Original article

Clinical significance of skip metastasis in patients with gastric cancer

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Abstract

Background. Metastasis appearing to bypass or skip tiers of lymph nodes (LNs) has been referred to as skip metastasis. The clinical impact of skip metastasis in gastric cancer remains unclear.

Methods. In patients with gastric cancer, the clinicopathological features and postoperative prognoses of 21 patients with skip metastasis were evaluated and compared with findings in patients with group 1 (N1) or group 2 (N2) LN metastasis.

Results. Of the 21 patients with skip metastasis, 9 patients had metastasis in the LN along the common hepatic artery (No. 8a), 8 patients had metastasis in the LN along the left gastric artery (No. 7), 2 patients had metastasis in LNs No. 7 and No. 8a, 1 patient had metastasis in the LN at the splenic hilum (No. 10), and 1 patient had metastasis in LN No. 10 and the LN along the splenic artery (No. 11). The mean diameter of the tumors in the patients with skip metastasis was 5.7 ± 2.4 cm, which was significantly smaller than those in the N1 patients (7.9 ± 4.1 cm) and N2 patients (9.3 ± 4.6 cm). The incidence of serosal invasion, lymphatic vessel invasion, and peritoneal metastasis was lower in patients with skip metastasis compared with N2 patients. The 5-year survival rates were 70.2%, 62.0%, and 31.2% in patients with skip metastasis, patients with metastasis in group 1 LNs, and those with metastasis in group 2 LNs, respectively. The prognosis of patients with metastasis in group 2 LNs was significantly worse than that of patients with either skip metastasis ($P = 0.0029$) or metastasis in group 1 LNs ($P < 0.0001$).

Conclusion. Our data indicate that both the clinicopathological characteristics and the prognoses of patients with skip metastasis were similar to those of patients with N1 LN metastasis, but these features were not similar to those in patients with N2 LN metastasis. The sites of skip metastasis presented in the current study may be the key for applying the concept of the sentinel node in gastric cancer.

Key words Gastric cancer · Skip metastasis · Prognosis · Lymph node metastasis

Introduction

Many studies have indicated that the presence or absence of lymph node (LN) metastasis is the most important prognostic factor in gastric cancer [1–3]. Lymph node (LN) metastases usually spread in an orderly fashion in relation to the lymphatic streams. On the other hand, metastasis appearing to bypass or skip tiers of LNs has been referred to as skip metastasis. The clinical impact of skip metastasis in gastric cancer has not been reported so far, although there are several studies of skip metastasis in other cancers [4–6].

In the current study, we investigated the sites and numbers of skip metastases with regard to the nature of the primary tumor, and we compared clinicopathological features between patients with and without skip metastasis. We then determined the clinical impact of skip metastasis on surgical outcome in patients with gastric cancer.

Patients and methods

Patients

This study examined 1985 patients with gastric adenocarcinoma who underwent gastrectomy at our institution between January 1975 and December 2000. The data were collected retrospectively. Ages ranged between 20 and 90 years, with an average of 62.0 years; 1266 patients were male and 719 were female. The clinicopathological findings were determined according to the *Japanese Classification of Gastric Carcinoma* [7].

At the time of analysis, the median follow-up for the 1067 survivors was 108 months. Of the 918 deaths, 558 were related to recurrence of gastric cancer, 65 were due to another malignancy, and 229 were due to another disease or to an accident. Patients who died of either

another malignancy, another disease, or accident were treated as censored cases in the survival analysis. Twenty-one patients whose causes of death were unknown and 45 patients who died of postoperative complications were excluded from the prognostic analysis.

Statistical analysis

The association between factors was evaluated by the χ^2 test and Fisher's exact probability test. The significance of differences among means was determined by the Mann-Whitney test. Survival rates were determined by the Kaplan-Meier method, and differences between survival curves were examined with the log-rank test. The accepted level of significance was $P < 0.05$. Stat View software (Abacus Concepts, Berkeley, CA, USA) was used for all statistical analyses.

