

# Pathological Predictors of Lymph Node Involvement in Submucosal Gastric Carcinoma: A Retrospective Analysis of Long-Term Outcome

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**Abstract.** *Background:* The incidence of nodal metastasis in early gastric cancer (EGC) ranges from 5.7 to 13%. Since most patients with EGC do not have lymph node metastasis, the validity of extended nodal dissection has been questioned. *Patients and Methods:* Clinicopathological data of 116 patients with EGC, all undergoing D2 lymphadenectomy, were analysed. Patients with or without lymph node metastases were compared in relation to age and gender distribution, tumour histopathology and 10-year prognosis. *Results:* The overall rate of nodal metastasis was 9.5%. The invasion of submucosa, Laurén's diffuse type, a diameter greater than 3 cm, and Pen-A and Pen-B growth patterns were significantly associated with an increased incidence of lymph node metastasis. On multivariate analysis, the diffuse type was an independent risk factor for lymph node involvement, regardless of tumour size and growth pattern ( $p=0.007$ ). Ten-year survival analysis showed no significant correlation with lymph node metastasis (86.5% vs. 71.6%). *Conclusion:* Submucosal carcinomas of intestinal type, under 2 cm in size, are eligible for minimally invasive surgery while, in diffuse-type carcinomas over 2 cm, standard surgery with D2 lymphadenectomy is recommended.

In 1962, the Japanese Society of Gastroenterological Endoscopy defined early gastric cancer (EGC) as an adenocarcinoma confined to the mucosa and the submucosa, irrespective of lymph node metastasis (1). Due to an aggressive screening practice, this tumour is most commonly

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**Key Words:** Early gastric cancer, lymph node metastasis, lymphadenectomy, prognosis.

diagnosed in Japan, where it represents more than 50% of all gastric cancers (2). In Western countries, the incidence of EGC has gradually increased over recent decades, currently accounting for 10-20% of operated carcinomas (3). Prognosis after surgery is remarkably good with a 5-year survival rate reaching 95%. The overall incidence of lymph node metastasis is closely related to the depth of neoplastic invasion and, although extremely rare in mucosal carcinomas (0-7%), is approximately 19-23% in tumours extending to the submucosa (4-5). Gastrectomy with dissection of group 1 and group 2 lymph nodes (D2) is generally considered as the gold standard treatment for EGC, albeit the low incidence of lymph node metastasis, especially in mucosal carcinomas, has led numerous authors to question the practice of extended lymphadenectomy (6-7). Considerable attention has been drawn to the quality of life after surgery, with limited surgical procedures (e.g. endoscopic mucosal resection, local gastric resection and gastrectomy with D1 lymph node dissection) being developed in patients with EGC (8-9). The aim of this study is to investigate the incidence and clinicopathological predictors of nodal metastasis in order to plan a strategy for the treatment of EGC.

## Patients and Methods

Between 1987 and 1992, a total of 841 patients underwent curative resection for gastric carcinoma at the University Hospital in Florence, Italy. Original pathology reports, discharge summaries and operative reports were reviewed to confirm patient age, gender, surgical resection, TNM stage, size, gross appearance and location of the tumour within the stomach.

Macroscopic classification was decided according to the criteria of the Japanese Society of Gastroenterological Endoscopy (10): the elevated type includes I, IIa, IIa + IIc and IIa + III lesions, while the depressed type includes IIc, III, IIc + III and IIc + IIa lesions. An experienced pathologist reviewed all sections of formalin-fixed and paraffin-embedded specimens stained with haematoxylin and eosin. Microscopic features were recorded according to the criteria of the Japanese Research Society for Gastric Cancer (JRS GC) classification

