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Review article

Predicting lymph node status in early gastric cancer

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Abstract
Accurate prediction of lymph node (LN) status is of crucial importance for appropriate treatment planning in patients with early gastric cancer (EGC). However, there is no definitive consensus yet on which patient and/or tumor characteristics are associated with LN metastasis. A systematic search for studies investigating the relationship between patient and/or tumor characteristics and LN metastasis in EGC was performed in PubMed/MEDLINE. Patient and/or tumor characteristics associated with LN metastasis were identified by meta-analyzing results of individual studies. Forty-five studies were included. Variables significantly associated with LN metastasis in gastric cancer limited to the mucosa were: age younger than 57 years, tumor location in the middle part of the stomach, larger tumor size, macroscopically depressed tumor type, tumor ulcerations, undifferentiated tumors, diffuse tumor type according to the Lauren classification, lymphatic tumor invasion, tumors with a proliferating cell nuclear antigen (PCNA) labeling index of more than 25%, and matrix metalloproteinase-9-positive tumors. Variables significantly associated with LN metastasis in gastric cancer limited to the submucosa were: female sex, tumor location in the lower part of the stomach, larger tumor size, undifferentiated tumors, increasing depth of submucosal invasion, lymphatic tumor invasion, vascular tumor invasion, increased submucosal vascularity, tumors with a PCNA labeling index of more than 25%, tumors with a gastric mucin phenotype, and vascular endothelial growth factor-C-positive tumors. We identified several variables associated with LN metastasis in EGC. These variables should be included in future research, in order to assess which of these variables remain as significant predictors of LN metastasis.

Key words Early gastric cancer · Lymph node metastasis · Prediction · Systematic review · Meta-analysis

Introduction

Early gastric cancer (EGC) is defined as gastric cancer confined to the mucosa or submucosa, regardless of the presence or absence of lymph node (LN) metastasis [1]. In the Eastern hemisphere, up to 70% of all gastric cancers are diagnosed as EGCs (due to mass population screening), whereas in the Western hemisphere, the rate of gastric cancers identified as EGCs accounts for only about 15% [2]. EGC shows a favorable prognosis compared to advanced gastric cancer, with 5-year cancer-specific survival rates exceeding 95% [3]. Accurate prediction of LN status is of crucial importance for appropriate curative treatment planning in EGC; LN-negative patients can be curatively treated with minimally invasive endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) [3], whereas LN-positive patients should undergo (sub) total gastrectomy with limited or extended LN dissection [4]. Gastrectomy with LN dissection is associated with high morbidity and mortality [4], and postoperative quality of life may be impaired because of weight loss, loss of appetite, and other metabolic and nutritional changes. Therefore, this aggressive surgical approach should be reserved only for EGC patients at high risk of LN metastasis. In an attempt to obtain predictive parameters, multiple studies have identified pathologic characteristics of the primary tumor that are associated with an increased likelihood of LN metastasis. Because established eligibility criteria for endoscopic resection of EGC [5] are debated [3, 6], we undertook a systematic review and meta-analysis to give more insight into those patient and/or tumor characteristics that emerge as associated with LN metastasis in EGC.

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Methods

Data sources

A computer-aided search of the PubMed/MEDLINE database was conducted to find English-language studies which reported patient and/or tumor characteristics in relation to LN metastasis in patients with EGC. The following search term was used: "node metastasis" or "node metastases" or "nodal metastasis" or "nodal metastases" or "node involvement" or "nodal involvement" or "metastatic nodes" or "metastatic lymph nodes" or "lymphatic metastasis" or "lymphatic metastases" or "lymphatic involvement" or "lymph node metastatic disease" and ("gastric cancer" or "stomach cancer" or "gastric carcinoma" or "stomach carcinoma"). No beginning date limit was used. The search was updated until 30 October, 2007. To expand the search, bibliographies of articles which finally remained after the selection process were screened for potentially suitable references.

