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Original article

Perigastric lymph node metastases in gastric cancer: comparison of different staging systems

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Abstract:
Background. **Perigastric lymph node metastases in gastric cancer are classified differently by different staging systems: the distance of positive nodes from the primary tumor is considered by the 1987 International Union Against Cancer (UICC)-TNM system, but not by the Japanese staging system (of the Japanese Research Society for Gastric Cancer [JRSGC]); the new UICC-TNM system of 1997 is based on the number of involved nodes without differentiating perigastric from regional nodes. The aim of the present study was to assess which classification was more useful to predict prognosis in gastric cancer patients with metastases to the perigastric nodes.**
Methods. **The results for 107 patients with lymph node metastases to the first and second tiers who underwent curative gastrectomy for gastric cancer from March 1988 to October 1997 were analyzed. In particular, we compared the clinical characteristics and the survival probabilities of: (1) patients with metastases to perigastric nodes located within 3 cm from the primary tumor, classified as N1; (2) patients with metastases to perigastric nodes located 3 cm beyond the primary tumor (N2 in the UICC-TNM and N1 in the Japanese classification), classified by us as N1–N2; and (3) patients with metastases to the second tier (classified by us as N2). We also assessed the number of positive nodes dividing the patients into groups according to the 1997 UICC TNM system.**
Results. **On multivariate survival analysis, the mortality risks in the N1 and N1–N2 patients were comparable (relative risk [RR], N1–N2 versus N1, 1.32; 95% confidence interval [CI], 0.53–3.51) and were half the mortality risk in N2 patients (RR, N2 versus N1, 2.52; 95% CI, 1.33–4.79). The N1 and N1–N2 categories, while presenting markedly different distributions in the number of metastatic nodes (patients with more than seven metastatic nodes constituted less than 20% of the N1 group and more than 60% of the N1–N2 group), showed similar prognostic significance.**
Conclusion. **In the present series, the distance of perigastric nodes from the primary tumor did not seem to exert a significant effect on prognosis, and the use of a combined classification based on anatomical location (JRSGC) and number of node metastases (UICC-TNM 1997) could be more useful than either system alone for prognostic purposes.**

Key words: gastric cancer, perigastric node metastases, surgery, staging systems, UICC-TNM and JRSGC classifications

Introduction

The classification of lymph node metastases in gastric carcinoma is still a matter of debate [1,2], and three different staging systems are used at present: (1) the pathologic tumor node metastasis classification (pTNM) adopted by the International Union Against Cancer (UICC) in 1987 [3]; (2) the pTNM classification of the Japanese Research Society for Gastric Cancer (JRSGC) [4]; and (3) the new pTNM of the UICC, proposed in 1997 [5]. The new N classification proposed by the UICC in 1997 is based only on the number of involved nodes, without considering the site of metastatic nodes; in particular, without differentiating perigastric from regional nodes.

In the UICC-TNM system of 1987, the N classification is based on both the site and the distance of metastatic nodes from the primary tumor: perigastric nodes are classified as N1 if located within 3 cm from the edge of the primary tumor, and as N2 if their distance from the primary tumor exceeds 3 cm.

In the JRSGC classification, the distance of perigastric nodes from the primary tumor is not taken into account, and the N classification is mainly based on the sites of both the lymph node metastases and the primary tumor. Indeed, most perigastric nodes are classified as N1, with the exception of the infrapyloric and, suprapyloric lymph nodes and lymph nodes along the right

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gastroepiploic artery in upper-third tumors, of the left cardial lymph nodes in middle-third tumors, and of the right and left cardial lymph nodes in lower-third tumors.

The aim of the present study was to assess which classification was more useful to predict prognosis in gastric cancer patients with metastases to the perigastric nodes. For this purpose, we compared the clinical characteristics and the survival probabilities of: (1) patients with metastases to perigastric nodes located within 3 cm from the primary tumor, (2) patients with metastases to perigastric nodes located 3 cm beyond the primary tumor but still classified as N1 by the JRSGC, and (3) patients with metastases to the second tier. Thus, only patients with metastases to the first and second tiers were selected, and patients without node metastases (N0) and those with metastases to non-regional nodes (N3–N4) were excluded.

