Original article

Evaluation of the ratio of lymph node metastasis as a prognostic factor in patients with gastric cancer

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Abstract:

Background. Lymph node metastasis in patients with gastric cancer is one of the important prognostic factors. However, there is no consensus concerning the best classification for lymph node metastasis as a prognostic factor. So, to evaluate the ratio of the number of metastatic lymph nodes to the total number of dissected lymph nodes (the ratio of LN meta) as a prognostic factor, we compared the ratio of LN meta with lymph node status according to the Japan Classification of Gastric Carcinoma and the total number of metastatic lymph nodes with multivariate analysis.

Methods. Between 1991 and 1997, a total of 360 patients with primary gastric cancer who underwent gastrectomy with D2 or more extended lymph node dissection were included in this study. Ten kinds of prognostic factors and three types of different classifications for lymph node metastasis were analyzed by multivariate analysis using the Cox regression.

Results. The average number of dissected lymph nodes and metastatic lymph nodes were 55.0 (range, 11–184) and 2.6 (range, 0–86), respectively. There were significant differences of the 5-year cumulative survival rates among each group of the ratio of LN meta (0%, 1%–9%, 10%–24%, and more than 25%). Age, tumor size, curability, and the ratio of LN meta were selected as independent prognostic factors by forward stepwise selection. The ratio of LN meta showed the highest hazard ratio by Cox regression.

Conclusion. The ratio of LN meta appears to be an important prognostic factor and the best classification factor for lymph node metastasis.

Key words: gastric cancer, lymph node metastasis, prognostic factors, ratio of involved to dissected lymph nodes, survival rate

Introduction

The survival of gastric cancer patients has recently improved because of early detection and several therapeutic modalities. However, gastric cancer is still a major cause of cancer death in Japan. Thus, it is important to reveal the prognostic significance in gastric cancer to obtain further improvement of therapeutic efficacy. Distant metastasis and depth of invasion are well known as strong prognostic factors [1–4]. Also, lymph node metastasis is considered an important prognostic factor [4–9]. In Japan, the extent of lymph node metastasis is classified by anatomical station of lymph node according to the Japanese Classification of Gastric Carcinoma (JCGC) [10]. In Western countries, extent of lymph node metastasis is classified by the number of regional lymph node metastases according to the International Union against Cancer (UICC) tumor node metastasis (TNM) staging categories [11]. Several investigators [6,12–16] have emphasized that the number of metastatic lymph nodes is a most reliable indicator as a prognostic factor.

There have been some reports [17–19] that the ratio of the number of metastatic lymph nodes to the total number of dissected lymph nodes (the ratio of LN meta) was more useful as a prognostic factor. It seems that the total number of metastatic lymph nodes is affected by the total number of lymph nodes dissected. We considered that the ratio of LN meta was capable of being a reliable classification. So, to reveal the most reliable classification of lymph node metastasis in gastric cancer patients without liver metastasis, peritoneal dissemination, and other distant metastasis, these three classifications of lymph node status were retrospectively compared with other kinds of prognostic factors by multivariate analysis using the Cox regression [20].

Patients and methods

Between January 1, 1990 and December 31, 1997, a total of 360 patients with primary gastric cancer who underwent gastrectomy with D2 or more extended lymph node dissection were included in this study. Patients with liver metastasis and peritoneal dissemination were excluded from the study.

Lymph nodes, after fixation in 20% formalin solution, were evaluated by sectioning into a slice in the plane of largest dimension of the node. Hematoxylin and eosin-stained slides were examined under a light microscope.

Three types of classifications for lymph node metastasis were as follows: groups (n0, n1, n2, n3, n4) of metastatic lymph nodes according to the JCGC, the total number of metastatic lymph nodes, and the ratio of LN meta. In the evaluation of the total number of metastatic lymph nodes, patients were divided into following four groups: 0, 1–6, 7–15, and more than 16. They were also divided into four groups as to the ratio of LN meta: 0%, 1%–9%, 10%–24%, and more than 25%. Cumulative survival rates were compared among each group in their respective classifications.

