were not found in the PG area. All patients were staged according to the TNM staging system of American Joint Commission on Cancer (AJCC) (7th edition) [16], and stage II-III patients were recommended to receive adjuvant chemotherapy. The administered regimens were 5-FU or cisplatin/oxaliplatin-based systemic chemotherapy.

Follow-up

All of GC patients who underwent curative resection in our institute were followed-up every 3 months for the first 2 years, every 6 months for the second 2 years and annually thereafter until death or last follow-up date. During the follow-up period, all patients were subjected to endoscopy, abdominal CT, ultrasonography and tumor biomarkers in order to monitor postoperative relapse.

Tumor recurrences included local relapse (gastric remnant or anastomotic site), regional LNs metastasis and distant metastasis (peritoneal seeding, hematogeneous dissemination or extraregional lymph nodes metastasis). All postoperative recurrences were diagnosed according to the clinical findings, imaging findings and pathological results. In our follow-up cohort, the median follow-up period was 31 months (range 1-276). The primary outcome was characterized as disease-free survival (DFS), which was the time span starting from the date of surgery to tumor recurrence or death.

Statistics

Categorical variables were compared using the Pearson's chi-square test or Fisher's exact test, and continuous variables were compared using Student's *t*-test.

Table 1. Baseline characteristics of 871 node-positive gastric cancer patients

Characteristics	*Patients*	*SK group vs PG group*			*SK group vs PG+EP group*	
	(n=871) n (%)	*SK group (n=53) n (%)*	*PG group (n=335) n (%)*	*p value*	*PG+EP group (n=483) n (%)*	*p value*
Age (years)				0.989		0.472
<60	452 (51.9)	26 (49.1)	164 (49.0)		262 (54.2)	
≥60	419 (48.1)	27 (50.9)	171 (51.0)		221 (45.8)	
Gender				0.106		0.055
Female	245 (28.1)	9 (17.0)	92 (27.5)		144 (29.8)	
Male	626 (71.9)	44 (83.0)	243 (72.5)		339 (70.2)	
Tumor location				0.307		0.121
Lower 1/3	571 (65.6)	34 (64.2)	231 (69.0)		306 (63.4)	
Middle 1/3	105 (12.1)	8 (15.1)	36 (10.7)		61 (12.6)	
Upper 1/3	97 (11.1)	9 (17.0)	38 (11.3)		50 (10.4)	
≥2/3 stomach	98 (11.3)	2 (3.8)	30 (9.0)		66 (13.7)	
Tumor size, cm				0.298		0.022
≤5	437 (50.2)	33 (62.3)	183 (54.6)		221 (45.8)	
>5	434 (49.8)	20 (37.7)	152 (45.4)		262 (54.2)	
Resection type				0.521		0.097
Subtotal	715 (82.1)	47 (88.7)	286 (85.4)		382 (79.1)	
Total	156 (17.9)	6 (11.3)	49 (14.6)		101 (20.9)	
Lauren type				0.731		0.033
Intestinal	301 (34.6)	23 (43.4)	137 (40.9)		141 (29.2)	
Diffuse	570 (65.4)	30 (56.6)	198 (59.1)		342 (70.8)	
Lymphatic invasion				0.118		<0.001
No	609 (69.9)	46 (86.8)	259 (77.3)		304 (62.9)	
Yes	262 (30.1)	7 (13.2)	76 (22.7)		179 (37.1)	
Infiltrating growth pattern*				0.526		0.223
α/β	401 (46.0)	26 (49.1)	180 (53.7)		195 (40.4)	
γ	470 (54.0)	27 (50.9)	155 (46.3)		288 (59.6)	
T stage				0.449		<0.001
T1	36 (4.1)	5 (9.4)	18 (5.4)		13 (2.7)	
T2	141 (16.2)	14 (26.4)	74 (22.1)		53 (11.0)	
T3	447 (51.3)	22 (41.5)	173 (51.6)		252 (52.2)	
T4	247 (28.4)	12 (22.6)	70 (20.9)		165 (34.2)	
N stage				<0.001		<0.001
N1	227 (26.1)	42 (79.2)	162 (48.4)		23 (4.8)	
N2	242 (27.8)	9 (17.0)	112 (33.4)		121 (25.1)	
N3a	279 (32.0)	2 (3.8)	54 (16.1)		223 (46.2)	
N3b	123 (14.1)	0 (0.0)	7 (2.1)		116 (24.0)	
Chemotherapy				0.596		0.680
No	599 (68.8)	38 (71.7)	228 (68.1)		333 (68.9)	
Yes	272 (31.2)	15 (28.3)	107 (31.9)		150 (31.1)	