Patients and methods

Between March 1988 and October 1997, 262 patients underwent gastric resection at the First Department of General Surgery, University of Verona; 216 of these patients underwent potentially curative resection with complete macroscopic and microscopic removal of the tumor. Twelve patients who died in hospital and 6 patients in whom liver or peritoneal metastases had been removed were excluded from the analysis. Of the remaining 198 patients, 107 had nodal metastases confined to the first and second tiers and thus were recruited for the study. The mean (±SD) age of these patients was 65.2 ± 11.6 years, and most patients in the cohort were male (78 men and 29 women). Among the 107 patients, the total number of dissected lymph nodes was 3645. The median number of dissected nodes per patient was 32 (range, 6–84) and the median number of metastatic nodes was 5 (range, 1–42).

Lymph node metastases were classified according to both the 1987 UICC-TNM staging system [3] and the general rules for gastric cancer study in surgery and pathology of the JRSGC [4]. As a consequence, patients were grouped into three different categories: (1) Patients with metastasis to perigastric nodes located within 3 cm from the primary tumor ($n = 53$), classified as N1 by both classifications (N1 group); (2) patients with metastasis to perigastric nodes located at a distance >3 cm from the edge of the primary tumor ($n = 11$), classified as N1 according to the JRSGC and as N2 according to the UICC-TNM 1987 (N1–N2 group); and (3) patients with metastasis to the regional nodes ($n = 43$), classified as N2 by both classifications (N2 group).

The three groups were compared with respect to survival probability and clinical characteristics, and with respect to the new 1997 UICC TNM system [5]. For this purpose, the number of lymph nodes involved by metastasis was assessed and patients were grouped accordingly.

Statistical analysis

Cancer-related mortality was taken into account for survival analysis, while one death from another cause was considered as a censored observation at the time of death.

The significance of differences among the N1, N1–N2, and N2 groups was assessed by analysis of variance (ANOVA) and the Tukey test for continuous variables (age and number of metastatic nodes), and by the χ^2 test for categorical variables (sex, site, histology, depth of tumor invasion). Since the number of metastatic nodes did not show a normal distribution according to the Kolmogorov-Smirnov test [6], a preliminary logarithmic transformation was required for ANOVA. Univariate survival analysis was carried out by the Kaplan-Meier method and the Cox regression model [7]. Multivariate survival analysis was accomplished through the Cox regression model, by taking into account nodal involvement (N1, N1–N2, N2), along with age, sex, histology (intestinal versus diffuse), and depth of tumor invasion. The analysis was carried out after stratification for tumor location (fundus, corpus, and antrum), which could not be included in the Cox model because it presented a significant interaction with time, according to the goodness-of-fit test.

The relative risk for the continuous variable (age) was computed on the basis of an increase in the value of 1 SD. None of the patients was lost to follow-up. The median follow-up for surviving patients was 48 months (range, 3–115 months).

Results

The demographic and main baseline clinical characteristics of the cohort under study are summarized in Table 1. The three groups were not significantly different with respect to any of the variables considered. It is worthy of note that more than 80% of the patients in the N1–N2 group were in advanced stages (T3 and T4) and there were no patients with early cancer.

As shown in Fig. 1, the survival curve of the N1–N2 group was superimposed on the survival curve of the N2 patients, and the two curves were quite separate from the survival curve of the N1 patients. Accordingly, on univariate survival analysis, the relative risk (RR), with respect to the N1 patients, was similar in the N1–N2 (RR, 1.63; 95% confidence interval [CI], 0.70–3.78) and N2 (RR, 1.59; 95% CI, 0.91–2.80) patients. However,

Table 1. Main demographic and clinical characteristics of the 107 patients with metastases to regional nodes who underwent curative resection for gastric cancer between March 1988 and October 1997