We selected the following ten prognostic factors: age, sex, tumor size, main tumor location, histological type, depth of invasion, lymphatic and venous invasion, level of lymph nodes dissection, and curability. Main tumor location of the stomach was divided into upper, middle, and lower portion; histological type was divided into differentiated and undifferentiated type; and depth of invasion (t1, t2, t3, t4), level of lymph node dissection (D2, D3, D4), and curability (A, B, C) were classified according to the JCGC. Lymphatic and venous invasion were divided into negative and positive. Three types of classifications for lymph node metastasis were compared with these prognostic factors by multivariate analysis.

Cumulative survival rates were calculated by the Kaplan–Meier method, and statistical significance was evaluated by log-rank test. The Statistical Package for the Social Sciences (SPSS 8.0, Chicago, IL, USA) for the Microsoft Windows program was used for simultaneous multivariate adjustment of all covariates by Cox regression analysis. Forward stepwise regression analysis (likelihood-ratio statistic) was performed to select good predictors of survival. The relative risk of death was compared by using exponential coefficient [$\exp(\beta)$]. A *P* value of less than 0.05 was considered to be statistically significant.

Results

Clinicopathological and surgical features

The median age of patients was 61.7 years (range, 92–31). The ratio of male to female was 2.19:1. The

proportion of tumors in the upper, middle, and lower portion of the stomach was 15.6%, 40.6%, and 43.8%, respectively. The median tumor size was 44.7 mm (range, 5–155 mm). The proportion of lymph node dissection was 73.1% in D2, 21.4% in D3, and 5.6% in D4. Proportion of depth of invasion, lymphatic invasion, venous invasion, lymph node dissection, and curability are shown in Table 1. The major reason for resulting in curability C was the remnant of metastatic lymph nodes without dissection.

Table 1. Clinicopathological characteristics

Sex	
Male:	247
Female:	113
Age (mean $\pm$ SD)	61.7 $\pm$ 10.3
Tumor size (mean $\pm$ SD)	44.79 $\pm$ 30.2 mm
Main location of tumor	
Lower	158 (43.8%)
Middle	146 (40.6%)
Upper	56 (15.6%)
Histological type	
Differentiated	216
Undifferentiated	144
Depth of invasion	
t1	213 (59.2%)
t2	107 (29.7%)
t3	33 (9.7%)
t4	7 (2.0%)
Lymphatic invasion	
Positive	170 (47.2%)
Negative	190 (52.8%)
Venous invasion	
Positive	248 (68.9%)
Negative	112 (31.1%)
Curability	
A	291 (80.8%)
B	49 (13.6%)
C	20 (5.6%)
Lymph node metastasis according to JCGC	
n0	258 (71.7%)
n1	55 (15.3%)
n2	23 (6.3%)
n3	6 (1.7%)
n4	18 (5.0%)
Number of metastatic lymph nodes	
0	257 (71.4%)
1–6	61 (17.0%)
7–15	28 (7.8%)
≥ 16	14 (3.9%)
Ratio of LN meta (%)	
0	257 (71.4%)
1–9	58 (16.1%)
10–24	29 (8.1%)
≥ 25	16 (4.4%)

JCGC, Japanese Classification of Gastric Carcinoma; ratio of LN meta, the ratio of the number of metastatic lymph nodes to the total number of dissected lymph nodes

Lymph node status

The average numbers of dissected lymph nodes and metastatic lymph nodes were 55.0 (range, 11–184) and 2.6 (range, 0–86) in a total of 360 gastric cancer patients. Those were 48.1 (range, 11–113) and 0.9 (range, 0–27) in D2 dissection, 71.1 (range, 21–131) and 5.5 (range, 0–86) in D3, and 86.2 (range, 39–184) and 11.8 (range, 0–70) in D4, respectively. The proportion of each group according to JCGC, the total number of metastatic lymph nodes, and the ratio of LN meta are shown in Table 1.

Morbidity and mortality

Of 75 deceased patients, 29 died of other diseases. Two patients died within 30 days after surgery because of intraperitoneal bleeding; one patient had undergone total gastrectomy and pancreaticosplenectomy with D4 dissection and the other patient distal gastrectomy and cholecystectomy with D3. The major complications after surgery were intraperitoneal bleeding (7 cases), intraperitoneal abscess (15 cases), anastomotic leakage (16 cases), and leakage of pancreatic juice (16 cases). Surgical morbidity and mortality rates were 18.1% and 2.8%, respectively.

