

Relation of number of positive lymph nodes to the prognosis of patients with primary gastric adenocarcinoma

C W Wu, M C Hsieh, S S Lo, S H Tsay, W Y Lui, F K P'eng

Abstract

Background—No nodal grouping category of gastric cancer has been universally accepted for the grading of the effectiveness of therapeutic regimens.

Aims—To establish an appropriate nodal grouping as a forecaster of distant disease and test its validity as a determinant in survival.

Patients—Five hundred and ten patients who underwent curative resections for gastric cancer were studied.

Methods—Retrospectively analyse the prognostic significance of the number of metastatic lymph nodes.

Results—A total of 17 176 lymph nodes with an average of 34 per specimen were removed, of which 2811 (16%) showed metastases. Among the 510 patients, 287 (56%) had lymph node metastases, with an average of 9.8 per metastatic case. The survival of all patients was related to their nodal status, an abrupt decrease in survival was seen between 0 and 1 and 4 compared with 5 or more nodes while little difference in survival existed among 1, 2, 3, and 4, and among 5, 6, 7, and 8 positive nodes. Multivariate analysis showed that the number of positive nodes (1-4, 5-8 versus ≥ 9 ; relative risk 2.2) and depth of cancer invasion (three levels; relative risk 1.9) were independently correlated with survival. The current nodal stage was not a prognostic factor.

Conclusions—Gastric cancer patients with 0, 1 to 4, 5 to 8, and >9 positive nodes may represent four appropriate prognostic groups and should be adopted for classification of nodal stage in gastric cancer.

(Gut 1996; 38: 525-527)

Keywords: positive nodes, gastric cancer, prognostic survival.

system, the General Rules for Gastric Cancer Study.⁴

During recent years a number of independent studies have shown that the prognosis in breast,⁵ colorectal,⁶ and gastric carcinoma⁷⁻¹¹ was not only related to the presence or absence of lymph node involvement, but also the number of positive nodes. There is no universally accepted classification for gastric cancer. Similarly, no agreement has been reached for the presentation of findings, with regard to the natural history of gastric cancer patients, or the effectiveness of therapeutic regimens. We began to perform gastrectomy with radical lymph node dissection routinely for curable gastric cancer in 1987.^{12 13} The purpose of this paper is to present data that provide some insight into an appropriateness of nodal grouping category and its relation to survival.

Methods

A total of 510 patients with adenocarcinoma of the stomach treated in the Veterans General Hospital, Taipei, between December 1987 and May 1994, were entered into this study. Patients with two primary tumours or with gastric remnant cancer who had previously undergone distal gastrectomy for benign or malignant disease were excluded. All patients were regularly followed up. Deaths from causes other than gastric cancer were treated as censored findings at the time of death.

The relation between the current nodal stage classification and the number of metastatic lymph nodes was analysed. Nodal involvements are n1, n2, n3, and n4 according to the Japanese Rules.¹⁴ In the TNM classification,³ n1 and n2 are defined as regional lymph nodes, whereas n3 and n4 as distant metastases. We chose age, sex, depth of cancer invasion, nodal stage, number of metastatic lymph nodes, site and size of tumour, and Lauren's histological classification¹⁵ as prognostic variables.

Data were stored on an IBM 4381 main-frame computer (IBM, Armonk, New York, USA) and statistical analyses carried out using a biomedical computer program (BMDP, Los Angeles, California, USA).¹⁶ Cumulative survivals have been used to summarise the distribution of survival. The number of patients at risk four years after gastrectomy is shown to provide the reader with an idea of the reliability of the estimates at that point. In the univariate analysis the cumulative survival rate was calculated using the Kaplan-Meier approach and the equality of the survival

