Original article

Risk factors for lymph node metastasis in patients with early gastric cancer and signet ring cell histology

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Background: **Early gastric cancer with signet ring cell histology has been reported as a favourable histological type. The aim of this study was to identify risk factors associated with lymph node metastasis in patients with this type of early gastric cancer.**

Methods: **A cross-sectional study of patients with early gastric cancer with differentiated and signet ring cell histology undergoing surgery was conducted. Risk factors were evaluated using multiple logistic regression analysis with odds ratios and 95 per cent confidence intervals.**

Results: **In 1362 patients undergoing gastrectomy for early gastric cancer, the rate of lymph node metastasis was similar for tumours with signet ring cell and differentiated histological findings (10·7 *versus* 9·0 per cent respectively; $P = 0·307$). Logistic regression analysis showed that depth of tumour invasion was predictive of lymph node metastasis in patients with signet ring cell histology ($P < 0·001$). Tumour size was not associated with lymph node metastasis in either univariable or multivariable analysis. Lesions smaller than 2 cm were not uncommon in patients with signet ring cell gastric tumours and lymph node metastases (six of 48; 13 per cent).**

Conclusion: **Patients with early gastric cancer with signet ring cell-type histology are probably best treated by gastrectomy with lymph node dissection.**

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Introduction

Treatment options for early gastric cancer include endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), wedge resection, laparoscopically assisted gastrectomy and open gastrectomy[1–4]. The likelihood of lymph node metastasis is the most important factor to consider when deciding on the most appropriate treatment. The absence of lymph node metastasis is a prerequisite for EMR/ESD[5]. The accuracy of preoperative computed tomography and endoscopic ultrasonography in the detection of lymph node metastasis is between 50 and 70 per cent[6,7]. Other clinical and pathological factors, such as ulcerated lesions, tumour size, depth of invasion and differentiation, can be used to aid in the assessment of risk of nodal metastasis[8,9].

Tumours with undifferentiated findings (poorly differentiated, signet ring cell or mucinous) on histological examination are generally thought to be unsuitable for ESD because of frequent lymph node metastasis[5]. Recent studies have shown, however, that early gastric cancer with signet ring cell histology rarely metastasizes to lymph nodes and has been associated with a favourable prognosis[10–14]. Patients with this type of early gastric cancer have been considered good candidates for ESD, where lesions are limited to the mucosa, less than 1–2 cm in size, and there is no ulceration or lymphatic involvement on pathological examination. Data published to date have been based on comparative studies of signet ring cell with poorly differentiated cancer types, representing only a relative risk for lymph node metastasis[10–14]. Risk factors for lymph node metastasis relating solely to signet ring cell gastric tumours have not been reported.

The aim of the present study was to identify risk factors for lymph node metastasis in patients with early gastric cancer with signet ring cell histology in order to guide management.

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Methods

A cross-sectional cohort study was conducted involving all patients who underwent surgery for early gastric cancer with well or moderately differentiated, and signet ring cell histological findings at the National Cancer Centre, Korea, between April 2001 and December 2008. Preoperative evaluation included oesophagogastroduodenoscopy with biopsy, abdominal computed tomography, chest radiography, standard blood testing and endoscopic ultrasonography as necessary. Well differentiated mucosal tumours smaller than 2 cm and without ulceration were excluded, because endoscopic resection was performed in these patients in accordance with institutional and Japanese treatment guidelines[15,16]. The presence of ulceration was defined grossly as type IIc or III according to the pathological findings[17].

Surgery

All patients underwent a gastrectomy with D1 + β or greater lymph node dissection[17]. A distal subtotal gastrectomy was performed if there was a tumour-free margin of 2 cm in early gastric carcinoma. The extent of lymph node dissection followed the recommendations of the Japanese Research Society for Gastric Cancer[17]. Cancers were staged according to the tumour node metastasis classification system as described by the International Union Against Cancer (UICC); a potentially curative resection was defined as R0 resection using the UICC residual tumour classification[18].

Pathological examination

All specimens were examined immediately after resection. World Health Organization criteria for histological typing of gastric tumours were used, where signet ring cell carcinoma is defined as 'an adenocarcinoma in which a predominant component (more than 50% of the tumour) is made up of isolated or small groups of malignant cells containing intracytoplasmic mucin'[19]. A single pathologist retrieved all lymph nodes by palpation under gross inspection. No size limitation was imposed for lymph node harvesting. Lymph nodes were examined in sections 4 mm thick along the long axis, embedded in paraffin blocks, and stained with haematoxylin and eosin.