Eligibility criteria

Original studies which investigated the relationship between patient and/or tumor characteristics and the presence or absence of LN metastasis in patients with histopathologically proven EGC were eligible for inclusion. EGC was defined as a tumor histopathologically confined to the mucosa or submucosa, regardless of disease duration, tumor size, presence of symptoms, presence of metastases, or curability [1]. Because risk of LN metastasis is substantially higher in gastric cancer invading the submucosa (submucosal cancer) than in gastric cancer limited to the mucosa (mucosal cancer), only studies which provided separate data for mucosal and/or submucosal cancer were included. Studies performed in animals, ex vivo studies, review articles, meta-analyses, abstracts, editorials or letters, case reports, studies investigating 15 or fewer patients, tutorials, and guidelines for management were excluded. Studies which only investigated the association between patient and/or tumor characteristics and immunohistochemically detected LN micrometastases were also excluded, because these LNs are regarded as pathologically negative for metastatic disease [7]. Only studies dealing with carcinoma were included, because this is overwhelmingly the most important and most common malignant tumor that occurs in the stomach (range, 90% to 95%) [1]. Studies which investigated only a specific type of gastric cancer (i.e., differentiated or undifferentiated gastric cancer, gastric cancer confined to a specific part of the stomach, or depressed gastric cancer) were excluded. Only studies which provided sufficient data to construct a 2×2 contingency table to calculate the association of one or more patient and/or tumor characteristics with LN metastasis were included. Among studies that (possibly) included overlapping patient populations, the article with the highest number of patients was selected for further analysis. However, (possibly) overlapping studies comprising a lower number of patients were also included if they investigated other patient and/or tumor characteristics than the ones in the study with the highest number of patients. In such cases, data analysis was performed only for the patient and/or tumor characteristics or type of EGC (i.e., either mucosal or submucosal cancer), which had not been investigated in the study with the highest number of patients.

Titles and abstracts of the retrieved articles were screened by two researchers (R. M. K. and T. C. K.), using the inclusion and exclusion criteria as mentioned above. Articles were rejected if they were clearly ineligible. Full-text versions of all articles that were found to be potentially eligible for inclusion were then evaluated to make a final decision regarding inclusion or exclusion. Discrepancies between the two researchers were solved by consensus.

Data analysis

For each included study, information was collected concerning the year of publication, country of origin, patient acquisition (consecutive vs nonconsecutive), number of investigated patients, percentage of patients with LN metastasis, extent of lymphadenectomy, variables in relation to LN metastasis analyzed in this review, blind assessment of variables to LN status, and blind assessment of LN status to the investigated variables.

Because of the use of various definitions, the variables "macroscopic tumor type", "histological type", "depth of mucosal or submucosal invasion", "vascular tumor invasion", and "lymphatic tumor invasion" were classified into dichotomized groups. Macroscopic tumor type was divided into depressed and nondepressed types. Among studies which applied the *Japanese classification of gastric carcinoma* [8], type IIc lesions, type III lesions, and mixed lesions in which either a type IIc or a type III component was present were classified as being depressed. Type I, type IIa, type IIb, and mixed lesions in which no type IIc or type III component was present were classified as being nondepressed. Lesions were excluded from analysis if it was unclear whether or not they were composed of a type IIc or type III component. Histological tumor type was divided into: (1) differentiated and undifferentiated type, or (2) defined according to the Lauren classification (which classifies gastric cancer into either intestinal or diffuse type) [9]. Well- and moderately differentiated tubular or papillary adenocarcinomas were classified as being

differentiated. Poorly differentiated adenocarcinomas and signet-ring cell carcinomas were classified as being undifferentiated. Mucinous adenocarcinomas were classified as either differentiated or undifferentiated, depending upon the other predominant elements (tubular, papillary, poorly differentiated, or signet-ring cell) [8]. Mucinous adenocarcinomas which could not be classified were excluded from analysis. If a study provided sufficient data, analyses for both histological classifications (1 and 2) were made. Depth of tumor invasion in cancer limited to the mucosa was classified as either presence or absence of invasion into the muscularis mucosae. Depth of tumor invasion in cancer limited to the submucosa was classified as follows: (1) submucosal invasion of more or less than 500 μm, or (2) presence or absence of invasion beyond the upper third or middle third of the submucosa. If a study provided sufficient data, analyses for both classifications of tumor invasion depth (1 and 2) were made. Vascular and lymphatic tumor invasion were both dichotomized into either presence or absence. If a study provided insufficient data, making a dichotomized classification of either macroscopic tumor type, histological type, depth of tumor invasion, vascular tumor invasion, or lymphatic tumor invasion not possible, no analysis of that tumor parameter was made for the study concerned.