in which differentiated carcinomas include papillary carcinomas and well to moderately differentiated tubular adenocarcinomas, while poorly differentiated carcinomas comprise poorly differentiated tubular adenocarcinomas and signet-ring cell carcinomas (10). The histological type of tumour was also determined according to the Laurén classification system (11). The Kodama classification was used to assess tumour size and growth pattern (12): the “super” or superficially spreading type is defined as a tumour measuring more than 4 cm in diameter, strictly confined to the mucosa (super-M) or focally infiltrating the submucosa (super-SM); the “small mucosal” type is a carcinoma less than 4 cm in diameter with or without minimal submucosal invasion, respectively small-SM and small-M; the “Pen” or penetrating variant is a lesion with a diameter under 4 cm, invading the submucosa in a penetrating fashion. The “Pen” type is further divided into two subgroups according to the pattern of invasion through the *muscularis mucosae*: the “Pen-A” tumours are characterised by expansive growth and complete destruction of the *muscularis mucosae* and the “Pen-B” tumours by infiltrative growth and fenestration of the *muscularis mucosae*. Involvement of regional lymph nodes was defined following the TNM classification of the International Union Against Cancer (UICC) (13).

**Statistical analysis.** By periodic linkage to Municipal Population Offices and to the Regional Mortality Registry, information was obtained for all patients regarding their survival. To eliminate bias due to operative deaths, patients who died within 30 days of surgery were excluded from the survival analysis. Survival rates were calculated according to the Kaplan-Meier method. The chi-square test for proportion was used to assess the association between clinicopathological parameters and lymph node involvement. Multivariate analysis regarding the prediction of lymph node metastasis was performed using logistic analysis. *P*-values of less than 0.05 were considered significant.

## Results

In 116 out of 841 patients (13.8%) undergoing curative surgery for primary gastric carcinoma, the tumour was confined to the mucosa or submucosa. The study consisted of 69 males (59.5%) and 47 females (40.5%), with a ratio of 1.4:1. Patient age ranged from 37 to 89 years (mean age, 69.5 years). Total gastrectomy was performed on 30 patients (25.8%) and subtotal resection on 86 (74.2%). In all cases, dissection of group 1 and group 2 lymph nodes was carried out together with gastrectomy. Clinicopathological findings of the patients are detailed in Table I. Tumours were located in the upper third of the stomach in 8 cases (6.9%), in the middle third in 29 (25.0%) and in the lower third in 73 (62.9%). EGC was limited to the mucosa in 43 patients (37%) and extended to the submucosa in 73 (63%). Lymph node involvement was found in 11 patients (9.5%) and was always concomitant with submucosal invasion (Table II).

The correlation between the lymph node status and the other parameters showed that the maximal risk for nodal metastasis depended on tumour diameter, in particular over 3 cm (*p*=0.027), submucosal invasion (*p*=0.007), diffuse histotype (*p*=0.043), and Pen-A or Pen-B type according to Kodama

Table I. Clinicopathological variables in patients with EGC according to the presence of lymph node metastasis.

Variable	Cases N	N+ N (%)	<i>P</i>
Age group			0.75
≤59	39	5 (12.8)	
60-69	35	2 (5.7)	
≥70	42	4 (9.5)	
Gender			0.77
Male	69	7 (10.1)	
Female	47	4 (8.5)	
Diameter			0.027
<2 cm	13	0	
2-3 cm	76	5 (6.6)	
>3 cm	27	6 (22.2)	
Site			0.55
Upper third	8	0	
Middle third	29	4 (13.8)	
Lower third	73	7 (9.6)	
Multiple	6	0	
Depth of invasion			0.007
Mucosal	43	0	
Submucosal	73	11 (15.1)	
Macroscopic type			0.69
Protruding	25	3 (10.7)	
Flat	56	4 (7.1)	
Depressed / Ulcerated	32	4 (12.5)	
Laurén classification			0.018
Intestinal	94	6 (6.4)	
Diffuse	22	5 (22.7)	
Kodama classification			0.026
Pen-A	41	8 (19.5)	
Pen-B	14	2 (14.3)	
Small-M	39	0	
Small-SM	15	0	
Super-M	3	0	
Super-SM	4	1 (25.0)	
JRSGC classification			0.11
Tubular, well-differentiated	32	0	
Tubular, moderately differentiated	46	4 (8.7)	
Poorly differentiated	19	3 (15.7)	
Mucinous	3	0	
Signet ring cell	13	3 (23.1)	
Papillary	3	1 (33.3)	
Type of surgery			0.91
Total gastrectomy	30	3 (10.0)	
Subtotal gastrectomy	86	8 (9.3)	

(*p*=0.012). Conversely, age, gender, type of gastrectomy, tumour location and macroscopic appearance were unrelated to the incidence of lymph node metastasis (Table I).