PG: perigastric, SK: extraperigastric. *INFα: infiltration growth pattern α; INFβ: infiltration growth pattern β; INFγ: infiltration growth pattern γ

The survival curves were constructed and plotted according to the Kaplan-Meier method, and statistical differences between different patient groups were compared using the log-rank test. The survival data was presented as 5-year DFS of each group. All statistical analyses were performed using the SPSS19.0 statistical package (SPSS Inc, Chicago, IL, USA). P value <0.05 was considered to be statistically significant.

Results

Clinicopathological characteristics of gastric cancer patients

A total of 1,343 GC patients who underwent curative gastrectomy met the inclusion criteria. In this patient cohort, 28.8% were female (n=387) and 71.2% were male (n=956), with mean age 57.4±11.3 years (range 19-87). A total of 34,981 LNs were retrieved from 1,343 GC patients, with median number of retrieved LNs 23 (range 15-100). Among these patients, the incidence of LN metastasis was 64.9% (871/1,343) and the median number of positive LNs was 6 (range 1-84). The clinicopathological features of 871 patients with LN metastasis are summarized in Table 1. Except for the distribution of N stage, there was no significant difference between the skip metastasis group and PG group in clinicopathological features. Compared with PG+EP group, skip metastasis patients were prone to diffuse type, smaller tumor size, lower incidence of lymphovascular invasion, and less advanced T and N stage (Table 1).

The incidence of skip metastasis was 3.9% (53/1,343) in all GC patients, 2.6% (5/192) in early GC patients, 4.2% (45/1,151) in advanced GC patients and 6.1% (53/871) in LN-positive GC patients. The most common location of skip metastasis was No.7 station (33 patients, 62.3%) and No.8a station (18 patients, 34.0%), followed by No.9 station (5 patients, 9.4%). The proportion of only one involved station accounted for 83.0% of all skip metastasis cases (n=44). According to the numeric-based N stage, the percentage of N1, N2, N3a and N3b stage was 79.2, 17.0, 3.8 and 0% in all patients with skip metastasis, respectively.

The total number of retrieved LNs was 23.7±8.9 in the skip metastasis group and 26.0±12.0 in the PG group (p=0.182). However, the number of retrieved LNs in the PG area was 13.7±5.9 in the skip metastasis group and 19.1 ±10.8 in the PG group (p<0.001). In the PG+EP group, the total number of retrieved LNs and the number of retrieved LNs in the PG area was 27.5±12.4 and 18.3±10.5, respectively. There was a significant difference between skip the metastasis group and the PG+EP group in the number of retrieved LNs, regardless of PG area or all two areas (p<0.05).