Statistical analysis

Statistical analyses were carried out using SAS® version 8 (SAS Institute, Cary, North Carolina, USA). Continuous variables were expressed as median (range). For between-group comparisons, continuous variables were analysed with Student's t test, and categorical variables with the χ^2 test. Multiple logistic regression analysis was used to determine risk factors for lymph node metastasis. For each variable, the odds ratio with 95 per cent confidence intervals was determined. $P < 0{\cdot}050$ (two tailed) was considered statistically significant.

Results

Of a total of 1362 patients, 448 (32·9 per cent) had tumours with signet ring cell-type histology. Patient demographics are shown in *Table 1*. Rates of lymphovascular invasion and lymph node metastasis were similar for tumours with differentiated and signet ring cell histology (*Table 1*).

The rate of lymph node metastasis was 9·0 per cent for differentiated tumours and 10·7 per cent for signet ring cell tumours (*Table 1*). The presence of ulceration and depth of invasion differed between patients with and without metastatic lymph nodes in both tumour types. Lymph node metastasis was associated with tumour size when analysed as a dichotomous variable in

Table 1 Comparison of clinicopathological characteristics

	Differentiated ($n = 914$)	Signet ring cell ($n = 448$)	P†
Sex			< 0·001
M	689 (75·4)	225 (50·2)	
F	225 (24·6)	223 (49·8)	
Age (years)*	62 (30–88)	50 (24–78)	< 0·001‡
Location			< 0·001
Lower third	542 (59·3)	264 (58·9)	
Middle third	247 (27·0)	184 (41·1)	
Upper third	125 (13·7)	0 (0)	
Tumour size (cm)*	2·8 (0·2–12·5)	3 (0·4–15)	< 0·001
Gross type			< 0·001
No ulceration	606 (66·3)	394 (87·9)	
Ulceration	308 (33·7)	54 (12·1)	
Lymphovascular invasion			0·113
No	880 (96·3)	423 (94·4)	
Yes	34 (3·7)	25 (5·6)	
Depth of invasion			< 0·001
Mucosa	455 (49·8)	304 (67·9)	
Submucosa 1	136 (14·9)	40 (8·9)	
Submucosa 2	140 (15·3)	53 (11·8)	
Submucosa 3	183 (20·0)	51 (11·4)	
Lymph node metastasis			0·307
No	832 (91·0)	400 (89·3)	
Yes	82 (9·0)	48 (10·7)	

Values in parentheses unless indicated otherwise; *values are median (range). †χ^2 test unless indicated otherwise; ‡Student's t test.

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Table 2 Comparison of patients according to presence of lymph node metastasis

	Lymph node metastasis (differentiated)			Lymph node metastasis (signet ring cell)		
	No ($n = 832$)	Yes ($n = 82$)	P†	No ($n = 400$)	Yes ($n = 48$)	P†
Age (years)*	62 (30–88)	63 (33–86)	0·222‡	50 (24–78)	48 (26–73)	0·544‡
Sex			0·118			0·974
M	633 (76·1)	56 (68)		201 (50·3)	24 (50)	
F	199 (23·9)	26 (32)		199 (49·8)	24 (50)	
Tumour size (cm)			0·007			0·111
< 2	214 (25·6)	10 (12)		90 (22·5)	6 (13)	
≥ 2	618 (74·3)	72 (88)		310 (77·5)	42 (88)	
Location of tumour			0·685			0·183
Lower third	490 (58·9)	52 (63)		240 (60·0)	24 (50)	
Middle third	228 (27·4)	19 (23)		160 (40·0)	24 (50)	
Upper third	114 (13·7)	11 (13)		0 (0)	0 (0)	
Ulceration			$< 0·001$			0·048
No	573 (68·9)	33 (40)		356 (89·0)	38 (79)	
Yes	259 (31·1)	49 (60)		44 (11·0)	10 (21)	
Depth of tumour invasion			$< 0·001$			$< 0·001$
Mucosa	448 (53·8)	7 (9)		286 (71·5)	18 (38)	
Submucosa	384 (46·2)	75 (91)		114 (28·5)	30 (63)	
Lymphovascular invasion			0·209			0·264
No	799 (96·0)	81 (99)		376 (94·0)	47 (98)	
Yes	33 (4·0)	1 (1)		24 (6·0)	1 (2)	

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †χ^2 test unless indicated otherwise; ‡Student's t test.

