

Risk Factors for Lymph Node Metastases and their Prognostic Significance in Early Gastric Cancer (EGC) for the Italian Research Group for Gastric Cancer (IRGGC)

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Background: Lymph node metastases are present in only about 15% of patients with early gastric cancer (EGC) and for this reason, the majority of these patients do not require lymphadenectomy. In Japan, EGC patients undergo less invasive treatment (endoscopic mucosal resection, wedge resection, laparoscopy). However, the indications for and results of these types of treatment are still uncertain.

Methods: In a multicentre retrospective study, we analysed the clinicopathological data referring to 584 early gastric cancer patients who underwent D2 gastrectomy. A comparison was made between patients with and without lymph node metastases in relation to numerous pre- and postoperative variables. Long-term survival and risk factors for lymph node metastases were analysed. The primary aim was to compare our results with those of Western and Japanese authors; we also evaluated the possibility of identifying a subset of patients at low risk of lymph node metastases who may be candidates for endoscopic treatment.

Results: The incidence of lymph node metastasis was 14.4%. Univariate and multivariate analyses showed that submucosal infiltration, diffuse histotype, tumour size and Kodama Pen A type were all related to the presence of lymph node metastases. Patients with types I, IIa and IIb mucosal tumours did not present lymph node metastases. Postoperative mortality was 2.2%. Five-year survival in relation to lymph node groups was 95% in N0 patients, 77% in N1 patients and 60% in N2 patients ($p = 0.0001$, Japanese N-stage). The number of positive lymph nodes also had a prognostic value. Patients with three or fewer positive lymph nodes presented a better 5-year prognosis (83%) than those with more than three positive lymph nodes (48%) ($p = 0.0001$).

Conclusions: Our study confirms that lymph node involvement is an extremely important prognostic factor. For this reason, the therapeutic strategy of our surgical units is as follows: 1) D2 gastrectomy is the standard treatment even in early gastric cancer (EGC); 2) endoscopic mucosal resection (EMR) could be considered first in types I, IIa and IIb tumours that are diagnosed as limited to the mucosal layer.

Key words: early gastric cancer – lymphadenectomy – surgical therapy

INTRODUCTION

Prognosis is generally favourable in early gastric cancer (EGC) when treated surgically, with a 5-year survival of more than

90%, as confirmed in both Japanese and Western studies (1–5).

The most important prognostic factor is undoubtedly metastatic lymph node involvement, the incidence of which ranges from 10 to 42% (1,2,6,7), with an average value of 15%. It therefore follows that about 85% of patients undergo unnecessary lymphadenectomy.

Preoperative staging, including endoscopic ultrasonography, is not specific enough to identify the presence of lymph node

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metastases (8). Only a retrospective examination of clinicopathological data obtained from patients previously treated for EGC is predictive of metastatic lymph node involvement. The present retrospective study analyses data referring to 584 patients operated on for EGC and focuses in particular on risk factors for lymph node metastases.

The aim of the present study was to compare our results with those of Western and Japanese authors and then evaluate the possibility of identifying a subset of patients at low risk of lymph node metastases who may be candidates for endoscopic treatment.

SUBJECTS AND METHODS

Five hundred and eighty-four patients were operated on for EGC at three Surgical Units (Divisione di Chirurgia 1, G. B. Morgagni Hospital, Forlì, Istituto di Semeiotica Chirurgica, University of Verona and Istituto di Scienze Chirurgiche, University of Siena) during the period 1976–97. Subtotal gastrectomy was carried out for tumours located in the lower two-thirds of the stomach and total gastrectomy for tumours in the upper third. Both surgical procedures were completed by level I (N1) and II (N2) lymphadenectomy (according to the JRSGC classification) (9). Lymph node metastases were classified as N0, N1 or N2 according to the Japanese system.

Macroscopic classification was carried out in accordance with the criteria of the Japanese Society of Gastroenterologic Endoscopy. Histological type and epithelium of origin were designated according to Lauren's classification (10) and multifocality was defined according to Moertel's criteria (11). Furthermore, patients were classified by the pathologist according to the Kodama classification (12), which evaluates tumour growth and development.

Kodama classifies EGC as follows: Super (superficial spreading) type, designated as a lesion having a diameter of >4 cm and confined to the mucosa (Super M) or with a slight invasion of the submucosa (Super SM); small mucosal type, a carcinoma with a diameter of <4 cm, with (Small mucosal SM) or without slight submucosal invasion (Small mucosal M); Pen (penetrating) type, a lesion with a diameter of <4 cm that has invaded the submucosa in a wide penetrating fashion. This type is further divided into two subtypes, according to the mode of invasion through the muscularis mucosae: Pen A type, invading expansively with complete destruction of muscularis mucosae, and Pen B type, growing infiltratively with fenestration of muscularis mucosae; mixed type represents a small number of tumours having growth patterns of both Super and Pen types, that is, a lesion >4 cm with massive invasion of the submucosa.