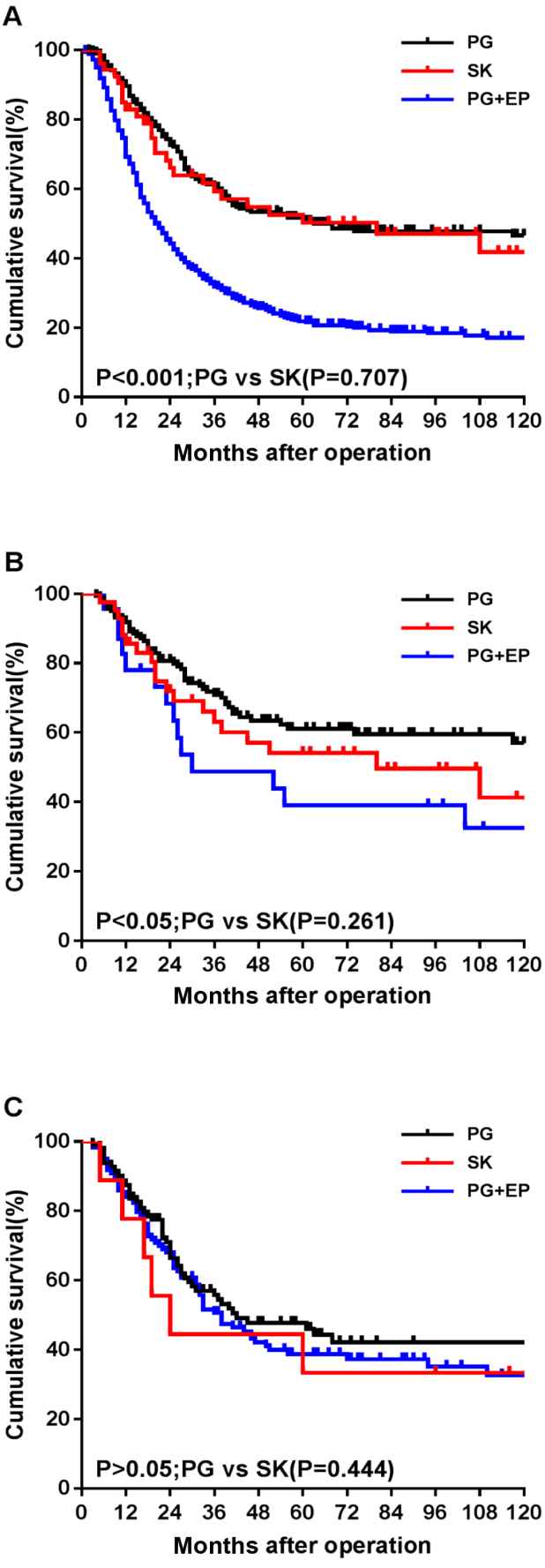

Figure 1. Comparison of survival curves between different groups before matching. **A:** for all node-positive patients. **B:** for N1 stage patients. **C:** for N2 stage patients.

The impact of skip metastasis on the prognosis of GC patients

As shown in Figure 1A, the Kaplan-Meier curves demonstrated that the prognosis of the skip metastasis (SK) group was not significantly different from that of the PG group before the matching (5-year DFS rate, PG group: 51.1% vs SK group: 50.2%, p>0.05). However, there were significantly prognostic differences between PG+EP and SK group (22.1 vs 50.2%, p<0.001), between PG+EP and PG group (22.1 vs 51.1%, p<0.001).

The Kaplan-Meier curves of three patient groups, stratified by the N stage, are shown in Figure 1B and 1C. For the N1 stage patients, the 5-year DFS rate of PG group, SK group and PG+EP group were 61.1, 54.1 and 39.0%, respectively. Although the prognostic difference between two groups did not reach statistical significance, the SK group showed a poorer prognosis than the PG group (Figure 1B). Of note, we found that there was significantly prognostic difference between the PG group and PG+EP group when the number of positive LNs was 1-2 (p<0.05) (Figure 1B). For the N2 stage patients, the 5-year DFS rate of the PG group, SK group and PG+EP group were 46.1, 33.3 and 38.7%, respectively. There was no significantly statistical difference between the PG group and SK group due to the limited sample size (p>0.05) (Figure 1C).