On multivariate analysis, the diffuse type proved to be the only independent predictive factor of lymph node involvement, regardless of tumour size and growth pattern (OR=7.50; 95% CI=1.75-32.17; *p*=0.007).

Kaplan-Meier survival curves based on cause-specific mortality (Figure 1) did not significantly differ between

Table II. Clinicopathological findings of 11 patients with lymph node involvement.

Case	Age (years)	Gender	Surgery	Site	Size (cm)	Depth	LN	Gross	Kodama	JRSGC	Laurén	Outcome
#19	78	M	TG	Body	2	SM	2/20	III	Pen-B	Tub. 2	Intestinal	Alive at 10 years
#41	69	F	STG	Body	3	SM	7/20	Ic + III	Pen-A	Poor	Diffuse	Alive at 10 years
#42	76	M	STG	Antrum	4	SM	2/22	I	Pen-A	Tub. 2	Intestinal	Alive at 10 years
#48	38	M	STG	Body	4	SM	3/19	Ic	Pen-B	Sig.	Diffuse	DWD at 98 months
#49	47	M	STG	Antrum	4	SM	1/12	III	Pen-A	Sig.	Diffuse	Alive at 10 years
#54	53	F	STG	Antrum	3	SM	5/18	III	Pen-A	Poor	Diffuse	Alive at 10 years
#66	79	F	STG	Antrum	4	SM	2/29	I	Pen-A	Pap.	Intestinal	DOD at 37 months
#69	67	F	STG	Antrum	3	SM	3/11	Ic + III	Pen-A	Poor	Intestinal	Alive at 10 years
#72	73	M	STG	Antrum	4	SM	6/22	I	Pen-A	Tub. 2	Intestinal	DWD at 2 months
#83	58	M	TG	Body	2	SM	9/29	Ia	Pen-A	Tub. 2	Intestinal	DWD at 13 months
#87	58	M	TG	Antrum	5	SM	4/35	Ia	Super-SM	Sig.	Diffuse	Alive at 10 years

TG: total gastrectomy; STG: subtotal gastrectomy; LN: lymph nodes; Tub. 2: tubular carcinoma, moderately differentiated type; Poor: poorly differentiated carcinoma; Sig.: signet-ring cell carcinoma; Pap.: papillary; DWD: dead with disease; DOD: dead from other diseases.

node-negative and node-positive cases, with a 5-year observed survival of 88.8% and 81.8%, respectively (log-rank test:  $p=0.25$ ), and a 10-year observed survival of 86.5% and 71.6%, respectively (log-rank test:  $p=0.18$ ). In addition, the comparison of survival curves based on mortality from all causes did not significantly differ between the two groups of patients, with a 5-year observed survival of 78.1% and 72.7%, respectively (log-rank test:  $p=0.73$ ), and a 10-year observed survival of 67.6% and 63.4%, respectively (log-rank test:  $p=0.80$ ).

## Discussion

Recent developments in diagnosis and the introduction of mass screening programmes have led to an increase in the detection of EGC. Despite the fact that gastrectomy with D2 lymphadenectomy is generally considered to be the gold standard, the extent of lymph node dissection remains a controversial issue in the management of EGC (14-18).

The present study analysed the risk factors for the occurrence of lymph node metastasis in a large Western series of EGC treated at a single institution. An overall rate of lymph node metastasis of 9.5% was found. In other Western series, the probability of a primary gastric carcinoma confined to the mucosa or submucosa being associated with nodal metastasis varies from 7 to 18% (3).