Patients were seen on average every 6 months for the first 5 years and thereafter once per year. Long-term survival was calculated from the date of surgery. Only deaths due to EGC were considered. Deaths due to other causes, included postoperative mortality, were censored at the date of death.

The study of the association between lymph node metastases and other clinicopathological variables was conducted using

the chi-squared test in univariate analysis and the multiple logistic regression model in multivariate analysis where tumour size was considered as a continuous variable.

The survival curve in function of lymph node status was traced using the Kaplan–Meier method (13). The difference between curves was tested using the log-rank test (14).

RESULTS

The 584 patients who underwent surgery represent 25% of the total number of patients treated for gastric cancer in the same period. Metastatic lymph node involvement was present in 84 patients (14.4%): 63 (10.7%) were classified as N1 and 21 (3.5%) as N2. Mucosal type cancer presented lymph node involvement in 3.7% of cases, in contrast to 25.3% of submucosal forms. The mean number of positive lymph nodes was 2 (range 1–29). The number of positive lymph nodes was ≤3 in 62 patients and >3 in 22. Table 1 shows the clinicopathological factors in relation to the presence or absence of lymph node metastases.

The diameter of the neoplasm was significantly greater and submucosal infiltration was more frequent in patients with lymph node metastases ($p < 0.001$). The diffuse histological type showed a high incidence of lymph node metastases ($p < 0.001$) and Kodama Pen A type more frequently involved lymph nodes than other Kodama types ($p < 0.001$).

When a stratified analysis of different variables with respect to the lymph node involvement was conducted, we observed that polypoid types I and IIa and flat type IIb, with mucosal involvement, did not develop lymph node metastases, independently of tumour dimensions and histological type. The above characteristics were found in 71 of our patients. In these patients, the tumour was localized in the upper third of the stomach in nine cases, the middle third in 23 cases and lower third in 39 cases.

Furthermore, all clinicopathological factors were evaluated by logistic regression analysis. Independent risk factors for lymph node metastases were as follows: submucosal invasion, Kodama Pen A type, diffuse histotype and tumour dimensions (Table 2).

Postoperative mortality was 2.2% (13 patients) and morbidity was 14.4% (84 patients). In the last decade, postoperative mortality has decreased to 1.3%. The mean follow-up duration was 8 years. One patient was lost to follow-up and was therefore excluded from the study. The 5-year survival rate of patients with negative lymph nodes (N–) was 95% (95% CI = 93–97), whereas that of node positive patients (N+) was 73% (95% CI = 62–84) (Fig. 1).

The 5-year survival rate in positive lymph node groups was 77% for N1 patients (95% CI = 65–89) and 60% for N2 patients (95% CI = 37–83) (Fig. 2).

The number of positive lymph nodes was also a prognostic factor; patients with ≤3 positive lymph nodes presented a better 5-year survival [83% (95% CI = 72–93)] than those with ≥4 lymph node metastases [48% (95% CI = 25–71)] (Fig. 3).

Table 1. Clinicopathological factors of patients with EGC with and without lymph node metastasis

Factor	Without lymph node metastasis		With lymph node metastasis		<i>p</i>
	500	(85.6%)	84	(14.4%)	
Gender					
M	303	(60.6%)	46	(54.8%)	0.313
F	197	(39.4%)	38	(45.2%)	
Age (years)					
≤65	231	(46.7%)	46	(54.8%)	0.175
>65	263	(53.3%)	38	(45.2%)	
Tumour location					
Upper	49	(9.9%)	8	(9.5%)	0.98
Middle	125	(25.3%)	22	(26.2%)	
Lower	320	(64.8%)	54	(64.3%)	
Tumour diameter (cm)					
<2	116	(23.5%)	10	(11.9%)	<0.001
2–3	207	(41.9%)	26	(31.0%)	
>3	171	(34.6%)	48	(57.1%)	
Histological depth of invasion					
Mucosa	285	(57.0%)	11	(13.0%)	<0.001
Submucosa	215	(43.0%)	73	(85.7%)	
Histological type					
Intestinal	391	(78.2%)	40	(47.6%)	<0.001
Diffuse	66	(13.2%)	29	(34.5%)	
Mixed	43	(8.6%)	15	(17.9%)	
Focality					
Monofocal	385	(77.0%)	63	(75%)	0.64
Multifocal	115	(23.0%)	21	(25%)	
Macroscopic type					
Polypoid (I–IIa)	99	(19.9%)	16	(19.1%)	0.44
Flat (IIb)	28	(5.6%)	2	(2.4%)	
Depressed-ulcerated (IIc–III)	370	(74.5%)	66	(78.6%)	
Kodama type					
Pen A	84	(16.9%)	50	(59.5%)	<0.001
Pen B	50	(10.1%)	6	(7.1%)	
Not Pen	362	(73.0%)	28	(33.3%)	

DISCUSSION

Gastrectomy with lymph node dissection is the most widespread surgical procedure used in the treatment of EGC both in Japan and Western countries (1,3,4,6,7,9,15). However, in Western reports there have been very few cases homogeneous or not as regards level of lymphadenectomy.