Survival rate

Figure 1 shows the survival curves for five groups according to JCGC of lymph node metastasis. There were no significant differences between n2 and n3–n4, n3, and n4. Figure 2 shows the survival curves for four

Fig. 1. Comparison of cumulative survival rates according to the Japanese Classification of Gastric Carcinoma (JCGC). There were significant differences between n0 and n1–n4, n1, and n2–n4 ($P < 0.005$; log-rank test)

groups divided by the total number of metastatic lymph nodes. There was no significant difference between 7–15 and more than 16. Figure 3 shows the survival curves for four groups divided by the ratio of LN meta. There were significant differences among each group.

Comparison of the hazard ratios

Ten prognostic factors and each of three types of different classifications were analyzed by Cox regression (forced entry method) (Tables 2–4). In all

Fig. 2. Comparison of cumulative survival rates according to the total number of metastatic lymph nodes. There were significant differences rates among each group except for 7–15 vs. more than 16 ($P < 0.005$; log-rank test)

Fig. 3. Comparison of cumulative survival rates according to the ratio of the number of metastatic lymph nodes to the total number of dissected lymph nodes. There were significant differences among each group ($P < 0.005$; log-rank test)

Table 2. Multivariate analysis of prognostic factors including extent of lymph node metastasis according to JCGC with Cox regression

Factor	Category	β	SE	Wald	P value	Exp(β)
Extend of lymph node metastasis according to JCGC	n0	0.0		6.6393	0.1562	
	n1	0.8106	0.3753	4.6653	0.0308	2.2491
	n2	0.9518	0.6109	2.4277	0.1192	2.5904
	n3	0.3247	0.8159	0.1584	0.6907	1.3836
	n4	1.2271	1.0492	1.3679	0.2422	3.4112
Sex	Female	0.0				
	Male	0.5542	0.3021	3.3650	0.0666	1.7405
Age		0.0408	0.0140	8.4489	0.0037	1.0417
Location	A	0.0		2.8302	0.9241	
	M	0.0359	0.3494	0.0105	0.9182	1.0365
	C	1.1136	0.2871	0.1567	0.6922	1.1204
Size		0.0092	0.0040	5.2072	0.0225	1.0092
Histological type	Differentiated	0.0				
	Undifferentiated	0.0334	0.2739	0.0149	0.9029	1.0340
Lymphatic invasion	Negative	0.0				
	Positive	0.1992	0.4727	0.1776	0.6735	1.2204
Venous invasion	Negative	0.0				
	Positive	0.1540	0.3707	0.1725	0.6779	1.1664
Depth of invasion	t1	0.0		3.2654	0.3525	
	t2	0.1058	0.7483	0.0200	0.8875	1.8180
	t3	0.6877	0.6212	1.2257	0.2682	2.7210
	t4	0.3794	0.5505	0.4128	0.5206	1.6494
Lymph node dissection	D2	0.0		2.8345	0.2424	
	D3	0.4083	0.3477	1.3785	0.2404	1.5042
	D4	0.7519	0.4601	2.6698	0.1023	2.1209
Curability	A	0.0		3.4330	0.1797	
	B	0.9029	0.6324	2.0388	0.1533	2.4668
	C	1.9996	1.1052	3.2734	0.0704	7.3863

JCGC, Japanese Classification of Gastric Carcinoma

analyses, curability showed the highest exp(β), and lymph node metastasis according to each of three different classifications showed higher exp(β) than lymph node dissection and depth of invasion (Tables 2–4). All factors including three types of different classification of lymph node metastasis were analyzed by forward stepwise selection with Cox regression (Table 5). Age, size, curability, and the ratio of LN meta were selected as independent prognostic factors. The ratio of LN meta showed the highest exp(β) among the independent prognostic factors.

Discussion

Grouping of lymph nodes according to the JCGC depends upon location of primary tumor and is decided by anatomical–physiological lymphatic flow. Skip metastasis [21–23] is one of the important problems on JCGC classification. Even one lymph node with skip metastasis changes the stage. Skip metastasis sometimes is a cause of stage migration. There were no significant differences in survival rates among n2–n4 in this study, and patients with n3 showed the same survival rate as

those with n2. This result suggests that it may not be necessary to divide n2 and n3 in respect to prognosis. The new grouping of lymph node metastasis proposed by the *Japanese Classification of Gastric Carcinoma* [24] was defined mainly on the basis of efficacy of dissection [23]. However, we have not yet evaluated the new classification of lymph node metastasis as a prognostic factor at present study. It is expected to be a candidate for an important prognostic factor.

