Minimum Number of Lymph Nodes that Should Be Examined for the International Union Against Cancer/American Joint Committee on Cancer TNM Classification of Gastric Carcinoma

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Abstract. The classification of lymph node metastasis based on the number of positive nodes has been adopted in the International Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC) TNM classification of gastric carcinoma. However, the N classification (for condition of the regional lymph nodes) would be underestimated when the number of examined nodes were too small. To determine the minimum number of lymph nodes to examine for a correct classification, we analyzed 926 patients undergoing curative resection for gastric carcinoma. The number of metastatic lymph nodes correlated significantly with the number of examined lymph nodes. The pN0 patients with 10 to 14 examined nodes showed a significantly higher survival rate than did those with 5 to 9 examined nodes, and they had as good a prognosis as those with 15 or more examined nodes. In the pN1 and pN2 categories, patients with 29 or fewer examined nodes tended toward lower survival rates than did patients with 30 or more examined nodes. Among the patients who were classified as stage IA, the survival rate for those with 5 to 9 examined nodes was significantly lower than that for patients with 30 or more examined nodes. Among the patients classified as stage III, those with 10 to 19 examined nodes and those with 20 to 29 examined nodes had lower survival rates than did patients with 30 or more examined nodes. In conclusion, the minimum number of lymph nodes examined for a correct pN0 classification can be reduced from 15 to 10. For pN1–3 classifications, 20 or more nodes should be examined, and examining 30 or more lymph nodes may be desirable.

The classification of lymph node metastasis based on the number of positive nodes has been adopted in the fifth edition of the International Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC) TNM classification of gastric carcinoma. Several reports have shown the superiority of this classification over the classification system based on the location of metastatic nodes as a prognostic determinant [1–4]. However, it has been shown that the more lymph nodes examined, the more likely it is that nodal metastases will be detected [5]. Nodal yields depend not only on the extent of lymphadenectomy but also on how and by whom lymph node retrieval is performed [6, 7]. Thus, when the number of exam-

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ined lymph nodes is insufficient for diagnosis, the nodal stage may be underestimated, which is so-called stage migration. It remains unclear how many lymph nodes should be examined for the UICC/AGCC TNM classification, although the examination of 15 or more lymph nodes is required for the pN0 classification. The aim of this study was to determine the minimum number of lymph nodes that should be examined in order to avoid stage migration.

Patients and Methods

A total of 925 consecutive patients undergoing curative resection for primary gastric carcinoma between 1982 and 1995 in the Department of Surgery I, National Defense Medical College Hospital, Tokorozawa, Japan, were chosen as subjects of this study. D2 or greater lymphadenectomy, as defined by the Japanese classification of gastric carcinoma [8], was performed in 783 patients (85%). Regional lymph nodes were removed from the surgical specimens immediately after the operation using scissors and forceps under gross inspection by senior residents who had participated in the operation. One section from each paraffin-embedded specimen of all lymph nodes dissected was stained conventionally with hematoxylin and eosin and examined by pathologists. Survival rates and background factors were analyzed according to the number of examined lymph nodes. Lymph node metastases were classified as pN0, pN1, pN2, or pN3 according to the UICC/AJCC TNM classification [9] irrespective of the number of examined lymph nodes.

The survival curves were generated from observed survival times using the Kaplan-Meier method. Deaths from causes other than gastric cancer were treated as censored observations at the time of death. The significance of the difference in survival rate was determined by log rank test. The age and the numbers of lymph nodes for the two groups were compared using the Mann-Whitney U-test. The frequency distributions between the two groups were tested by the chi-square test, Fisher's exact test, or the Mann-Whitney U-test. A p value of less than 0.05 was considered significant.

Table 1. Survival rates according to the number of examined lymph nodes.

Number of examined nodes	Nodal classification			
	pN0 (n = 522)	pN1 (n = 240)	pN2 (n = 98)	pN3 (n = 65)
1–4	75/75* (n = 8)	(n = 0)[a]	(n = 0)[a]	(n = 0)[a]
5–9	87/82** (n = 34)	60/60*** (n = 9)	(n = 2)[a]	(n = 0)[a]
10–14	95/92 (n = 44)	73/73 (n = 11)	(n = 3)[a]	(n = 0)[a]
15–19	91/87 (n = 66)	81/71 (n = 29)	29/29 (n = 7)	(n = 0)[a]
20–29	95/91 (n = 152)	76/72 (n = 72)	61/30 (n = 18)	(n = 2)[a]
≥ 30	97/95 (n = 218)	86/80 (n = 119)	45/39 (n = 68)	19/10 (n = 63)

Data are 3–5-year survival rates with numbers of patients in parentheses.