Here we found a 14.4% incidence of lymph node metastases, similar to that indicated by other authors (1,5). Kitamura et al. (5) reported an average of 2.64 positive lymph nodes per

Table 2. Logistic regression analysis for variables associated with lymph node metastasis in EGC

Explanatory variable	Odds ratio	95% CI	<i>p</i>
Depth of invasion			
Mucosa	1.00		
Submucosa	2.29	1.56–3.36	<0.0001
Kodama type			
Not Pen A	1.00		
Pen A	1.36	1.17–1.58	<0.0001
Histological type			
Intestinal	1.00		
Diffuse	5.70	2.88–11.31	<0.0001
Mixed	4.19	1.89–9.32	0.0004
Tumour size (per cm)	1.34	1.13–1.59	0.0008

patient, which is similar to our own experience of 2.0 lymph nodes per patient.

Our results show that intramucosal carcinoma infiltrated lymph nodes in only 3.7% of cases, which is in agreement with data presented by Yamao et al. (16) and Tsujitani et al. (17). In contrast, submucosal carcinoma had a 25.3% lymph node involvement, which is higher than that reported by Kurihara et al. (18) and Kitamura et al. (5), but similar to that described by Ohta et al. (6) and Sowa et al. (19).

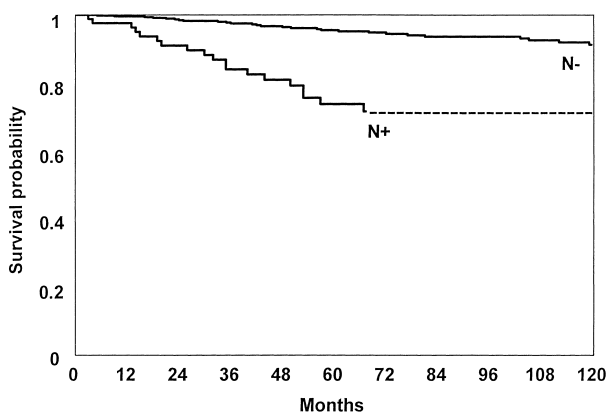
The distribution of I and II level lymph node metastases in our series was 10.7 and 3.5%, respectively, which matches data reported in the Japanese literature (19,20).

The 2.2% hospital mortality is similar to that observed by other Western centres (21,22), but higher than that by Japanese authors (1,15). This is probably due to the fact that in Japan there are surgeons with wide experience in gastric surgery, which obviously helps to improve results. Looking at our own series of patients over the past 10 years, it can be seen that experience has undoubtedly lowered postoperative mortality (1.3%).

The presence of lymph node metastases (N+) in EGC worsens prognosis, as reported by Kitamura et al. (5), Maehara et al. (1) and Katai et al. (23) and as observed in our study. Nio et al. (24) reported for EGC a 5-year survival of 93% for N1 patients and 68.4% for N2 patients and Miwa (25) observed similar rates of 90 and 79%, respectively.

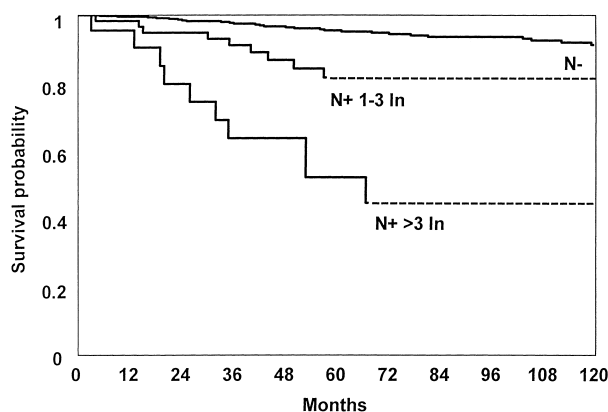
According to the old TNM classification (26), Katai et al. (23) observed that for patients with N1 and N2 involvement, the 5-year survival is 91%.

Seto et al. (20) reported a 5-year survival of 74% for patients with >4 positive lymph nodes. Our series had a substantially lower 5-year survival, especially as regards N2 patients (60%) and patients who presented >3 metastatic lymph nodes (48%). The poor prognosis of our N2 patients can probably be attributed to the smaller case series than those of Japanese authors. Furthermore, some N2 patients with >3 metastatic lymph



N. pts at risk				
N-	499	382	256	164
N+	84	58	28	16

Figure 1. Long-term disease specific survival curves for patients with (positive node, N+) and without (negative node, N-) lymph node metastases. Log rank test = 32.43, $p = 0.0001$.