Table 3 Multiple linear regression analysis of risk factors for lymph node metastasis

	Differentiated tumours		Signet ring cell tumours	
	Odds ratio	P	Odds ratio	P
Sex (M *versus* F)	1·70 (1·01, 2·87)	0·047	0·93 (0·50, 1·74)	0·823
Age (years)	1·01 (0·99, 1·04)	0·290	0·98 (0·96, 1·01)	0·214
Ulceration (no *versus* yes)	1·30 (0·78, 2·16)	0·317	0·08 (0·92, 4·61)	0·078
Lymphovascular invasion (no *versus* yes)	3·08 (0·40, 23·77)	0·280	3·15 (0·41, 24·47)	0·273
Size (< 2 *versus* ≥ 2 cm)	1·57 (0·77, 3·18)	0·215	1·41 (0·56, 3·55)	0·462
Depth of invasion (mucosa *versus* submucosa)	10·83 (4·68, 25·08)	$< 0·001$	4·42 (2·30, 8·48)	$< 0·001$

Values in parentheses are 95 per cent confidence intervals.

differentiated tumours but not in signet ring cell tumours (*Table 2*).

Multiple regression analysis showed that depth of invasion contributed to the risk of lymph node metastasis both in patients with differentiated tumours and in those with signet ring cell cancers (*Table 3*). Female sex was a risk factor for the presence of lymph node metastasis in patients with differentiated tumours (*Table 3*).

Six signet ring cell tumours smaller than 2 cm had metastasized to between one and 13 lymph nodes. The smallest tumour with lymph node metastasis was 0·9 cm and had invaded the submucosa. One tumour of 1·7 cm without submucosal invasion, lymphatic invasion or ulceration had metastasized to lymph nodes.

Discussion

This study showed that the rate of lymph node metastasis in early gastric cancer with signet ring cell histology is similar to that in cancers with differentiated histology, and that tumour size did not predict lymph node metastasis. There was a risk of lymph node metastasis in signet ring cell tumours smaller than 2 cm that exhibited any of the risk factors for nodal spread (submucosal invasion, lymphatic invasion or ulceration). The rate of lymph node metastasis in differentiated cancers smaller than 2 cm has been reported previously as 0 per cent[2,3].

Gastrectomy is associated with significant postoperative symptoms[20] and attempts to minimize these by pylorus

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and vagal nerve preservation have been disappointing[21,22]. Lymph node metastasis is the most important consideration when deciding on stomach preservation[5].

Unlike advanced gastric cancers, early gastric cancers with signet ring cell histology have been reported more frequently in women, and mucosal tumours tend to be larger than poorly differentiated early gastric cancers[10,11]. Consistent with the findings of previous reports[10,11], the present study showed that nearly half of the patients were women and nearly 70 per cent of tumours were confined to the mucosa.

The frequency of lymph node metastasis in mucosal cancers with signet ring cell histology was 5·9 per cent (18 of 304), similar to the overall lymph node metastasis rate for early gastric cancers confined to the mucosa[1,3], regardless of histological type. Other studies have found a lymph node metastasis rate for mucosal cancers with signet ring cell histology of 3 per cent or less[10–14]. The reason for this difference is unclear.

Recent studies[10,11] have shown that early gastric cancer with signet ring cell histology rarely metastasizes to lymph nodes and has a favourable prognosis. Patients with this type of early gastric cancer have been considered good candidates for ESD when lesions are limited to the mucosa, less than 2 cm in diameter and there is no lymphatic involvement. These recommendations are, however, based on pathological examinations that included both signet ring cell and poorly differentiated tumour types.

Multivariable analysis showed that depth of tumour invasion was the only risk factor for lymph node metastases in both histological types of tumour.

Large tumours are frequently accompanied by other risk factors for lymph node metastasis. The present study, however, failed to identify tumour size as an independent risk factor for nodal metastases in patients with early gastric cancer with signet ring cell histology when tumour size was analysed as a dichotomous variable. Lymph node metastases in small signet ring cell tumours were not uncommon. It is acknowledged that actual tumour size tends to be larger than that determined by endoscopy or endoscopic ultrasonography in tumours with signet ring cell histology[23].

On the basis of the present results, patients with early gastric cancer with signet ring cell-type histology are probably best treated by gastrectomy with lymph node dissection.

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