Results

Of 313 patients with metastasis in group 2 lymph nodes (LNs), 21 patients (6.7%) did not have metastasis in

group 1 LNs. The profiles of the 21 patients with skip LN metastases are shown in Table 1. Nine patients had metastasis in the LN along the common hepatic artery (No. 8a), 8 patients had metastasis in the LN along the left gastric artery (No. 7), 2 patients had metastasis in LNs No. 7 and No. 8a, 1 patient had metastasis in the LN at the splenic hilum (No. 10), and one patient had metastasis in LN No. 10 and the LN along the splenic artery (No. 11).

The clinicopathological data of the patients with skip metastasis were compared with the data of those with metastasis in only group 1 nodes (N1, 348 patients) and those with metastasis in both group 1 and 2 nodes (N2, 292 patients; Table 2). The mean size ($\pm$ SD) of tumors in patients with skip metastasis was 5.7 ± 2.4 cm, which was significantly smaller than those in N1 patients (7.9 ± 4.1 cm) and N2 patients (9.3 ± 4.6 cm). The incidence of serosal invasion was 38.1% for patients with skip metastasis, which was significantly lower than that for N1 patients (56.7%) and N2 patients (78.4%). Lymphatic vessel invasion was less frequent in patients with skip metastasis (81.0%) compared with N2 patients (93.2%). The incidence of peritoneal metastasis was

Table 1. Profiles of 21 patients with skip metastasis

	Age (years)	Sex	No. (+) LN (station No.)	Location ^a	No. LNs retrieved	Gross type	Size (cm)	Histology ^b	T ^c	Ly ^d	V ^e
1	66	F	1 (No. 8a)	L, ant	81	2	6	D	2	3	0
2	56	M	1 (No. 8a)	L, circ	26	3	7	D	2	2	0
3	72	M	1 (No. 8a)	L, less	65	2	5	U	2	3	2
4	65	F	1 (No. 8a)	L, post	36	3	10	D	2	3	1
5	78	F	1 (No. 8a)	L, less	17	1	1.2	D	1	1	0
6	70	F	1 (No. 7)	L, great	56	2	8	U	2	3	1
			2 (No. 8a)								
7	65	F	2 (No. 10)	U, great	32	2	4	D	3	2	2
8	60	M	1 (No. 7)	U, less	25	0	4.5	D	1	0	1
9	54	M	1 (No. 8a)	U, less	55	2	9	U	3	0	2
10	51	M	1 (No. 8a)	U, ant	44	2	2.4	D	3	3	0
11	70	M	1 (No. 7)	U, circ	31	3	8.8	D	4	0	3
12	34	M	1 (No. 7)	M, post	30	2	2	U	2	1	0
13	51	F	1 (No. 8a)	M, less	41	3	5	U	3	2	1
14	73	M	1 (No. 7)	M, post	24	2	4	U	2	3	1
15	68	M	2 (No. 10)	M, ant	92	3	4.5	U	3	0	0
			1 (No. 11)								
16	71	M	1 (No. 7)	M, ant	17	2	6	U	2	3	0
17	71	F	1 (No. 8a)	M, ant	42	3	4	D	2	3	3
18	65	M	1 (No. 7)	M, great	18	5	7	U	4	3	3
19	68	F	1 (No. 7)	M, less	17	0	5.5	D	2	2	0
20	67	M	2 (No. 7)	M, ant	46	2	8	U	2	1	2
			1 (No. 8a)								
21	72	F	6 (No. 7)	M, less	44	3	8	U	4	3	3

LN, lymph node

^aU, upper one-third of the stomach; M, middle one-third of the stomach; L, lower one-third of the stomach; circ, circular; ant, anterior; post, posterior; less, lesser curvature; great, greater curvature

^bD, papillary or tubular adenocarcinoma; U, poorly differentiated or mucinous adenocarcinoma, or signet-ring cell carcinoma

^cT1, tumor has invaded lamina propria or submucosa; T2, tumor has invaded the muscularis propria or the subserosa; T3, tumor penetrating the serosa; T4, tumor invading adjacent organs