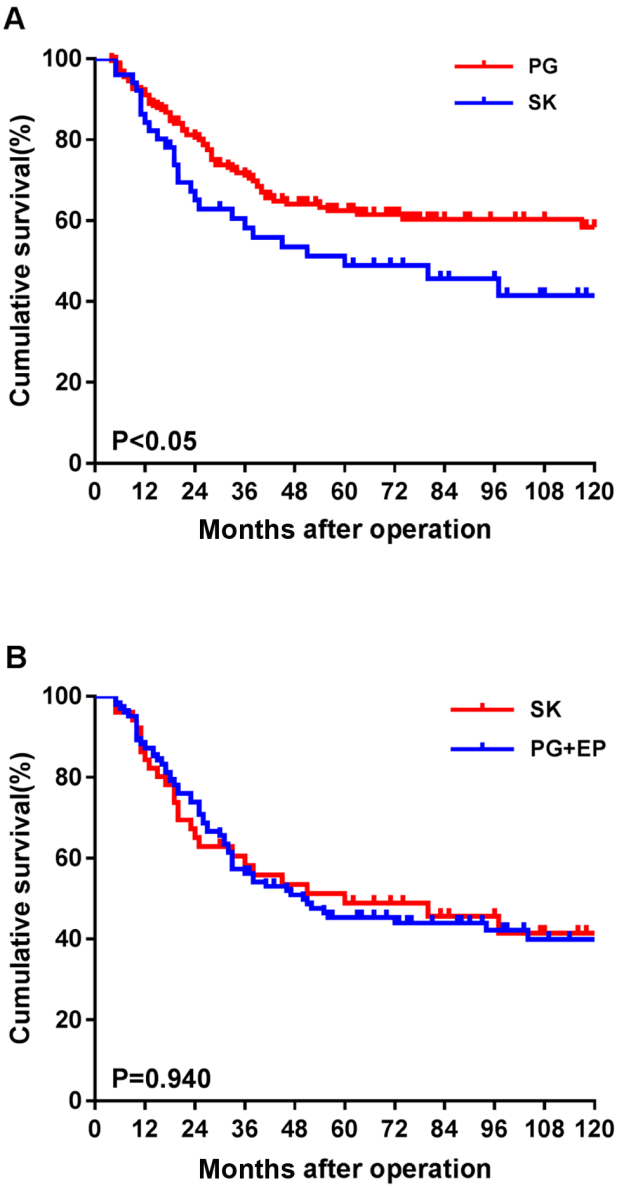

Figure 2. Comparison of survival curves between different groups after matching. **A:** SK group vs PG group. **B:** SK group vs PG+EP group.

In view of discordant baseline characteristics between the different groups, we performed propensity score matching to further evaluate the impact of skip metastasis on the prognosis of GC patients. Due to the distributed difference in the N stage (only two patients were identified as N3a stage and no patient was identified as N3b stage in the SK group), we excluded those patients who were identified as N3 stage in three patient groups. A 1:4 matching was performed to compare the prognostic difference between SK group and PG group and found no significant difference between SK group and PG group in clinicopathological features after propensity score matching (Table 2). On the other hand, a 1:2 matching was performed to compare the prognostic difference between the SK group and PG+EP group. Except for the distribution of N stage and gender, the baseline characteristics between SK group and PG+EP group were comparable (Table 2). After propensity score matching was performed, we found that the prognosis of SK group was poorer than that of PG group (48.9 vs 62.4%, p<0.05), but was similar to that of PG+EP group (SK group: 48.9 vs PG+EP group: 45.3%, p>0.05) (Figure 2A, 2B).

Discussion

Lymph node metastasis has been proved to be an important factor associated with unfavorable prognosis of GC patients. The survival rate of GC patients decreased gradually with increased number of positive Lns [4,5]. In addition to the number of positive LNs, the prognosis of GC patients was associated with the anatomical location of positive LNs [17-19]. Son et al. reported that the patients with extraperigastric involvement had a poorer prognosis than those with only perigastric involvement [17]. In general, tumor cells could spread stepwise from the perigastric area to the extraperigastric area. Due to complicated lymphatic network, the occurrence of skip metastasis was not

infrequent in GC patients. Whether skip metastasis had a negative impact on the prognosis of GC patients remains controversial.