[a] Not calculated because of the small number of cases.
*$p = 0.007$, vs. 10–14; $p = 0.0003$, vs. ≥ 15.
**$p = 0.02$, vs. 10–14; $p = 0.001$, vs. ≥ 15.
***$p = 0.07$, vs. ≥ 30.

Results

Of the 925 patients, 522 (56%) were classified as pN0, 240 (26%) as pN1, 98 (11%) as pN2, and 65 (7%) as pN3 when the numbers of examined lymph nodes were not taken into account. The average number of examined lymph nodes in the entire subject group was 32 ± 17 (mean $\pm$ SD) with a median value of 30. The number of examined nodes increased in the order of pN0, pN1, pN2, and pN3 categories (29 ± 15, 33 ± 16, 38 ± 18, and 49 ± 15, respectively), and the difference between each pair of categories was statistically significant. Linear regression analysis revealed a significant positive correlation between the number of examined lymph nodes and the number of metastatic lymph nodes ($r = 0.39$, $p < 0.0001$, $n = 403$).

Survival Rates According to the Number of Examined Lymph Nodes

Among the patients without any lymph node metastasis, 8 patients with 1 to 4 examined nodes and 34 patients with 5 to 9 examined nodes showed significantly lower survival rates than 44 patients with 10 to 14 examined lymph nodes and 436 patients with 15 or more examined lymph nodes. However, the survival rate for patients with 10 to 14 examined lymph nodes was as good as for those with 15 or more examined lymph nodes (Table 1). No difference existed in average age between the patients with 10 to 14 examined nodes and those with 15 or more examined nodes, although the average age of the patients with 5 to 9 examined nodes was significantly higher than that of the patients with 10 or more examined nodes. No difference was observed in the pT category among these three groups (Table 2).

Among the patients classified as pN1, patients with 29 or fewer examined lymph nodes tended toward lower survival rates than patients with 30 or more examined lymph nodes, although the difference was not statistically significant. The number of examined nodes had no significant impact on the survival rate in the pN1 patients with 10 to 29 examined nodes (Table 1). No differences were observed in regard to age, the number of metastatic nodes, and pT category among the pN1 patients with 10 to 19 examined

nodes, those with 20 to 29 examined nodes, and those with 30 or more examined nodes (Table 2).

Stage-stratified Survival Rates According to the Number of Examined Lymph Nodes

Among the patients who were classified as stage IA, the survival rate for patients with 5 to 9 examined nodes was significantly lower than that for patients with 30 or more examined nodes. In the stage III patients, the survival rate for patients with 10 to 19 examined nodes was significantly lower than that for patients with 30 or more examined nodes. Patients with 20 to 29 examined nodes had a tendency to a lower survival rate than did patients with 30 or more examined nodes in stage III, although the difference was not statistically significant ($p = 0.11$) (Table 3).

Discussion

The number of metastatic lymph nodes correlated significantly with the number of examined lymph nodes in patients with gastric carcinoma, which agrees with previous reports [6, 10]. These results indicate that the minimum number of regional lymph nodes to be examined should be established for an accurate nodal classification based on the number of metastatic lymph nodes. The UICC/AJCC TNM classification (5th edition) requires histological examination of 15 or more lymph nodes for pN0 classification [9]. Siewert et al. have reported that the prevalence of lymph node metastasis was not dependent on the number of lymph nodes dissected, provided that 15 or more nodes were removed [11]. Karpeh et al. have reported that the survival rate for patients with 15 or more lymph nodes examined was significantly higher than that for patients with fewer than 15 nodes examined in each of N1, N2, and N3 classification, or stage II, IIIA, and IIIB [12]. Bruno et al. have reported that the examination of at least 15 nodes is necessary to define a case as N0 [13]. However, these authors did not clarify the reason they chose 15 as a cut-off point in their analyses.