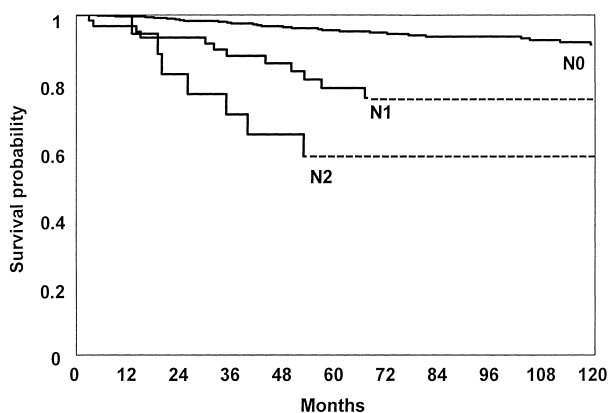
N. pts at risk				
N0	499	382	256	164
N+1-3 ln	62	47	24	13
N+ >3 ln	22	11	4	2

Figure 3. Long-term disease specific survival curves in relation to the number of lymph node metastases: negative node (N-), positive node ≤ 3 (N+ 1-3 ln), positive node >3 (N+ >3 ln). Log rank test = 63.06, $p = 0.0001$.

nodes may have been understaged (we do not perform D3 gastrectomy for EGC).

Univariate analysis showed that lymph node metastases were significantly associated with large tumours, submucosa-infiltrating lesions, diffuse histotype and Pen A type according to Kodama (Table 1). Maehara et al. (1) observed that independent risk factors for lymph node metastases are large tumour dimension, lymphatic involvement and submucosal invasion. Yamao et al. (16) also reported that lymphatic invasion, the histological ulceration of the tumour and larger tumor size are independent risk factors for lymph node metastases of intramucosal EGC.

In the present series, multivariate analysis showed that the risk of lymph node metastasis was associated with submucosal infiltration, tumour size and diffuse histotype (Table 2).



N. pts at risk				
N0	499	382	256	164
N1	63	47	22	14
N2	21	11	6	2

Figure 2. Long-term disease specific survival curves in relation to the groups of lymph nodes involved: negative node (N0), first group positive node (N1), second group positive node (N2). Log rank test = 39.97, $p = 0.0001$.

Kodama Pen A type was also observed as an independent risk factor in relation to the growing characteristics of the tumour, which invades the submucosa expansively, completely destroying the muscularis mucosae.

Sano et al. (27) reported that tumours with the following characteristics generally do not metastasize to lymph nodes: (1) mucosal infiltration, (2) tumour dimension of <1.5 cm in diameter, (3) elevated macroscopic type, (4) depressed macroscopic type without ulceration or ulcer scar and (5) histologically differentiated type. In our series, the 71 patients who had mucosal tumours and macroscopic type I, IIa or IIb did not present lymph node metastases, regardless of tumour dimension and histotype.

Several authors (1,17,18,28,29) have concluded that D2 gastrectomy is indicated when EGC presents with large tumour dimension and invasive characteristics. In our experience, it is possible to determine tumour size and histotype perioperatively, but difficult to obtain accurate information on the degree of submucosal invasion.

The introduction of endoscopic ultrasonography with 20 MHz probes has undoubtedly improved diagnostic accuracy, but unfortunately it still remains far from satisfactory (30).

Sano et al. (27) and Yamao et al. (16) stated that it is necessary to examine the whole resected lesion in order to confirm whether the tumour is confined to the mucosa. The 'strip biopsy' or endoscopic mucosal resection (EMR), proposed by Tada et al. (31), can, in some cases, achieve this objective. Yamao et al. (16) maintained that, in patients with intramucosal EGC without risk factors for lymph node metastasis, EMR should be considered not only as a diagnostic procedure but also a radical treatment.

In contrast, Baba et al. (15) and Siewert et al. (32) claimed that D2 lymphadenectomy also improves prognosis in patients without lymph node metastases (N0), the reason being that the micrometastases present in about 10% of cases can only be

detected with immunohistochemical techniques that are not routinely used.

Noda et al. (33) believe that endoscopic treatment is a useful approach in a limited number of cases because conventional surgery has an extremely high 5-year survival rate (98%) that endoscopic treatment has yet to achieve.

Our experience confirms these data and we also observe good long-term survival, but dependent on the number of metastatic lymph nodes (4,34).

On the basis of our results, we conclude that (1) even in EGC, D2 gastrectomy should be considered the standard treatment where it can be safely performed; and (2) lesions diagnosed as mucosal cancer type I, IIa or IIb should first be treated by EMR. If histological examination of the EMR specimen reveals that there is submucosal invasion, D2 gastrectomy should be performed.

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