The results of the present study indicate that the prognosis of skip metastasis was similar to that of only perigastric involvement, but was better than of both perigastric and extraperigastric involvement before propensity score matching. The results were in accordance with those of previous studies [6,12]. Kim et al. reviewed survival data of 2,963 GC patients who underwent adequate lymphadenectomy, and their results showed that there was no prognostic difference between N1 station metastasis and skip metastasis, but there was a significant

Table 2. Clinicopathological characteristics of node-positive patients after matching

Characteristics	*Patients*	*SK group vs PG group*			*SK group vs PG+EP group*	
	(n=357) n (%)	*SK group (n=51) n (%)*	*PG group (n=204) n (%)*	*p value*	*PG+EP group (n=102) n (%)*	*p value*
Age (years)				0.802		0.647
<60	183 (51.3)	25 (49.0)	104 (51.0)		54 (52.9)	
≥60	174 (48.7)	26 (51.0)	100 (49.0)		48 (47.1)	
Gender				0.074		0.012
Female	102 (28.6)	8 (15.7)	58 (28.4)		36 (35.3)	
Male	255 (71.4)	43 (84.3)	146 (71.6)		66 (64.7)	
Tumor location				0.430		0.413
Lower 1/3	253 (70.9)	33 (64.7)	151 (74.0)		69 (67.6)	
Middle 1/3	47 (13.2)	7 (13.7)	22 (10.8)		18 (17.6)	
Upper 1/3	39 (10.9)	9 (17.6)	21 (10.3)		9 (8.8)	
≥2/3 stomach	18 (5.0)	2 (3.9)	10 (4.9)		6 (5.9)	
Tumor size, cm				0.896		0.249
≤5	216 (60.5)	32 (62.7)	130 (63.7)		54 (52.9)	
>5	141 (39.5)	19 (37.3)	74 (36.3)		48 (47.1)	
Resection type				0.599		0.862
Subtotal	319 (89.4)	45 (88.2)	185 (90.7)		89 (87.3)	
Total	38 (10.6)	6 (11.8)	19 (9.3)		13 (12.7)	
Lauren type				0.949		0.556
Intestinal	143 (40.1)	21 (41.2)	85 (41.7)		37 (36.3)	
Diffuse	214 (59.9)	30 (58.8)	119 (58.3)		65 (63.7)	
Lymphatic invasion				0.333		0.637
No	293 (82.1)	44 (86.3)	164 (80.4)		85 (83.3)	
Yes	64 (17.9)	7 (13.7)	40 (19.6)		17 (16.7)	
Infiltrating growth pattern*				0.345		0.731
α/β	187 (52.4)	25 (49.0)	115 (56.4)		47 (46.1)	
γ	170 (47.6)	26 (51.0)	89 (43.6)		55 (53.9)	
T stage				0.927		0.653
T1	35 (9.8)	5 (9.8)	18 (8.8)		12 (11.8)	
T2	88 (24.6)	14 (27.5)	55 (27.0)		19 (18.6)	
T3	156 (43.7)	21 (41.2)	90 (44.1)		45 (44.1)	
T4	78 (21.8)	11 (21.6)	41 (20.1)		26 (25.5)	
N stage				0.639		<0.001
N1	227 (63.6)	42 (82.4)	162 (79.4)		23 (17.6)	
N2	130 (36.4)	9 (17.6)	42 (20.6)		79 (77.5)	
N3a	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	
N3b	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	
Chemotherapy				0.413		0.790
No	252 (70.6)	38 (74.5)	140 (68.6)		74 (77.5)	
Yes	105 (29.4)	13 (25.5)	64 (31.4)		28 (27.5)	