The number of examined lymph nodes depends mainly on the extent of lymphadenectomy. Patients with a smaller number of examined nodes may include more patients at high surgical risk from such factors as advanced age or cardiovascular disease, who tend to die of causes other than gastric cancer. Therefore, such deaths were treated as censored observations when survival rates were calculated. In this study, we showed that node-negative patients with 10 to 14 examined lymph nodes had a prognoses as good as that for node-negative patients with 15 or more examined lymph nodes. This result indicates that the minimum number of lymph nodes to be examined for the pN0 classification can be reduced from 15 to 10. Klein Kranenbarg et al. have reported that examining at least 5 lymph nodes could justify the pN0 classification based on the data from the Dutch D1-D2 Gastric Cancer Trial [14]. In our study, patients with 5 to 9 examined nodes showed significantly lower survival rates than pN0 patients with 10 to 14 examined lymph nodes in pN0 classification and in stage IA, which suggests that the examination of fewer than 10 lymph nodes may lead to underestimation of the nodal classification. Fourteen or fewer lymph nodes were examined in 86 (16%) of the 523 patients without any lymph node metastasis, and those patients were categorized as unclassifiable in terms of the TNM classification (5th edition). If the minimum number of lymph nodes examined to satisfy the pN0 classification were

Table 2. Relationship between the number of examined nodes and background factors.

Number of examined nodes	Average age[a]	Number of metastatic nodes[a]	Tumor depth[b]			
			pT1	pT2	PT3	pT4
pN0						
1–4 ($n = 8$)	61 ± 20	0	4 (50)	2 (25)	2 (25)	0
5–9 ($n = 34$)	67 ± 12*	0	28 (83)	3 (9)	3 (9)	0
10–14 ($n = 44$)	61 ± 12	0	35 (80)	8 (18)	0	1 (2)
≥ 15 ($n = 437$)	59 ± 12	0	333 (76)	82 (19)	20 (5)	2 (0.5)
pN1						
5–9 ($n = 9$)	70 ± 9	1.8 ± 0.8	3 (33)	4 (44)	2 (22)	0
10–19 ($n = 40$)	57 ± 11	2.8 ± 1.7	8 (20)	20 (50)	10 (25)	2 (5)
20–29 ($n = 72$)	59 ± 12	2.3 ± 1.5	13 (18)	39 (54)	19 (26)	1 (1)
≥ 30 ($n = 119$)	58 ± 12	2.6 ± 1.6	18 (15)	64 (54)	33 (28)	4 (3)
pN2						
≤ 19 ($n = 12$)	66 ± 14	9.6 ± 2.6	2 (17)	3 (25)	6 (50)	1 (8)
20–29 ($n = 18$)	60 ± 11	10.1 ± 2.7	2 (11)	8 (44)	8 (44)	0
≥ 30 ($n = 68$)	60 ± 11	10.1 ± 2.5	1 (1)	32 (47)	29 (43)	6 (9)

[a]Mean ± S.D.
[b]Data are numbers of patients, with percentages in parentheses.
*$p < 0.05$, vs. patients with 10–14 examined nodes; $p < 0.001$, vs. patients with ≥ 15 examined nodes.

Table 3. Stage-stratified survival rates according to the number of examined lymph nodes.

Number of examined nodes	Stage				
	IA	IB	II	III	IV
5–9	92/92* ($n = 28$)	($n = 6$)[a]	($n = 7$)[a]	($n = 3$)[a]	($n = 0$)[a]
10–19	96/92 ($n = 91$)	86/86 ($n = 23$)	79/79 ($n = 25$)	47/27** ($n = 18$)	($n = 3$)[a]
20–29	97/94 ($n = 117$)	93/90 ($n = 43$)	78/72 ($n = 46$)	58/42*** ($n = 36$)	($n = 3$)[a]
≥ 30	99/97 ($n = 160$)	95/95 ($n = 63$)	82/74 ($n = 77$)	61/54 ($n = 95$)	24/14 ($n = 73$)

Data are 3–5-year survival rates, with numbers of patients in parentheses.
[a]Not calculated because of the small number of cases.
*$p = 0.002$, vs. ≥ 30.
**$p = 0.04$, vs. ≥ 30.
***$p = 0.11$, vs. ≥ 30.

reduced to 10, the number of unclassifiable patients would decrease to 42 (8%).