Isozaki et al. [12] reported that the 5-year survival rate was significantly different among four groups (0, 1–4, 5–10, and more than 11) according to the total number of metastatic lymph nodes. In this study, groups of the total number of metastatic lymph nodes were divided by referring to the TNM classification, except for including lymph nodes on the posterior surface of the pancreatic head, along the superior mesenteric vein and the middle colic vessel, and around the abdominal aorta. Survival rate according to the total number of metastatic lymph nodes was significantly different among each group, except 7–15 vs. more than 16. Roder et al. [6] reported the usefulness of TNM classification. There were highly significant differences in the survival rates among pN1, pN2, and pN3. Thus, we calculated

Table 3. Multivariate analysis of prognostic factors including the total number of metastatic lymph nodes with Cox regression

Factor	Category	β	SE	Wald	<i>P</i> value	Exp(β)
Number of metastatic lymph nodes	0	0.0		9.2410	0.0263	
	1–6	0.5008	0.3903	1.6462	0.1995	1.6500
	7–15	1.3578	0.4733	8.2303	0.0041	3.8876
	≥ 16	1.3173	0.5958	4.8881	0.0270	3.7331
Sex	Female	0.0				
	Male	0.4422	0.3006	2.1638	0.0143	1.5561
Age		0.0398	0.0140	8.0824	0.0045	1.0406
Location	A	0.0		1.1371	0.5664	
	M	0.0257	0.3475	0.0055	0.9410	1.0260
	C	0.3038	0.2982	1.0375	0.3084	1.3549
Size		0.0094	0.0041	5.3062	0.0213	1.0095
Histological type	Differentiated	0.0				
	Undifferentiated	0.0545	0.2718	0.0402	0.8410	1.0560
Lymphatic invasion	Negative	0.0				
	Positive	0.0116	0.4665	0.0006	0.9801	1.0117
Venous invasion	Negative	0.0				
	Positive	0.2917	0.3798	0.5897	0.4425	1.3387
Depth of invasion	t1	0.0		3.8474	0.2784	
	t2	0.4561	0.7572	0.3628	0.5468	1.5779
	t3	0.9213	0.6081	2.2851	0.1298	2.5125
	t4	0.4038	0.5656	0.5098	0.4752	1.4976
Lymph node dissection	D2	0.0		3.0611	0.2164	
	D3	0.4489	0.3472	1.6712	0.1961	1.5666
	D4	0.7786	0.4759	2.6759	0.1019	2.1783
Curability	A	0.0		12.7604	0.0017	
	B	0.9521	0.4499	4.4795	0.0343	2.5912
	C	1.9388	0.5434	12.7305	0.0004	6.9504

survival rates of patients accurately followed by TNM classification. The population and survival rate of each group according to TNM classification were almost the same as those according to the total number of metastatic lymph nodes as described in this study (data not shown). These results suggest that patients with extended lymph node metastasis have also a large number of metastatic lymph nodes in the regional lymph nodes, mainly due to the setting of a cutoff point.

Wu et al. [15] described significant prognostic differences between patients with 8 or fewer metastatic lymph nodes and those with 9 or more. Three other investigators [5,12,13] showed significant differences of survival rate with cutoff points of 9–13. Roder et al. [6] considered that those discrepancies could be explained with small patient populations and other different backgrounds. We considered that it was difficult to compare the prognostic difference of the total number of metastatic lymph nodes among many institutions, because the difference of the total number of dissected lymph nodes might change the total number of metastatic lymph nodes. So, we considered the ratio of LN meta.

The four groups (0%, 1%–9%, 10%–24%, and more than 25%) in the evaluation of the ratio of LN meta

were determined in the light of survival rate. Kwon and Kim [17] reported that significant correlation was found between the relative risk of death and the ratio of LN meta in advanced gastric cancer patients, when patients were grouped as 1%–15%, 16%–30%, and more than 31%. However, survival rates were not significantly different between 16%–30% and more than 31%. Kim et al. [19] reported that there were significant survival differences according to the ratio of LN meta when patients were divided into the ratio of 0%, up to 10%, up to 30%, up to 50%, and more than 50%. We also demonstrated significant differences in survival rates among each group of the ratio of LN meta using our grouping system. Therefore, the ratio of LN meta appeared to be a most reliable classification of lymph node metastasis with univariate analyses.