^dLymphatic vessel invasion: ly 0-ly 3, grade of lymphatic vessel invasion

^eBlood vessel invasion: v 0-v 3, grade of venous invasion

Table 2. Clinicopathologic characteristics according to the status of lymph node metastasis

Variables	Skip meta (n = 21)	N1 (n = 348)	N2 (n = 292)
Age, years (mean $\pm$ SD)	64.1 $\pm$ 10.1	62.7 $\pm$ 12.1	62.9 $\pm$ 11.7
Sex			
Male	13 (61.9%)	220 (63.2%)	180 (61.6%)
Female	8 (38.1%)	128 (36.8%)	112 (38.4%)
Histology			
Differentiated	10 (47.6%)	123 (35.3%)	87 (29.8%)
Undifferentiated	11 (52.4%)	225 (64.7%)	205 (70.2%)
Size, cm (mean $\pm$ SD)	5.7 $\pm$ 2.4***	7.9 $\pm$ 4.1*	9.3 $\pm$ 4.6
Serosal invasion			
Negative	13 (61.9%)*	151 (43.3%)*	63 (21.6%)
Positive	8 (38.1%)	197 (56.7%)	229 (78.4%)
Lymphatic vessel invasion			
Negative	4 (19.0%)*	70 (20.1%)*	20 (6.8%)
Positive	17 (81.0%)	278 (79.9%)	272 (93.2%)
Blood vessel invasion			
Negative	8 (38.1%)	156 (44.8%)*	99 (33.9%)
Positive	13 (61.9%)	192 (55.2%)	193 (66.1%)
Peritoneal metastasis			
Negative	21 (100%)*	316 (90.8%)*	235 (80.5%)
Positive	0 (0%)	32 (9.2%)	57 (19.5%)
Liver metastasis			
Negative	21 (100%)	335 (96.3%)*	269 (92.1%)
Positive	0 (0%)	13 (3.7%)	23 (7.9%)
Curability			
Curative	19 (90.5%)	299 (85.9%)*	208 (71.2%)
Noncurative	2 (9.5%)	49 (14.1%)	84 (28.8%)

* $P < 0.05$ compared to patients with N2; ** $P < 0.05$ compared to patients with N1

lower in patients with skip metastasis compared with N2 patients.

The disease-specific survival of the patients, according to the status of LN metastasis, defined by the *Japanese Classification of Gastric Carcinoma* [7], is illustrated in Fig. 1A. The 5-year survival rates were 70.2%, 62.0%, and 31.2% in patients with skip metastasis, metastasis in group 1 LNs, and metastasis in group 2 LNs, respectively. The prognosis of patients with metastasis in group 2 LNs was significantly worse than that of the patients with either skip metastasis ($P = 0.0029$) or metastasis in group 1 LNs ($P < 0.0001$). Figure 1B shows the disease-specific survival of the patients according to the status of LN metastasis defined by the TNM classification. The 5-year survival rates were 70.2%, 60.6%, and 27.3% in patients with skip metastasis, those with N1, and those with N2, respectively. The prognosis of patients with N2 was significantly worse than that of patients with either skip metastasis ($P = 0.0002$) or N1 ($P < 0.0001$).

Discussion

Evaluation of the status of LN metastasis is extremely important to predict the outcome of patients with

many kinds of cancer, including gastric cancer. Gastric cancer has been assumed to spread sequentially through the anatomical regional lymphatic bed. In the current study, however, 21 patients (6.7%) had skip metastasis.

Skip metastasis can be explained by nonsequential spread through the lymphatic basin, or nonanatomical spread. The results of sentinel LN biopsy provide some important information. Sentinel LN biopsy has recently been introduced in patients with melanoma and breast cancer to assess tumor involvement in regional LNs; the procedure has less morbidity than but accuracy equal to that of complete lymphadenectomy [8–12]. The sentinel node concept is that LN metastases spread in an orderly fashion in relation to the lymphatic streams, and that the negative tumor-bearing status of the first LN into which the primary tumor drains indicates the negative tumor status of the entire region of LNs beyond. Ichikura et al. [13], using indocyanine green solution, reported that green nodes, indicating sentinel LNs, were distributed beyond the perigastric area in 31% of patients. Kitagawa et al. [14] also reported that approximately one-third of the radioactive tracer they used was directly distributed to the group 2 LNs, and seven patients (5.1%) had skip sentinel nodes. These results indicate that the anatomical nodal grouping in the conventional