Patients with 29 or fewer examined nodes tended toward a lower survival rate than did patients who had 30 or more nodes examined in the pN1 and pN2 categories. The stage III patients with 10 to 19 examined nodes had a significantly lower survival rate than did the stage III patients who had 30 or more nodes examined. Thus, when lymph node metastasis is detected, the examination of 19 or fewer lymph nodes may lead to under-staging, and the examination of 30 or more lymph nodes may be desirable for a correct classification. Hundahl et al. and Lee et al. have also mentioned that 15 examined nodes may be inadequate for assignment to stage IIIB [15, 16].

In conclusion, the number of nodes examined had a significant prognostic impact within each pN category in gastric carcinoma, and it should be taken into account when staging the disease. The minimum number of lymph nodes to examine in order to determine pN0 classification can be reduced from 15 to 10. For pN1, pN2, and pN3 classifications, 20 or more lymph nodes should be examined, and examining 30 or more lymph nodes may be desirable.

Résumé. La classification des ganglions métastatiques basée sur le nombre de ganglions positifs a été adoptée pour la classification UICC/ AJCC TNM dans le cancer gastrique. Cependant, la classification «N» serait sous-estimée si le nombre de ganglions examinés était insuffisamment petit. Afin de déterminer le nombre minimum de ganglions qu'il faut examiner pour assurer une classification adéquate, nous avons analysé les dossiers de 926 patients ayant eu une résection à visée curative pour cancer gastrique. Le nombre de ganglions métastatiques corrélait de façon significative avec le nombre de ganglions examinés. La survie des patients pN0 patients avec 10–14 ganglions examinés était similaire à celle des patients chez lesquels on a examiné plus de 15 ganglions, mais significativement meilleure que celle des patients chez lesquels on n'a examiné que 5–9 ganglions. Chez les patients pN1 et pN2, la survie était moins bonne (tendance) lorsqu'il y avait 29 ganglions ou moins examinés que lorsqu'on a examiné plus de 30 ganglions. Parmi les patients qui avaient été classés stade IA, la survie des patients dont on a examiné 5–9 ganglions a été significativement moins longue que celle des patients chez lesquels on a pu examiner 30 ganglions ou plus. Parmi les patients classés stade III, les patients avec 10–19 ou 20–29 ganglions examinés avaient une survie plus basse que celle lorsqu'on a pu examiner plus de 30 ganglions. En conclusion, le nombre minimum de ganglions lymphatiques examinés pour une classification pN0 correcte peut être réduit de 15 à 10. Pour les tumeurs classées pN1–3 il faut examiner 20 ganglions ou plus: le chiffre nécessaire pourrait être une trentaine.

Resumen. La clasificación de las metástasis ganglionares con base en el número de ganglios positivos ha sido adoptada en la clasificación TNM de UICC/AJCC del carcinoma gástrico. Pero la clasificación N quedaría subestimada si el número de los ganglios examinados es insuficientemente reducido. Con el propósito de determinar el número mínimo de ganglios linfáticos que deber ser examinado para una correcta clasificación, hemos analizado las historias de 926 pacientes sometidos a resección curativa por carcinoma gátrico. El número de ganglios metastásicos se correlacionó en forma significativa con el número de ganglios examinados. Los pacientes pN0 con 10–14 ganglios examinados demostraron una tasa de supervivencia significativamente mejor que aquellos con 5–9 ganglios examinados, y tuvieron un pronóstico tan bueno como aquellos con 15 ó más ganglios examinados. En las categorías pN1 y pN2, los pacientes con

29 ó menos ganglios examinados exhibieron una tendencia hacia peores tasas de supervivencia que aquellos con 30 ó más ganglios examinados. Entre los pacientes clasificados como Estado III, aquellos con 10–19 y con 20–29 ganglios examinados, tuvieron peores tasas de supervivencia que aquellos con 30 ó más ganglios examinados. En conclusión, el número mínimo de ganglios examinados para una correcta clasificación pN0 puede reducirse de 15 a 10. Para clasificación pN 1–3, se deben examinar 20 ó más ganglios, y examinar 30 ó más puede ser deseable.

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