*See footnote of Table 1. PG: perigastric, SK: extraperigastric

prognostic difference between skip metastasis and stepwise N2 station metastasis [6]. Similarly, Saito et al. reported that the prognosis of skip metastasis was not significantly different from that of only N1 station involvement, but two groups showed a better prognosis than stepwise N2 station metastasis [12]. However, the baseline characteristics between three groups were not comparable in these studies, especially for T and N stage. In the study of Choi et al. propensity score matching analysis was performed to minimize the impact of different clinicopathological factors on the prognostic evaluation. The results indicated that the prognosis of patients with skip metastasis was poorer compared with those with only perigastric involvement, but was similar to those with both perigastric and extraperigastric involvement [10], which was in accordance with our findings. In addition, we found that the PG+EP group had a worse prognosis than the PG group in this study, especially for N1 stage patients. There may still be a prognostic difference among these patients, despite the equivalent number of positive LNs. Recently, Chen et al. proposed a novel N staging scheme which incorporated the information on anatomical location of positive LNs and the number of positive LNs. In their study, N1-N2 stage patients with N2 station involvement were correspondingly upstaged compared with those with N1 station involvement [19]. The new staging system was proved to have a better prognostic performance than the single numeric-based staging. Therefore, the prognostic significance of the anatomical location of positive LNs may not be ignored. Further studies involving larger patient cohorts should be necessary to confirm the impact of skip metastasis on the prognosis of GC patients. In the present study, the incidence of skip metastasis was 3.9% (53/1,343) in all GC patients, 2.6% (5/192) in early GC patients, 4.2% (45/1,151) in advanced GC patients and 6.1% (53/871) in node-positive GC patients respectively, which were similar to previous reports [6,8,10]. The most common location of skip metastasis was No.7 and No.8a station. Also, 79.2% of patients with skip metastasis had no more than two positive LNs, and the number of involved station was usually confined to 1 station. These findings may provide useful information and guidance for the extent of LN dissection. To date, the prognostic value of D2 LN dissection has been validated in some studies [2,20], and it has been regarded as standard procedure for advanced GC patients in many countries and areas. In this study, a high proportion of skip metastasis was observed in advanced GC patients. Therefore, adequate LN dissection should be indispensable for these patients.

There was also no consensus opinion on risk factors associated with skip metastasis. Lee et al. demonstrated that larger tumor size and lymphatic invasion were two independent risk factors correlated with skip metastasis [8]. In the study of Kim et al., however, the authors found that there were no constant risk factors except for older age to predict the occurrence of skip metastasis, when compared with N1 station metastasis or stepwise N2 station metastasis [6]. They considered that the degeneration of lymphatic system in elder individuals could lose the ability to filter out tumor cells, which may promote the development of LNs metastasis and skip metastasis [6]. However, similar results were not validated in other studies [11,12,21]. At present, there is no sufficient evidence to support any significant risk factors associated with skip metastasis. Therefore, it is difficult to predict the presence of skip metastasis before operation or during the operation, which limits the clinical application of sentinel lymph node biopsy in GC patients.

The exact mechanism of skip metastasis is still uncertain. Several possible reasons may explain the presence of the extraordinary metastasis pattern. Firstly, LN micrometastasis in the perigastric area may increase the possibility of missed lesions during the routine pathological examination [21]. Secondly, aberrant and complicated lymphatic network may result in the direct lymphatic stream from the primary tumor to extraperigastric Lns [22,23]. Thirdly, the lymphatic stream from the perigastric area to the extraperigastric area may be blocked by tumor cells, which could provide other spread routes for the migration of GC cells [8]. Fourthly, skip metastasis may be caused by the inadequate number of retrieved LNs [10]. In this study, we found that the skip metastasis group had fewer number of retrieved LNs than the PG and PG+EP group, especially in the perigastric area. This finding was also reported in other studies [6,10,11]. Therefore, the impact of inadequate LN dissection on the identification of skip metastasis could not be ignored, despite at least 15 retrieved LNs in all patient groups.

Some limitations should be emphasized in the present study. Firstly, due to the retrospective nature of our study, all of the results could have been influenced by some confounding or unknown factors. Furthermore, the relatively small number of skip metastasis cases might affect the prognostic assessment. Secondly, the number of retrieved LNs may be influenced by the surgeons. In the present study, the cases with <15 retrieved LNs were excluded to ensure the stage reliability. However, it may still be not enough to determine skip metastasis. Thirdly, immunohistological examination

was not routinely performed in our research institute. The possibility of LN micrometastasis or isolated tumor cells was not completely excluded. Therefore, some patients may be regarded as "skip metastasis" and a portion of "node-negative" patients may be not real N0 stage patients. In the future, immunohistological staining may provide a more reliable method for the identification of skip metastasis.

In summary, our results indicated that the prognosis of skip metastasis was poorer than that of only perigastric involvement, but was similar to that of both perigastric and extraperigastric involvement after baseline characteristics were adjusted and matched. The anatomical location of positive lymph nodes may be not ignored in GC patients. Although it is difficult to accurately predict the presence of skip metastasis before operation or during the operation, adequate lymph node dissection should be indispensable for GC patients.