Department of
Surgery
C W Wu
M C Hsieh
S S Lo
W Y Lui
F K P'eng

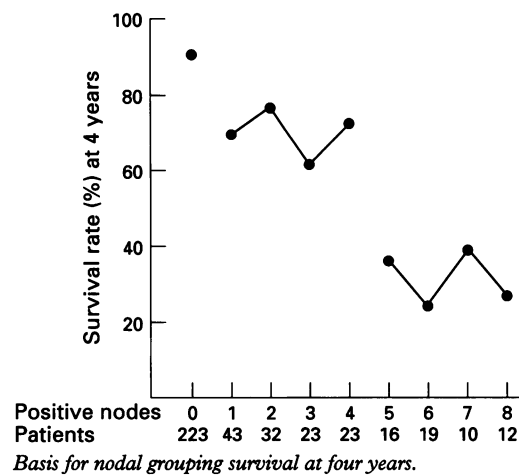
and Pathology
S H Tsay

Veterans General
Hospital-Taipei and
School of Medicine,
National Yang-Ming
University, Taiwan

Correspondence to:
Dr Chew-Wun Wu,
Department of Surgery,
Veterans General Hospital-
Taipei, Shih-Pai, Taipei,
Taiwan, 11217, ROC.

Accepted for publication
31 October 1995

It is generally accepted that the two important factors influencing survival in resectable gastric cancer are the depth of invasion through the gastric wall and the presence or absence of regional lymph node involvement.^{1 2} To assess the extent of malignancy, determine prognosis, and aid in the selection of treatment, a TNM system³ emphasising the two prognostic factors is commonly used. In this system, the assessment of lymphatic spread is based on its anatomical extension (level of nodal involvement). The same is true in the Japanese



curves was tested using the method of generalised Wilcoxon analysis. In the multivariate analysis independent prognostic factors for survival were determined using a Cox proportional hazard model. Statistical significance was specified as $p < 0.05$.¹⁷

Results

The mean age of the patients was 65 years (range 26 to 91) with a male: female ratio of 4.7:1. Most of them (374; 73%) were advanced cancers. A total of 17 176 lymph nodes with an average of 33.7 per specimen (range: 7–111) were removed, of which 2811 (16.4%) showed metastases. Among the 510 patients, 287 (56.3%) had lymph node metastases, with an average of 9.8 per metastatic specimen.

The four year survival rate was 91% for patients without nodal involvement compared with 39.2% for patients with lymph node metastasis. When the survival of all patients was related to their nodal status, a distinct difference was seen between those with all negative nodes and those with one positive node (91% versus 70%). There was a little difference in survival between those having one, two, three, or four nodes, with tumour. A second sharp decrease in survival (from 73% to 35%) was seen between patients with four positive nodes and those with five or more nodes containing tumour. While little difference in survival existed between those with five, six, seven, or eight, greater numbers of involved nodes were associated with a progressively worse prognosis (Figure and Table I).

TABLE I Number of positive nodes from gastric adenocarcinoma correlated with survival

No of nodes positive	Initial no of patients	Survival (%)			
		1 Year	2 Years	3 Years	4 Years
0	223	98.6 (223)	94.1 (208)	90.8 (168)	90.8 (113)
1-4	121	91.0 (121)	79.0 (98)	74.1 (73)	70.5 (55)
1	43	94.9 (43)	83.7 (37)	80.2 (29)	70.0 (22)
2	32	89.7 (32)	81.6 (24)	77.0 (19)	77.0 (17)
3	23	86.4 (23)	61.7 (19)	61.7 (10)	61.7 (7)
4	23	90.5 (23)	85.2 (18)	72.9 (15)	72.9 (8)
≥5	166	62.7 (166)	32.4 (93)	22.6 (42)	16.9 (23)
5-8	57	78.6 (57)	54.0 (38)	37.6 (23)	26.8 (13)
5	16	75.0 (16)	45.0 (11)	36.0 (6)	36.0 (3)
6	19	71.1 (19)	40.1 (11)	24.0 (5)	24.0 (2)
7	10	77.8 (10)	77.8 (7)	51.9 (7)	38.9 (4)
8	12	100.0 (12)	66.7 (9)	53.3 (5)	26.7 (4)
≥9	109	54.8 (109)	21.9 (35)	15.5 (19)	12.2 (10)

Figures in parentheses are number of patients at risk.

