Original article

Predictive factors for lymph node metastasis in patients with poorly differentiated early gastric cancer

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Background: Endoscopic submucosal dissection is gaining popularity in the treatment of early gastric cancer. This study aimed to identify clinicopathological factors predictive of lymph node metastasis in patients with the poorly differentiated early gastric cancer to assess the feasibility of using endoscopic submucosal dissection for these cancers.

Methods: The records of patients with poorly differentiated early gastric cancer who had undergone gastric cancer surgery between January 2002 and December 2009 were reviewed. Associations between clinicopathological factors and the presence of lymph node metastasis were analysed by univariable and multivariable logistic regression analysis.

Results: Some 1005 patients were included in the analysis. Univariable analysis indicated that lymph node metastasis was associated with sex, ulceration, tumour size, depth of invasion, macroscopic type, lymphatic invasion and venous invasion. Logistic regression revealed that lymph node metastasis was significantly associated with sex, tumour size, depth of tumour invasion and lymphatic involvement. In the group with none of these risk factors (men with mucosal tumour no larger than 2 cm in size, with no lymphatic involvement), lymph node metastasis was present in four (3·2 per cent) of 124 patients.

Conclusion: In the present study 3·2 per cent of patients who were negative for all identified risk factors had lymph node metastasis. The use of endoscopic submucosal dissection should be considered carefully in the treatment of poorly differentiated early gastric cancer.

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Introduction

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are widely accepted treatments for early gastric cancer (EGC) in patients with appropriate criteria[1–3]. These procedures preserve gastric function and maintain quality of life by avoiding radical gastrectomy. Definite indications include: differentiated adenocarcinoma, intramucosal cancer, tumour size up to 20 mm and absence of ulceration[3–6]. The application of EMR or ESD has been limited to differentiated-type EGC because of an increased risk of lymph node metastasis (LNM) in undifferentiated tumours[7–9]. Gastrectomy with lymph node dissection is generally considered the appropriate treatment for fit patients in this group.

Undifferentiated gastric cancers include poorly differentiated, signet ring and mucinous adenocarcinomas. It has recently been suggested that the indications for ESD could be expanded to include undifferentiated EGC[10]. Controversy exists regarding the role of ESD for the signet ring cell type. One series found no LNM with mucosal tumours smaller than 2 cm in the absence of lymphatic involvement[11]. Others, however, reported that depth of tumour invasion was the only risk factor for LNM in these patients and the frequency of LNM in mucosal cancer approached 5·9 per cent, suggesting that these tumours were best treated by gastrectomy and lymph node dissection[12]. Mucinous adenocarcinoma is another rare type of undifferentiated gastric cancer that usually presents at a locally advanced stage. A previous report from this centre indicated that all early mucinous gastric cancers were submucosal lesions with no tumours limited to the mucosa, implying that endoscopic resection was not suitable for mucinous-type cancer[13].

There have been no reports of poorly differentiated cancers in a large patient sample. This study focused on a

large patient cohort with poorly differentiated EGC who had undergone gastric cancer surgery, to identify predictive factors for LNM and to assess the feasibility of applying ESD in such patients.

Methods

The records of all patients with EGC who had undergone a curative gastrectomy at the Department of Surgery, Samsung Medical Centre between January 2002 and December 2009 were analysed to identify those diagnosed with poorly differentiated EGC. Patients with a previous history of subtotal gastrectomy for gastric cancer or ulcer were excluded, as were those with multiple cancers in whom not all lesions were poorly differentiated.

Total or distal gastrectomy with a combined D2 lymphadenectomy was performed, depending on the location and macroscopic type of tumour[14]. After surgery, lymph nodes were examined as follows. For nodes more than 4 mm thick, which was the height of the cassette, the lymph node was bisected along its longest axis. The bisected lymph node was placed cut surface down in a histology processing cassette and immersed in a formalin container for later histological processing. Lymph nodes smaller than 4 mm were processed whole. Cytokeratin immunostaining was not performed. Staging was carried out according to the American Joint Committee on Cancer Staging Manual (7th edition)[15], where node categories were defined as follows: N1, one or two positive lymph nodes; N2, three to six positive lymph nodes; N3a, seven to 15 positive lymph nodes; and N3b, 16 or more positive lymph nodes.

Clinicopathological factors (sex, age, multiplicity, presence of ulceration, tumour size, depth of invasion, tumour location, macroscopic type, Laurén type, lymphatic, venous and perineural invasion) were compared between the LNM-positive and -negative groups.