The numbers of patients with metastasis-positive and metastasis-negative LNs for each patient and/or tumor characteristic were abstracted from each study. A standard correction of adding 0.5 to all cells of the 2×2 contingency table was applied if there were no patients in one of the four cells. Study-specific odds ratios with 95% confidence intervals (CIs) were calculated for positive versus negative LN status for each tumor/patient characteristic under investigation. The common odds ratios across studies were estimated by means of a Mantel-Haenszel fixed-effects model, weighting individual studies by their variance [10]. Point estimates and 95% CIs for the common odds ratios were reported for characteristics supported by abstracted data from at least two studies. Confidence intervals that did not overlap the referent (1.0) were considered to be statistically significant. Heterogeneity was tested using the Higgins and Thompson test (Higgins et al. [11]), calculating the I^2 statistic. This statistic uses the conventional Cochran's Q statistic to calculate the percentage of total variation across studies that can be attributed to inter-study heterogeneity, ranging from 0 (no heterogeneity) to 100% (all variance due to heterogeneity). In contrast to Cochran's Q, the I^2 is less affected by the number of studies included in a meta-analysis [11]. If no or moderate heterogeneity is found ($I^2 \leq 50\%$), pooling is justified. Statistical analyses were executed using Meta-DiSc statistical software version 1.4 (Unit of Clinical Biostatistics, Ramón y Cajal Hospital, Madrid, Spain).

Results

The computer-aided search revealed 6246 articles from PubMed/MEDLINE. After screening titles and abstracts, 147 articles remained for possible inclusion. After reviewing the full article, 102 articles were excluded. Reasons for exclusion were: no separate analysis for mucosal and/or submucosal cancer was made or could be extracted ($n = 71$), insufficient data to construct a 2×2 contingency table to calculate the association of one or more patient and/or tumor characteristics with LN involvement ($n = 13$), no association between any patient and/or tumor characteristic and LN status in either mucosal or submucosal cancer was investigated ($n = 10$), same data used in another article by the same group, comprising a larger number of patients ($n = 4$), and only the association between patient and/or tumor characteristics and immunohistochemically detected LN micrometastases was determined ($n = 4$). Eventually, 45 studies were included in this systematic review [6, 12–55]. Screening the references of these articles did not result in other potentially relevant articles. The characteristics of the included studies are presented in Table 1. No studies meeting the inclusion criteria had a prospective study design. The number of patients per study for mucosal cancer varied between 18 and 3584 (median, 269). The number of patients per study for submucosal cancer varied between 22 and 2625 (median, 170). Twenty-six studies stated that patients were included in a consecutive way. Among these studies, the percentage of LN-positive cases in patients with mucosal cancer varied between 0.0 and 20.3% (median, 3.2%). For submucosal cancer, the percentage of LN-positive patients varied between 10.2% and 33.3% (median, 19.2%). In total, 18 different patient and/or tumor characteristics were investigated for mucosal cancer. For submucosal cancer, 24 different patient and/or tumor characteristics were investigated.

Mucosal cancer

In patients with mucosal cancer, there was no significant association between sex, depth of mucosal tumor infiltration, submucosal vascularity, infiltration of dendritic cells, gastritis cystica profunda (GCP)-like glandular proliferation of the tumor, DNA ploidy, mucin phenotype, matrix metalloproteinase (MMP)-2 expression, and *erb*B-2 expression, and the presence of LN metastasis.

Variables significantly associated with LN metastasis were: age younger than 57 years, tumor location in the middle part of the stomach, larger tumor size, macroscopically depressed tumor type, tumor ulcerations, undifferentiated tumors, diffuse tumor type according to the Lauren classification [9], lymphatic tumor