TABLE II Univariate analysis of clinicopathological factors in 287 patients with node positive gastric adenocarcinoma

Variable	Patients	Survival	p Value
Age			
<65	119	35.2	
≥65	168	42.2	0.5674
Sex			
Male	237	37.1	
Female	50	48.5	0.1007
Site			
Upper stomach	35	47.3	
Middle stomach	64	45.6	
Lower stomach	151	37.8	
Whole stomach	37	29.1	0.1599
Size			
<4 cm	40	61.2	
4-8 cm	156	39.5	
>8 cm	91	27.8	0.0004
Lauren's histology			
Intestinal type	117	47.2	
Diffuse type	146	31.8	
Others	24	42.5	0.0299
Positive nodes			
1-4	121	70.5	
5-8	57	26.7	
≥9	109	12.1	0.0001
Nodal groups (Japanese rules)*			
n1	104	54.4	
n2	115	38.8	
n3	40	22.2	
n4	28	8.8	0.0001
Depth of cancer invasion			
Mucosa and submucosa	15	92.9	
Muscle and subserosa	51	62.4	
Serosa	221	29.4	0.0001

*n1 and n2 are defined as regional lymph nodes, whereas n3 and n4 as distant metastasis in TNM system.

The cancer specific survival of patients was significantly influenced both by the number of positive nodes and their nodal group ($p = 0.0001$). In addition, survival was closely related to tumour size, Lauren's histological classification, and depth of invasion (Table II). The independent prognostic factors identified by multivariate analysis were number of positive nodes and depth of cancer invasion. The levels of positive nodes were no longer a prognostic factor (Table III).

Discussion

This study based on survival data provides nodal grouping categories that can be adopted for classification of nodal stage in gastric cancer. We found a small survival difference in patients with 1-4 and with 5-8 positive nodes. The survival rates in patients with 0, 1-4, 5-8, and ≥9 were 90.8%, 70.5%, 26.8%, and 12.2%, respectively.

Most studies⁷⁻¹¹ on the prognostic role of the number of metastatic nodes in gastric cancer categorised positive nodes into 1-3 and ≥4, which is customary in breast cancer.⁵ The findings in this study showed that four years after operation there was a considerable difference (20%) in the survival between those with negative lymph nodes and those with 1-4 positive nodes. There was comparatively little difference in the outcome of patients with 1, 2, 3, or 4 positive nodes, but there was a sharp decrease in survival when a fifth node was involved, emphasising the need to divide patients into the two positive nodal groups (Figure and Table I). Similar data can be seen in the report from Ichikura *et al.*,¹¹ although they categorised patients into those having 1-3 and ≥4 positive nodes. In this study a 54% difference in the survival was found between

TABLE III Multivariate analysis showing independent prognostic factors in patients with node positive gastric adenocarcinoma

Variable (observed value)	Coefficient	Standard error	Relative risk	p Value
Number of positive nodes (1-4, 5-9, ≥ 9)	0.779	0.108	2.180	0.000
Depth of cancer invasion (mucosa and submucosa, muscle and subserosa, serosa)	0.635	0.241	1.887	0.004

those with 1 to 4 and those with ≥ 5 positive nodes. Thus, it is more appropriate to classify patients as having 1 to 4 or ≥ 5 positive nodes than to merely consider them as node negative or positive. The major difference in survival between those with 5 to 8 and those with ≥ 9 positive nodes suggests that there is a risk in combining all patients with ≥ 5 positive nodes into a single group. Such a unification may provide misleading information regarding the prognosis of patients and treatment strategy.

Of interest is the finding that a multivariate survival analysis including number of positive lymph nodes (categorised as 1-4, 5-8, and ≥ 9) showed that number of positive nodes was the most important prognostic determinant (relative risk 2.18) and current nodal stage (either TNM system or Japanese Rules) was not independently prognostic (Tables II and III). Similar results were obtained recently by Adachi *et al*¹⁰ and Ichikura *et al*.¹¹ These data show that the number of positive nodes rather than the level of nodal involvement (anatomical extension) should be adopted for classification of nodal stage in gastric cancer.

It is generally accepted that the depth of cancer invasion is also an important prognostic indicator in gastric adenocarcinoma.^{1,2} In this study, survival was significantly linked to the depth of cancer invasion, independently of the number of positive lymph nodes (Table III). The Lauren's histological classification is not an independent variable, which is in accord with those previously described by Haugstvedt *et al*¹⁸ and Rohde *et al*.¹⁹

This study was supported in part by a grant from National Science Council of the Republic of China (NSC 83-2331-B-075-081).