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Conflict of interests

The authors declare no conflict of interests.

References

1. Torre LA, Bray F, Siegel RL et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.
2. Songun I, Putter H, Kranenbarg EM et al. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 2010;11:439-49.
3. Ferlay J, Soerjomataram I, Dikshit R et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86.
4. Warneke VS, Behrens HM, Hartmann JT et al. Cohort study based on the seventh edition of the TNM classification for gastric cancer: proposal of a new staging system. J Clin Oncol 2011;29:2364-71.
5. Sano T, Coit DG, Kim HH et al. Proposal of a new stage grouping of gastric cancer for TNM classification: International Gastric Cancer Association staging project. Gastric Cancer 2017;20:217-225.
6. Kim DH, Choi MG, Noh JH et al. Clinical significance of skip lymph node metastasis in gastric cancer patients. Eur J Surg Oncol 2015;41:339-45.
7. Nakagawa M, Choi YY, An JY et al. Difficulty of predicting the presence of lymph node metastases in patients with clinical early stage gastric cancer: a case control study. BMC Cancer 2015;15:943.
8. Lee SE, Lee JH, Ryu KW et al. Sentinel node mapping and skip metastases in patients with early gastric cancer. Ann Surg Oncol 2009;16:603-8.
9. Lee JH, Lee HJ, Kong SH et al. Analysis of the lymphatic stream to predict sentinel nodes in gastric cancer patients. Ann Surg Oncol 2014;21:1090-8.
10. Choi YY, An JY, Guner A et al. Skip lymph node metastasis in gastric cancer: is it skipping or skipped? Gastric Cancer 2016;19:206-15.
11. Park SS, Ryu JS, Min BW et al. Impact of skip metastasis in gastric cancer. ANZ J Surg 2005;75:645-9.
12. Saito H, Tsujitani S, Ikeguchi M. Clinical significance of skip metastasis in patients with gastric cancer. Gastric Cancer 2007;10:87-91.
13. Japanese Gastric Cancer Treatment Guidelines 2010 (version 3). Gastric Cancer 2011;14:113-23.
14. Japanese Gastric Cancer A. Japanese Classification of Gastric Carcinoma - (2nd English Edn). Gastric Cancer 1998;1:10-24.
15. Japanese Classification of Gastric Carcinoma (3rd English Edn). Gastric Cancer 2011;14:101-12.
16. Washington K. 7th edition of the AJCC cancer staging manual: stomach. Ann Surg Oncol 2010;17:3077-9.
17. Son T, Hyung WJ, Kim JW et al. Anatomic extent of metastatic lymph nodes: still important for gastric cancer prognosis. Ann Surg Oncol 2014;21:899-907.
18. Galizia G, Lieto E, Auricchio A et al. Comparison of the current AJCC-TNM numeric-based with a new anatomical location-based lymph node staging system for gastric cancer: A western experience. PLoS One 2017;12:e0173619.
19. Chen J, Chen C, He Y et al. A new pN staging system based on both the number and anatomic location of metastatic lymph nodes in gastric cancer. J Gastrointest Surg 2014;18:2080-8.
20. Seevaratnam R, Bocicariu A, Cardoso R et al. A meta-analysis of D1 versus D2 lymph node dissection. Gastric Cancer 2012;15 (Suppl 1):S60-9.
21. Li C, Kim S, Lai JF et al. Solitary lymph node metastasis in gastric cancer. J Gastrointest Surg 2008;12:550-4.
22. Bilchik AJ, Saha S, Tsioulias GJ et al. Aberrant drainage and missed micrometastases: the value of lymphatic mapping and focused analysis of sentinel lymph nodes in gastrointestinal neoplasms. Ann Surg Oncol 2001;8:82s-5s.
23. Miwa K, Kinami S, Taniguchi K et al. Mapping sentinel nodes in patients with early-stage gastric carcinoma. Br J Surg 2003;90:178-82.