Major risk factors for lymph node metastasis in EGC include large tumour size, lymphatic vessel involvement and submucosal invasion (19-23). In a survey of 748 patients, Sano *et al.* reported a significant difference ( $p<0.001$ ) between the mean size of node-negative and node-positive carcinomas (24). Out of 239 tumours with a diameter of 2 cm or less, lymph node involvement was seen only in 6 cases, 5 of which were submucosal carcinomas. Hochwald *et al.* found that those tumours that were limited to the mucosa and

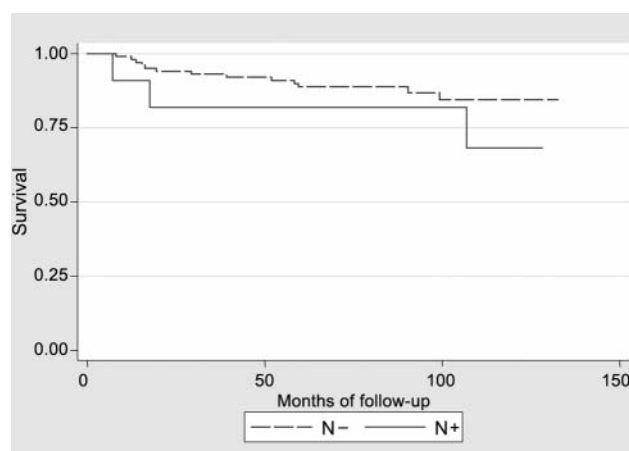


Figure 1. Kaplan-Meier survival curves based on cause-specific mortality, stratified by nodal status.

under 4.5 cm in size had a 96% rate of negative nodes. In contrast, tumours having a diameter of 4.5 cm or more and penetrating the submucosa showed a 5.6% probability of positive nodes (25). Habu *et al.* demonstrated that there is a greater incidence of metastasis in protruding neoplasms which are larger than 4 cm and invade the submucosa (26). The presented results are in accordance with data from the literature. Indeed, tumour diameter exceeded 2 cm in all patients with nodal metastasis, with 6 cases of submucosal carcinoma (54.5%) measuring >3 cm in greatest dimension, while the remaining cases measured 2-3 cm. The 43 patients who had mucosal carcinomas did not show lymph node involvement, regardless of tumour dimension.

In a multicentre study carried out by the JRSGC comprising 27,574 gastric carcinomas limited to the mucosa, 630 cases (2.8%) had lymph node metastases. Of the 630

neoplasms, 87.9% were of the depressed type (IIc, IIc+IIa, IIc+III). At histology, ulceration was found in 64.6% (10). Ulceration seems to facilitate lymph node dissemination, probably due to the breakdown of the *muscularis mucosae* increasing the chance of lymphatic vessel invasion by neoplastic cells. However, in submucosal tumours the rate of lymph node metastasis is similar whether ulceration is present or not (20-30% vs. 23-24%) (17). In this series, no difference was found in the distribution of macroscopic type.

Tumour growth pattern and vascular invasion have also been reported to be associated with lymph node metastasis. Data on record show that Super and Pen-B lesions have no tendency to vascular invasion, and only occasionally metastasise to lymph nodes (7.1% in Super-M; 15.2% in Super-SM; 7.7% in Pen-B), thus carrying a good prognosis with a 10-year survival rate of 90% (27). Pen-A type lesions, on the other hand, more often invade lymphatics (43.8% of cases) and veins (25%), and spread to regional lymph nodes (25%). Prognosis in such cases worsens, with a survival rate at 10 years falling to 64.8% (28). In this series, tumour type according to Kodama was observed as a risk factor in univariate analysis, with positive nodes being detected in only 9.1% of the non Pen-A submucosal tumours, but was not a significant risk factor in further multivariate analysis.

Data concerning the prognostic significance of histological type in EGC are contradictory. Although some researchers found that poorly differentiated cancers are significantly associated with a higher incidence of lymph node metastasis (20-21), others could not confirm these findings (22, 29). In this study, tumour histotype according to Laurén significantly predicted lymph node metastasis in multivariate analysis. High risk was particularly demonstrated for the diffuse type corresponding to the poorly differentiated type reported by Japanese authors.

In conclusion, with the increasing recognition of “good prognostic factors”, a recent trend in the treatment of EGC has been to limit surgery in order to optimise the patient’s quality of life and achieve a complete cure. These results strongly suggest that minimally invasive surgical procedures, such as laparoscopic partial resection, are recommended in cases of submucosal gastric carcinoma with negligible risk of lymph node metastasis (intestinal type and under 2 cm in size).

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*Received October 20, 2008*  
*Revised December 18, 2008*  
*Accepted January 27, 2009*