Statistical analysis

Differences in clinicopathological parameters between patients with and without LNM were determined by

Table 1 Risk factors for lymph node metastasis in poorly differentiated early gastric cancer

	LNM			Proportion in each subcategory with LNM
	Positive ($n = 162$)	Negative ($n = 843$)	P†	
Age (years)			0·935	
< 60	107 (66·0)	554 (65·7)		107 of 661 (16·2)
≥ 60	55 (34·0)	289 (34·3)		55 of 344 (16·0)
Sex			0·012	
M	85 (52·5)	531 (63·0)		85 of 616 (13·8)
F	77 (47·5)	312 (37·0)		77 of 389 (19·8)
Multiplicity			0·732	
Single	159 (98·1)	830 (98·5)		159 of 989 (16·1)
Multiple	3 (1·9)	13 (1·5)		3 of 16 (19)
Ulceration*			0·001	
Yes	80 (51·9)	538 (66·0)		80 of 618 (12·9)
No	74 (48·1)	277 (34·0)		74 of 351 (21·1)
Size (cm)			< 0·001	
≤ 2	19 (11·7)	295 (35·0)		19 of 314 (6·1)
> 2	143 (88·3)	548 (65·0)		143 of 691 (20·7)
Depth of invasion			< 0·001	
Mucosa	30 (18·5)	480 (56·9)		30 of 510 (5·9)
Submucosa	132 (81·5)	363 (43·1)		132 of 495 (26·7)
Location			0·168	
Upper third	12 (7·4)	106 (12·6)		12 of 118 (10·2)
Middle third	55 (34·0)	278 (33·0)		55 of 333 (16·5)
Lower third	95 (58·6)	459 (54·4)		95 of 554 (17·1)
Macroscopic type			0·001	
Elevated	11 (6·8)	54 (6·4)		11 of 65 (17)
Flat	10 (6·2)	122 (14·5)		10 of 132 (7·6)
Depressed	112 (69·1)	591 (70·1)		112 of 703 (15·9)
Mixed	29 (17·9)	76 (9·0)		29 of 105 (27·6)
Laurén type			0·402	
Indeterminate	0 (0)	5 (0·6)		0 of 5 (0)
Diffuse	118 (72·8)	603 (71·5)		118 of 721 (16·4)
Intestinal	26 (16·0)	164 (19·5)		26 of 190 (13·7)
Mixed	18 (11·1)	71 (8·4)		18 of 89 (20)
Lymphatic invasion			< 0·001	
No	61 (37·7)	734 (87·1)		61 of 795 (7·7)
Yes	101 (62·3)	109 (12·9)		101 of 210 (48·1)
Venous invasion			0·001	
No	154 (95·1)	836 (99·2)		154 of 990 (15·6)
Yes	8 (4·9)	7 (0·8)		8 of 15 (53)
Perineural invasion			0·139	
No	154 (95·1)	820 (97·3)		154 of 974 (15·8)
Yes	8 (4·9)	23 (2·7)		8 of 31 (26)

Value in parentheses are percentages. *Analysis based on 969 patients with available data. LNM, lymph node metastasis. †χ^2 test.

Table 2 Multivariable stepwise logistic regression analysis of risk factors for lymph node metastasis in poorly differentiated early gastric cancer

	Odds ratio	P
Sex (F *versus* M)	1·53 (1·01, 2·31)	0·045
Macroscopic type		
Mixed *versus* elevated	0·56 (0·22, 1·42)	0·224
Mixed *versus* flat	0·57 (0·23, 1·44)	0·235
Mixed *versus* depressed	0·77 (0·44, 1·37)	0·381
Ulceration (yes *versus* no)	1·28 (0·84, 1·95)	0·260
Size (> 2 *versus* ≤ 2 cm)	2·47 (1·39, 4·40)	0·002
Depth of invasion (submucosa *versus* mucosa)	2·42 (1·46, 3·99)	0·001
Lymphatic invasion (yes *versus* no)	6·50 (4·14, 10·19)	< 0·001
Venous invasion (yes *versus* no)	2·67 (0·78, 9·10)	0·117

Values in parentheses are 95 per cent confidence intervals.