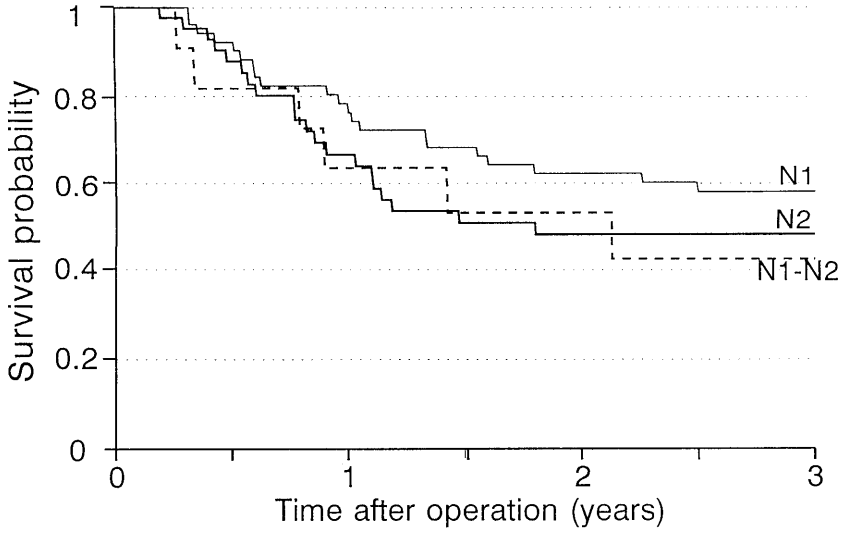
Variables	N1[a] (n = 53)	N1–N2[b] (n = 11)	N2 (n = 43)	P value[c]
Age (years)	65.5 (12.5)	67.2 (11.9)	64.3 (10.6)	0.74
Sex (men)	37 (69.8)	9 (81.8)	32 (74.4)	0.69
Site				
Upper third	24 (45.3)	1 (9.1)	15 (34.9)	
Middle third	12 (22.6)	5 (45.5)	12 (27.9)	0.23
Lower third	17 (32.1)	5 (45.5)	16 (37.2)	
Histology				
Intestinal	26 (49.1)	4 (36.4)	20 (46.5)	0.74
Diffuse	27 (50.9)	7 (63.6)	23 (53.5)	
Depth of tumor invasion				
T1	9 (17.0)	—	6 (14.0)	
T2	13 (24.5)	2 (18.2)	11 (25.6)	0.82
T3	28 (52.8)	8 (72.7)	23 (53.5)	
T4	3 (5.7)	1 (9.1)	3 (7.0)	

Patients were grouped into three categories according to the type of node involvement. Values are reported as means (SD) for continuous variables and as absolute values (percent values) for categorical variables

[a] Metastasis in perigastric nodes less than 3 cm from the edge of the primary tumor

[b] Metastasis in perigastric nodes more than 3 cm from the edge of the primary tumor

[c] P values were obtained by one-way analysis of variance (ANOVA) for the continuous variables and by χ^2 for categorical variables



N1	53	47	38	34	30	26
N1-N2	11	9	6	5	5	3
N2	43	35	25	19	16	14

Fig. 1. Kaplan-Meier estimates of survival probability in the N1, N1–N2, and N2 groups. See text for explanation of these groups

this finding was not confirmed on multivariate survival analysis (Table 2), in which the mortality risks in the N1 and N1–N2 patients were comparable (RR, N1–N2 versus N1, 1.32; 95% CI, 0.52–3.51), and were half the mortality risk in the N2 patients (RR, N2 versus N1, 2.52; 95% CI, 1.33–4.79). Indeed, when depth of tumor invasion was added to the model, the estimate of the relative risk with respect to N1 patients decreased markedly in the N1–N2 patients (from RR, 1.80; CI, 0.72–4.49 to RR, 1.32; CI, 0.52–3.51), while increasing in the N2 patients (from RR, 1.89; CI, 1.05–3.38, to RR, 2.52; CI, 1.33–4.79). Among the other variables considered, depth of tumor invasion and age also appeared to be independent prognostic factors (Table 2).

N1–N2 patients, while experiencing a risk of death similar to that in N1 patients, had a significantly higher number of metastatic nodes (9.9 ± 6.4 versus 3.6 ± 2.6), close to the value observed in N2 patients (10.7 ± 9.4). Indeed, patients with more than seven metastatic lymph nodes constituted less than 20% of the N1 group (10/53) and more than 60% of the N1–N2 group (7/11) (Table 3).