Fig. 1. **A** Disease-specific survival of the patients according to the status of lymph node metastasis defined by the *Japanese Classification of Gastric Carcinoma* [7]. The 5-year survival rates were 70.2%, 62.0%, and 31.2% in patients with skip metastasis (*skip meta*), patients with metastasis in group 1 lymph nodes (*N1*), and those with metastasis in group 2 lymph nodes (*N2*), respectively. The prognosis of patients with metastasis in group 2 lymph nodes was significantly worse than that of patients with either skip metastasis ($P = 0.0029$) or

metastasis in group 1 lymph nodes ($P < 0.0001$). **B** Disease-specific survival of the patients according to the status of lymph node metastasis defined by the TNM classification. The 5-year survival rates were 70.2%, 60.6%, and 27.3% in patients with skip metastasis, those with *N1*, and those with *N2*, respectively. The prognosis of patients with *N2* was significantly worse than that of the patients with either skip metastasis ($P = 0.0002$) or *N1* ($P < 0.0001$)

classification does not always correspond to tumor spread.

There is another possibility that metastasis cannot be detected because of either an overlooking of the metastasis or the presence of micrometastasis, although metastasis does exist in group 1 LNs, indicating sequential anatomical LN metastasis. In this regard, Natsugoe et al. [15] demonstrated that, with a single-section examination of dissected nodes, metastasis could be overlooked in many cases in patients with gastric cancer. On the other hand, recent molecular techniques allow the detection of micrometastases. In this regard, we [16] found, by immunohistochemistry using anti-cytokeratin (CK) monoclonal antibody, that 2 of 83 patients with stage II gastric cancer (pT3N0M0) had only group 2 LN metastasis. Arai et al. [17] demonstrated, with CK staining of level I nodes from 7 patients thought to have skip metastasis, that although all patients were negative with hematoxylin and eosin staining, three were CK-positive. On the other hand, Merrie et al. [5] demonstrated a higher incidence of skip metastasis in colon cancer, assessed by molecular techniques, than has previously been reported. More extensive study is needed to determine the exact frequency of skip metastasis in gastric cancer.

The *Japanese Classification of Gastric Carcinoma* (JCGC) defines N stage by the location of LN metastasis relative to the primary tumor [7]. On the other hand, the

Union Internationale Contre le Cancer (UICC) defines N stage by the number of LN metastases. In the current study, we used the N stage defined by the JCGC and found that the clinicopathological characteristics of patients with skip metastasis were similar to those of patients with group 1 LN metastasis, but not to those of patients with group 2 LN metastasis. Moreover, the prognosis of patients with skip metastasis was similar to that of patients with group 1 LN metastasis and was significantly better than that of patients with group 2 LN metastasis. Park et al. [18] also reported better prognosis of patients with skip metastasis compared to that of patients with group 2 LN metastasis, although the difference was not statistically significant. Of importance is that all but 1 of the 21 patients with skip metastasis in the current study had only one or two positive nodes, and therefore they were classified as *N1* by the TNM classification, although they were classified as *N2* by the JCGC. Although it still remains elusive as to which is important, the location or the number of positive LNs, some studies indicate that the number-based N staging has greater prognostic power than the anatomical-based system [19]. Our results may also support the prognostic reliability of the current UICC/AJCC (American Joint Committee on Cancer) TNM staging system, in which LN status is evaluated by the number of positive nodes, and not by the topographical station, as in the JCGC.

In conclusion, our data indicate that both the clinicopathological characteristics and the prognoses of patients with skip metastasis were similar to these parameters in patients with group 1 LN metastasis, but not in patients with group 2 LN metastasis. The sites of skip metastasis presented in the current study may be the key for applying the concept of the sentinel node in gastric cancer.

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