Table 1. Characteristics of the included studies

Study	Year of publication, country	No. of patients (% of patients with LN metastases)	Consecutive series of patients	Extent of lymphadenectomy	Variables in relation to LN involvement analyzed in this review	Assessment of variables blinded to LN status	Assessment of LN status blinded to variables
Okabayashi [12]	2007, Japan	m: 179 (0.6) sm: 196 (13.8)	NR	D1 lymphadenectomy and resection of the no. 7 LNs (96 patients), D2 lymphadenectomy (268 patients), and D3 lymphadenectomy (11 patients)	Macroscopic type Histological type Lymphatic invasion Vascular invasion	NR	NR
Lo [13]	2007, Taiwan	m: 272 (4.4) sm: 207 (20.3)	Yes	D1 lymphadenectomy and resection of the no. 7, 8a, 9 and 11 LNs, or D2 lymphadenectomy	Tumor size	NR	NR
Nakamoto [14]	2007, Japan	sm: 108 (10.2)	Yes	NR	Sex Tumor location Macroscopic type Histological type Depth of tumor invasion Lymphatic invasion Vascular invasion Mucin phenotype expression	NR	NR
Ishikawa [15]	2007, Japan	m: 156 (3.8) sm: 122 (23.0)	Yes	D2 lymphadenectomy	Tumor ulceration Main histological type	NR	NR
Kunisaki [16]	2006, Japan	sm (1st population): 615 (19.3)	Yes	D1 lymphadenectomy and resection of the no. 7 LNs (279 patients), D2 lymphadenectomy (329 patients), and D3 lymphadenectomy (7 patients)	Age Sex Tumor location Tumor size Macroscopic type Histological type Lymphatic invasion Vascular invasion	NR	NR
		sm (2nd population): 186 (18.8)	NR	NR	Tumor size Main histological type-Lymphatic invasion		
Onogawa [17]	2005, Japan	sm: 140 (15.7)	Yes	NR	VEGF-C and VEGF-D expression	Yes	Yes
Son [18]	2005, Korea	sm: 248 (50.0[a])	NR	NR	Tumor location Macroscopic type Histological type Depth of tumor invasion Lymphatic invasion	NR	NR

Table 1. *Continued*

Study	Year of publication, country	No. of patients (% of patients with LN metastases)	Consecutive series of patients	Extent of lymphadenectomy	Variables in relation to LN involvement analyzed in this review	Assessment of variables blinded to LN status	Assessment of LN status blinded to variables
Park [19]	2004, Korea	sm: 105 (22.9)	NR	NR	Sex Tumor location Tumor size Macroscopic type Histological type Depth of tumor invasion Lymphatic invasion	NR	NR
Song [20]	2004, Korea	m: 120 (33.3[a])	No	NR	Tumor location Macroscopic type Tumor ulceration Histological type Depth of tumor invasion Submusocal vascularity GCP-like glandular proliferation	NR	NR
Yoshikawa [21]	2003, Japan	sm: 715 (19.0)	Yes	D2 lymphadenectomy	Tumor location Macroscopic type Main histological type	NR	NR
Higashi [22]	2003, Japan	sm: 118 (19.5)	Yes	A median of 24.1 LNs were dissected per patient; range, 6–73	Macroscopic type Depth of tumor invasion Vascular invasion	NR	NR
Matsuzaki [23]	2003, Japan	sm: 92 (19.6)	Yes	NR	Tumor location Tumor size Macroscopic type Tumor ulceration Histological type Depth of tumor invasion Lymphatic invasion Vascular invasion	NR	NR
Shimoyama [24]	2002, Japan	sm: 294 (18.4)	NR	D1 lymphadenectomy and resection of the no. 7 LNs (78 patients), D1 lymphadenectomy and resection of the no. 7, 8, and 9 LNs (99 patients), or ≥D2 lymphadenectomy (117 patients)	Sex Tumor location Macroscopic type Depth of tumor invasion Lymphatic invasion Vascular invasion	NR	NR
Kabashima [25]	2002, Japan	m: 114 (0.9)	No	NR	Mucin phenotype expression	NR	NR
Takeno [26]	2001, Japan	sm: 80 (16.3)	NR	D2 lymphadenectomy	Tumor size Macroscopic type Main histological type p53 overexpression	NR	NR

Shimada [27]	2001, Japan	m: 621 (2.3) sm: 430 (19.8)	Yes	D1 (in patients with advanced age and/or poor physical state) or D2 lymphadenectomy	Sex Macroscopic type Depth of tumor invasion	NR	NR
Yamada [28]	2001, Japan	sm: 104 (14.4)	NR	NR	Sex Tumor location Tumor size Tumor ulceration Histological type Lymphatic invasion Vascular invasion	NR	NR
Seto [29]	2001, Japan	m: 3584 (2.5) sm: 2625 (17.6)	No	D1 or more extensive lymphadenectomy	Tumor size Histological type	NR	NR
Gotoda [6]	2000, Japan	m: 3016 (2.2) sm: 2249 (17.9)	NR	NR	Sex Tumor location Tumor size Macroscopic type Tumor ulceration Depth of tumor invasion	NR	NR
Shimoyama [30]	2000, Japan	m: 345 (3.2) sm: 266 (19.2)	Yes	D1 lymphadenectomy and resection of the no. 7 LNs in patients not suspected of having LN metastases, or D2 lymphadenectomy in patients with submucosal gastric cancer	Tumor size Macroscopic type	NR	NR
Kabashima [31]	2000, Japan	m: 74 (20.3)	Yes	NR	Tumor ulceration Depth of tumor invasion Lymphatic invasion Vascular invasion MMP2 and MMP9 expression	NR	NR
Jiang [32]	2000, China	m: 275 (1.5) sm: 245 (22.0)	NR	D1 lymphadenectomy and resection of the no. 7 LNs (66 patients), ≥D2 lymphadenectomy (259 patients); remaining patients, type of lymphadenectomy NR	Macroscopic type Tumor ulceration	NR	NR
Takano [33]	2000, Japan	m: 36 (0) sm: 118 (49.2)	No	D1 lymphadenectomy	Histological type	NR	NR