- Arveux P, Faivre J, Boutron MC, Piard F, Dusserre-Guion L, Monnet E, *et al*. Prognosis of gastric carcinoma after curative surgery. A population-based study using multivariate crude and relative survival analysis. *Dig Dis Sci* 1992; 37: 757-63.
- Maruyama K. The most important prognostic factors for gastric cancer patients. *Scand J Gastroenterol* 1987; 22 (suppl 133): 63-8.
- Hermanek P, Sobin LH. *TNM Classification of malignant tumors*. 4th ed, 2nd revision. Berlin: Springer-Verlag, 1992: 45-8.
- Japanese Research Society for Gastric Cancer. *Japanese classification of gastric carcinoma*. Tokyo: Kanehara, 1995.
- Fisher B, Bauer M, Wickerham L, Redmond CK, Fisher E. Relation of number of positive axillary nodes to the prognosis of patients with primary breast cancer. An NSABP update. *Cancer* 1983; 52: 1551-7.
- Brodsky JT, Richard GK, Cohen AM, Minsky BD. Variables correlated with the risk of lymph metastasis in early rectal cancer. *Cancer* 1992; 69: 322-6.
- Shiu MH, Perrotti M, Brennan MF. Adenocarcinoma of the stomach: a multivariate analysis of clinical, pathologic and treatment factors. *Hepatogastroenterology* 1989; 36: 7-12.
- Okusa T, Nakane Y, Boku T, Takada H, Yamamura M, Hioki K, *et al*. Quantitative analysis of nodal involvement with respect to survival rate after curative gastrectomy for carcinoma. *Surg Gynecol Obstet* 1990; 170: 488-94.
- Makino M, Moriwaki S, Yonekawa M, Oota M, Kimura O, Kaibara N. Prognostic significance of the number of metastatic lymph nodes in patients with gastric cancer. *J Surg Oncol* 1991; 47: 12-6.
- Adachi Y, Kamakura T, Mori M, Baba H, Machara Y, Sugimachi K. Prognostic significance of the number of positive lymph nodes in gastric carcinoma. *Br J Surg* 1994; 81: 414-6.
- Ichikura T, Tomimatsu S, Okusa Y, Uefuji K, Tamakuma S. Comparison of the prognostic significance between the number of metastatic lymph nodes and nodal stage based on their location in patients with gastric cancer. *J Clin Oncol* 1993; 11: 1894-900.
- Wu CW, Hsieh MC, Tsay SH, Lui WY, P'eng FK. Adenocarcinoma of midstomach. Clinical and pathoanatomic relation to lymph node metastases. *J Clin Gastroenterol* 1994; 19: 259-63.
- Wu CW, Hsieh MC, Lo SS, Tsay SH, Lui WY, P'eng FK. Lymph node metastasis from carcinoma of the distal one-third of the stomach. *Cancer* 1994; 73: 2059-64.
- Japanese Research Society for Gastric Cancer. The general rules for the gastric cancer study in surgery and pathology. *Jpn J Surg* 1981; 11: 127-45.
- Lauren P. The two histological main types of gastric carcinoma. Diffuse and so-called intestinal type carcinoma: an attempt at a histoclinical classification. *Acta Pathol Microbiol Scand* 1965; 64: 31-49.
- Dixon WJ. *BMDP Statistical Software*. Berkeley: University of California Press, 1988: 229-744.
- Cox DR. Regression models and life tables. *Journal of the Royal Statistical Association* 1972; 34: 187-220.
- Haugstvedt TK, Viste A, Eide GE, Soreide O, members of the Norwegian Stomach Cancer Trial. Norwegian multicenter study of survival and prognostic factors in patients undergoing curative resection for gastric carcinoma. *Br J Surg* 1993; 80: 475-8.
- Rohde H, Gebbensleben B, Bauer P, Stutzer H, Zieschang J. Has there been any improvement in the staging of gastric cancer? Findings from the German Gastric Cancer TNM Study Group. *Cancer* 1989; 64: 2465-81.