Table 3 Classification of poorly differentiated early gastric cancer according to depth of invasion, tumour size, lymphatic invasion, sex and lymph node metastasis

Depth of invasion	Size (cm)	Lymphatic invasion	Sex	LNM		Node category†
				Negative	Positive*	
Mucosa	≤ 2	No	M	120	4 (3·2)	N1 (3), N2 (1)
			F	71	2 (3)	N1 (1), N2 (1)
		Yes	M	2	1 (33)	N1 (1)
			F	1	1 (50)	N1 (1)
	> 2	No	M	167	5 (2·9)	N1 (4), N2 (1)
			F	111	10 (8·3)	N1 (7), N2 (1), N3a (2)
		Yes	M	6	3 (33)	N1 (2), N3a (1)
			F	2	4 (67)	N1 (2), N2 (1), N3a (1)
Submucosa	≤ 2	No	M	56	3 (5)	N1 (2), N3a (1)
			F	28	3 (10)	N1 (1), N2 (1), N3b (1)
		Yes	M	9	4 (31)	N1 (1), N2 (2), N3a (1)
			F	8	1 (11)	N1 (1)
	> 2	No	M	123	19 (13·4)	N1 (11), N2 (7), N3a (1)
			F	58	15 (21)	N1 (10), N2 (5)
		Yes	M	48	46 (49)	N1 (26), N2 (11), N3a (7), N3b (2)
			F	33	41 (55)	N1 (18), N2 (18), N3a (5)

Values in parentheses are *percentages and †number of patients. LNM, lymph node metastasis.

means of the χ^2 test. Variables with $P < 0{\cdot}050$ in univariable analysis were included in the multivariable analysis. Multivariable stepwise logistic regression analysis was used to identify independent risk factors for LNM. The hazard ratio and 95 per cent confidence interval were calculated. $P < 0{\cdot}050$ was considered statistically significant. Statistical analysis was carried out using the statistical software SPSS® version 12.0 for Windows® (IBM, Armonk, New York, USA).

Results

LNM was confirmed pathologically in 162 (16·1 per cent) of 1005 patients with poorly differentiated EGC treated by D2 resection. Univariable analysis indicated that LNM was significantly associated with female sex, the presence of ulceration, tumour size larger than 2 cm, submucosal invasion, macroscopic mixed type and the presence of lymphatic or venous invasion (*Table 1*). There were no significant differences in terms of age, multiplicity, tumour location, Laurén type and perineural invasion between the two groups. Multivariable analysis revealed that sex, tumour size, depth of tumour invasion and lymphatic invasion were independent risk factors for LNM (*Table 2*).

LNM was still found in four (3·2 per cent) of the 124 patients with none of these identified risk factors (men with mucosal tumours no larger than 2 cm, without lymphatic invasion) (*Table 3*). Three of these patients had only one metastatic lymph node among a total of 30, 45 and 37 retrieved lymph nodes, with tumour sizes of 1·2, 2·0 and 1·6 cm respectively. The fourth patient had three metastatic lymph nodes among a total of 20 retrieved lymph nodes and the disease was therefore classified as N2.

Of 74 patients with all the identified risk factors (women with tumours larger than 2 cm with submucosal invasion and lymphatic invasion, 41 (55 per cent) had LNM, with the disease classified as N3a in five. Of 94 men with submucosal invasion, tumours larger than 2 cm and lymphatic invasion, 46 (49 per cent) had LNM and the nodal status of nine patients was N3a or N3b.

Discussion

In this study the independent risk factors for LNM in poorly differentiated EGC were submucosal invasion, a tumour size greater than 2 cm, presence of lymphatic invasion and female sex. Of 74 patients with all of these risk factors, 41 (55 per cent) had LNM. Four (3·2 per cent) of 124 patients who were negative for all four risk factors also had LNM.

The study confirmed female sex as an independent risk factor. This has been found previously to be predictive of LNM in both depressed EGC and differentiated submucosal EGC[5,16], although the nature of the link between sex and LNM remains unclear.

The presence of ulceration is considered an important predictor for LNM in EGC in the absence of other features[17]. The present study, however, identified two patients without ulceration or other independent risk

factors who had LNM, suggesting that applying ESD in this situation still has limitations.