To evaluate the reliability of the classification for lymph node metastasis, we performed multivariate analysis with ten prognostic factors and three types of different classification for lymph node metastasis using the Cox regression (forced entry method). Each classification of lymph node metastasis showed higher hazard ratio (exp(β)) than the other prognostic factors except for curability. To determine the independent prognostic factor, we then performed forward stepwise

Table 4. Multivariate analysis of prognostic factors including lymph node metastasis according to the ratio of LN meta

Factor	Category	β	SE	Wald	<i>P</i> value	Exp(β)
Ratio of LN meta (%)	0	0.0		8.9809	0.0295	
	1–9	0.4652	0.3880	1.4379	0.2305	1.5924
	10–24	1.0465	0.4683	4.9935	0.0254	2.8477
	≥ 25	1.5173	0.5304	8.1826	0.0042	4.5602
Sex	Female	0.0				
	Male	0.4762	0.2947	2.6110	0.1061	1.6100
Age		0.0375	0.0138	7.4283	0.0064	1.0382
Location	A	0.0		0.7776	0.6779	
	M	0.1084	0.3509	0.0955	0.7573	1.1145
	C	0.2584	0.2932	0.7772	0.3780	1.2949
Size		0.0091	0.0040	5.1018	0.0239	1.0091
Histological type	Differentiated	0.0				
	Undifferentiated	0.1244	0.2760	0.2031	0.6522	1.1324
Lymphatic invasion	Negative	0.0				
	Positive	0.0524	0.4623	0.0129	0.9097	1.0538
Venous invasion	Negative	0.0				
	Positive	0.1596	0.3780	0.1782	0.6729	1.1730
Depth of invasion	t1	0.0		3.5092	0.3196	
	t2	0.3316	0.7601	0.1904	0.6626	1.3932
	t3	0.8348	0.6156	1.8391	0.1751	2.3045
	t4	0.3959	0.5666	0.4882	0.4847	1.4857
Lymph node dissection	D2	0.0		3.1111	0.2111	
	D3	0.5051	0.3535	2.0409	0.1531	1.6571
	D4	0.7060	0.4583	2.3737	0.1234	2.0259
Curability	A	0.0		10.7480	0.0046	
	B	0.9485	0.4498	4.4472	0.0350	2.5819
	C	1.7863	0.5455	10.7237	0.0011	5.9675

Ratio of LN meta, the ratio of the number of metastatic lymph nodes to the total number of dissected lymph nodes

Table 5. Detection of independent prognostic factors with stepwise selection and Cox regression

Factor	Category	β	SE	Wald	<i>P</i> value	Exp(β)	95% CI
Ratio of LN meta (%)	0	0.0		14.3755	0.0043		
	1–9	0.7641	0.3513	4.7296	0.0296	2.1471	1.0784–4.2748
	10–24	1.2294	0.4227	8.4567	0.0036	3.4190	1.4930–7.8297
	≥ 25	1.7575	0.4742	13.7352	0.0002	5.7980	2.2889–14.6869
Age		0.0327	0.0124	6.9924	0.0082	1.0332	1.0085–1.0586
Size		0.0083	0.0035	5.6379	0.0176	1.0084	1.0015–1.0153
Curability	A	0.0		11.5352	0.0023		
	B	0.8559	0.3538	5.8518	0.0156	2.3534	1.1764–4.7083
	C	1.5593	0.4693	11.0408	0.0009	4.9556	1.8956–11.9306

selection. Age, size, curability, and the ratio of LN meta were selected as independent prognostic factors. The ratio of LN meta (the hazard ratio of more than 25% to 0%) showed the highest hazard ratio among these prognostic factors by Cox regression (likelihood method).

In conclusion, lymph node metastasis and curability were considered to be significant prognostic factors, and the ratio of LN meta appeared to be the best classification for lymph node metastasis as a prognostic

factor in gastric cancer patients without distant metastasis.

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