Discussion

The prognostic significance of the N staging system adopted by the JRSGC has been recently confirmed by several authors [8–11]. In particular, prognosis was reported to be markedly worse in the N2 group compared with the N1 group.

Since the Japanese criteria for classifying perigastric node metastases are rather complicated, the UICC TNM adopted a different classification, based on the distance of involved perigastric nodes from the primary tumor. Also, for this staging system, many studies have shown a significant difference in survival between N1 and N2 patients [12–15]. However, to date, no investigation has addressed survival in N2 patients with metastases restricted to perigastric nodes.

The main results of the present study were: (1) In patients with metastases to perigastric nodes located at a distance >3 cm from the primary tumor (N1–N2), the number of positive nodes was comparable to that in patients with metastases to the regional nodes (N2 patients) and was significantly greater than that in patients with metastases to perigastric nodes within 3 cm from the primary tumor (N1 patients). (2) The survival of N1–N2 patients, while similar to the survival of N2 patients on univariate analysis, approached the survival of N1 patients after being controlled for T staging. In other words, the higher mortality observed in N1–N2 patients with respect to the N1 group seemed to reflect more advanced disease, as suggested by the greater number of metastatic nodes and by the greater proportion of T3 and T4 patients, rather than reflecting a direct adverse effect of distant positive perigastric nodes.

Thus, in the present series, the distance from the primary tumor of positive nodes within the first tier did not seem to exert a significant effect on prognosis. As a consequence, the JRSGC classification seemed to be more useful for prognostic purposes than the UICC TNM classification. However, from a practical point of view, the gain in prognostic information was rather small, as N1–N2 patients represented only a minor fraction (11/107; 10.3%) of patients with nodal metastases confined to the first and second tiers.

Patients with positive perigastric nodes 3 cm beyond the primary tumor, while presenting with approximately the same number of positive nodes as patients with metastases to regional lymph nodes, achieved approximately the same survival as patients with perigastric node metastases within 3 cm of the primary tumor.

Recently, great prognostic significance has been attributed to the number of positive nodes classified by the new TNM system [16], and other studies with large numbers of patients have recently confirmed these findings [17,18]. However, in a previous study in our

Table 2. Multivariate survival analysis, showing relative risks (with 95% confidence intervals in parentheses) of death from gastric cancer in the 107 patients who underwent curative resection

Variables	Relative risk, adjusted for all other variables	*P* value
Sex (women vs men)	1.21 (0.60–2.46)	0.60
Age (SD = 12.0 years)	1.51 (1.08–2.13)	0.015
Histology (diffuse versus intestinal)	1.30 (0.74–2.28)	0.35
Depth of tumor invasion		
T2 vs T1	1.52 (0.38–6.03)	
T3 vs T1	7.25 (2.17–24.21)	<0.001
T4 vs T1	14.77 (3.18–68.66)	
Nodal involvement		
N1–N2 vs N1	1.32 (0.52–3.51)	
N2 vs N1	2.52 (1.33–4.79)	0.016

Relative risks and significance of differences were derived from the Cox regression model, after stratifying for tumor location and controlling for all other variables. Calculation of the relative risk for age was based on an increase in the values of 1 SD

Table 3. Distribution of the 107 gastric cancer patients according to the JRSGC and UICC-TNM 1997 classification systems

JRSGC [4]/ TNM 1987 [3]	New TNM (1997) [5]		
	N1 (1–6 positive nodes)	N2 (7–15 positive nodes)	N3 (≥16 positive nodes)
N1	43 (81.1%)	10 (18.9%)	—
N1–N2	4 (36.4%)	5 (45.5%)	2 (18.2%)
N2	21 (48.8%)	14 (32.6%)	8 (18.6%)

Percent frequencies in parentheses are row percentages
JRSGC, Japanese Research Society for Gastric Cancer; UICC, International Union Against Cancer

whole series [19], we showed that both the anatomical location and the number of node metastases were important predictors of survival in gastric cancer patients, and we recommended the use of a combined classification based on both the anatomical location and the number of node metastases.

Although the patients analyzed in the present study were strictly selected, with findings for only those who underwent D2 lymphadenectomy being analyzed, caution should be used in interpreting these findings, which are based on a small number of patients, and further experiences involving a larger number of patients are needed to verify these results.

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