Endoscopic resection has been proposed in patients with poorly differentiated EGC limited to the mucosa, less than 20 mm in diameter and without lymphatic vessel involvement, on the basis that no LNM was detected in such a cohort[18]. Another study that looked at poorly differentiated EGC less than 15 mm in size, confined to the mucosa or with minimal submucosal infiltration (500 μm or less) also reported no LNM, concluding that endoscopic resection could be considered for treatment of these patients[19]. These studies, however, were based on small sample sizes (85 and 234 patients with poorly differentiated EGC respectively). LNM has recently also been found in patients with undifferentiated mucosal cancer satisfying the expanded criteria for ESD (intramucosal cancer, 20 mm or less in diameter without lymphatic–vascular involvement and ulcerative findings)[20,21]; this was thought to reflect lymphatic involvement in the mucosa, suggesting practical limitations in detection of LNM through routine histological examination. The present study also showed that poorly differentiated cancer satisfying the expanded criteria for ESD does carry the possibility of LNM. Using ESD to treat poorly differentiated EGC requires a considered clinical approach.

It has been suggested that the combination of local resection of the primary tumour using EMR or ESD and a laparoscopic lymph node dissection might be another treatment option for obtaining a better quality of life for patients with EGC[22]. Such sentinel node-based surgery (sentinel node navigation surgery) could be helpful in detecting possible LNM that requires radical surgery as well as obviating the need for radical surgery in those with a negligible risk of LNM. The sensitivity of sentinel lymph node biopsy and the incidence of skip metastasis have been reported to be anywhere between 45·5 and 100 per cent, and 0 and 11·8 per cent respectively[23]. The problems of false-negative and skip metastasis should be addressed to ensure that a combination of limited lymph node dissection and endoscopic surgery can be applied appropriately.

Disclosure

The authors declare no conflict of interest.

References

1 Ishikawa S, Togashi A, Inoue M, Honda S, Nozawa F, Toyama E *et al*. Indications for EMR of ESD in cases of early gastric cancer: relationship between histological type, depth of wall invasion, and lymph node metastasis. *Gastric Cancer* 2007; **10**: 35–38.

2 Makuuchi H, Kise Y, Shimada H, Chino O, Tanaka H. Endoscopic mucosal resection for early gastric cancer. *Semin Surg Oncol* 1999; **17**: 108–116.

3 Gotoda T, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. *J Gastroenterol* 2006; **41**: 929–942.

4 Ono H, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D *et al*. Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001; **48**: 225–229.

5 Abe N, Watanabe T, Suzuki K, Machida H, Toda H, Nakaya Y *et al*. Risk factors predictive of lymph node metastasis in depressed early gastric cancer. *Am J Surg* 2002; **183**: 168–172.

6 Li C, Kim S, Lai JF, Oh SJ, Hyung WJ, Choi WH *et al*. Risk factors for lymph node metastasis in undifferentiated early gastric cancer. *Ann Surg Oncol* 2008; **15**: 764–769.

7 Hyung WJ, Cheong JH, Kim J, Chen J, Choi SH, Noh SH. Application of minimally invasive treatment for early gastric cancer. *J Surg Oncol* 2004; **85**: 181–185.

8 Abe N, Watanabe T, Sugiyama M, Yanagida O, Masaki T, Mori T *et al*. Endoscopic treatment or surgery for undifferentiated early gastric cancer? *Am J Surg* 2004; **188**: 181–184.

9 Nasu J, Nishina T, Hirasaki S, Moriwaki T, Hyodo I, Kurita A *et al*. Predictive factors of lymph node metastasis in patients with undifferentiated early gastric cancers. *J Clin Gastroenterol* 2006; **40**: 412–415.

10 Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer* 2011; **14**: 113–123.

11 Ha TK, An JY, Youn HK, Noh JH, Sohn TS, Kim S. Indication for endoscopic mucosal resection in early signet ring cell gastric cancer. *Ann Surg Cncol* 2008; **15**: 508–513.

12 Lee JH, Choi IJ, Kook MC, Nam BH, Kim YW, Ryu KW. Risk factors for lymph node metastasis in patients with early gastric cancer and signet ring cell histology. *Br J Surg* 2010; **97**: 732–736.

13 Choi MG, Sung CO, Noh JH, Kim KM, Sohn TS, Kim S *et al*. Mucinous gastric cancer presents with more advanced tumor stage and weaker b-catenin expression than nonmucinous cancer. *Ann Surg Oncol* 2010; **17**: 3053–3058.

14 Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma – 2nd English Edition. *Gastric Cancer* 1998; **1**: 10–24.

15 American Joint Committee on Cancer. *AJCC Cancer Staging Manual* (7th edn). Springer: New York, 2010.

16 Abe N, Sugiyama M, Masaki T, Ueki H, Yanagida O, Mori T *et al*. Predictive factors for lymph node metastasis of differentiated submucosally invasive gastric cancer. *Gastrointest Endosc* 2004; **60**: 242–245.

17 Yamao T, Shirao K, Ono H, Kondo H, Saito D, Yamaguchi H *et al*. Risk factors for lymph node metastasis from intramucosal gastric carcinoma. *Cancer* 1996; **77**: 602–606.

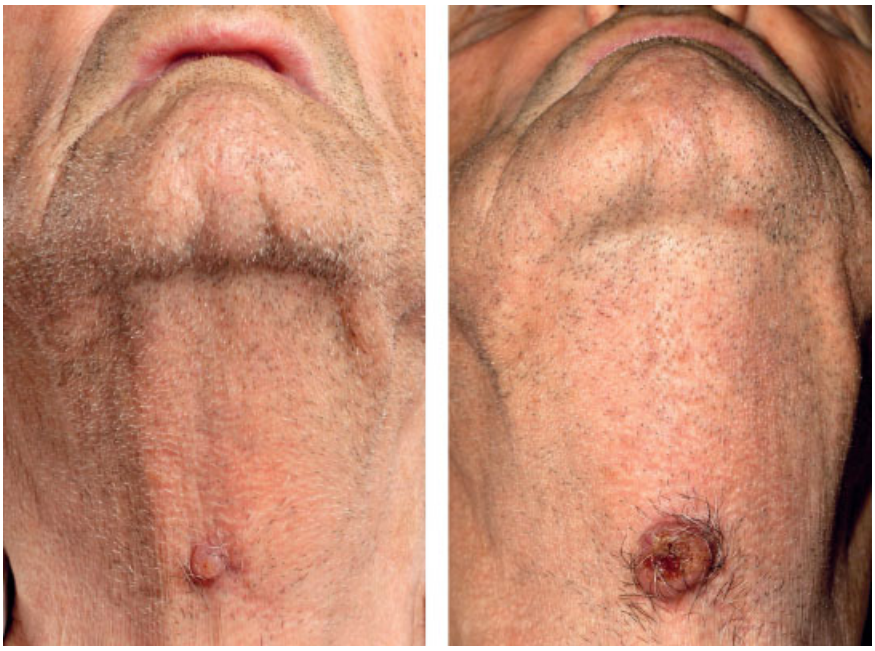
18 Li H, Lu P, Lu Y, Liu CG, Xu HM, Wang SB *et al*. Predictive factors for lymph node metastasis in poorly

differentiated early gastric cancer and their impact on the surgical strategy. *World J Gastroenterol* 2008; **14**: 4222–4226.
19 Park YD, Chung YJ, Chung HY, Yu W, Bae HI, Jeon SW *et al*. Factors related to lymph node metastasis and the feasibility of endoscopic mucosal resection for treating poorly differentiated adenocarcinoma of the stomach. *Endoscopy* 2008; **40**: 7–10.
20 Hirasawa T, Fujisaki J, Fukunaga T, Yamamoto Y, Yamaguchi T, Katori M *et al*. Lymph node metastasis from undifferentiated-type mucosal gastric cancer satisfying the expanded criteria for endoscopic resection based on routine histological examination. *Gastric Cancer* 2010; **13**: 267–270.
21 Hirasawa T, Gotoda T, Miyata S, Kato Y, Shimoda T, Taniguchi H *et al*. Incidence of lymph node metastasis and the feasibility of endoscopic resection for undifferentiated-type early gastric cancer. *Gastric Cancer* 2009; **12**: 148–152.
22 Abe N, Mori T, Takeuchi H, Yoshida T, Ohki A, Ueki H *et al*. Laparoscopic lymph node dissection after endoscopic submucosal dissection: a novel and minimally invasive approach to treating early-stage gastric cancer. *Am J Surg* 2005; **190**: 496–503.
23 Lips DJ, Schutte HW, van der Linden RL, Dassen AE, Voogd AC, Bosscha K. Sentinel lymph node biopsy to direct treatment in gastric cancer. A systematic review of the literature. *Eur J Surg Oncol* 2011; **37**: 655–661.

Snapshot Quiz

Snapshot Quiz 12/21

Question: An 86-year-old man noticed a skin lesion on his neck, 5 months after laparoscopic anterior resection of a Dukes' C1 rectosigmoid adenocarcinoma. A single 1-cm nodule was excised by his general practitioner (**a**). Eight weeks later it had recurred (**b**). What is this lesion?



a **b**

The answer to the above question is found on page 1717 of this issue of *BJS*.

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