Table 1. *Continued*

Study	Year of publication, country	No. of patients (% of patients with LN metastases)	Consecutive series of patients	Extent of lymphadenectomy	Variables in relation to LN involvement analyzed in this review	Assessment of variables blinded to LN status	Assessment of LN status blinded to variables
Yasuda [34]	1999, Japan	sm: 118 (13.6)	NR	NR	Tumor size Macroscopic type Histological type Depth of tumor invasion	NR	NR
Ishigami [35]	1999, Japan	sm: 170 (21.8)	Yes	D0 (5 patients), D1 (86 patients), or D2 or more extensive (79 patients) lymphadenectomy	Lymphatic invasion	NR	NR
Tsujitani [36]	1999, Japan	m: 440 (0.9) sm: 448 (15.8)	Yes	D1 (all patients), D2 (most cases), or ≥D3 (occasionally, as a result of operative findings of suspected nodal involvement) lymphadenectomy	Tumor size Macroscopic type	NR	NR
Ishigami [37]	1998, Japan	sm: 114 (21.9)	Yes	D0 (6 patients), D1 (56 patients), or >D2 (52 patients) lymphadenectomy	Sex Tumor location	NR	NR
Namieno [38]	1998, Japan	m: 701 (2.3) sm: 884 (15.0)	Yes	NR	Macroscopic type	NR	NR
Kurihara [39]	1998, Japan	sm: 245 (13.9)	Yes	D2 lymphadenectomy	Age Sex Tumor location	NR	NR
Morita [40]	1998, Japan	sm: 452 (15.7)	Yes	D2 or D3 lymphadenectomy	Sex Family history of gastric cancer Past history of other cancers Tumor location Macroscopic type Histological type Lymphatic invasion Vascular invasion	NR	NR
Takeshita [41]	1998, Japan	sm: 228[b] (13.2)	NR	NR	Macroscopic type Depth of tumor invasion	NR	NR

Kanai [42]	1997, Japan	sm: 75[c] (18.7)	Yes	NR	Sex Macroscopic type Histological type Lymphatic invasion Vascular invasion p53 overexpression	NR	NR
Namieno [43]	1996, Japan	m: 575 (2.6) sm: 562 (16.5)	Yes	NR	Tumor location Macroscopic type	NR	NR
Yamao [44]	1996, Japan	m: 1196 (3.6)	Yes	NR	Age Lymphatic invasion	NR	NR
Maeda [45]	1996, Japan	m: 42 (2.4) sm: 60 (21.7)	NR	D2 lymphadenectomy	PCNA labeling index	NR	NR
Ichikura [46]	1995, Japan	sm: 196 (19.4)	Yes	NR	Tumor location Macroscopic type Histological type Growth pattern Lymphatic invasion Vascular invasion	NR	NR
Maekawa [47]	1995, Japan	m: 265 (2.3) sm: 42 (19.4)	Yes	NR	Tumor size	NR	NR
Tsuchiya [48]	1995, Japan	sm: 80 (18.8)	Yes	D2 lymphadenectomy	Sex Tumor location Histological type Depth of tumor invasion	NR	NR
Oya [49]	1995, Japan	m: 943 (2.2)	NR	NR	Sex Tumor location Histological type	NR	NR
Takeda [50]	1995, Japan	m: 314 (3.2) sm: 296 (17.9)	Yes	NR	Tumor location Macroscopic type Histological type	NR	NR
Jatzko [51]	1992, Austria	m: 29 (0) sm: 24 (33.3)	Yes	NR	Macroscopic type	NR	NR
Yonemura [52]	1992, Japan	m: 120 (7.5) sm: 100 (20.0)	NR	D1 or D2 lymphadenectomy	*erb*B-2 expression	NR	NR
Tsujitani [53]	1990, Japan	m: 18 (11.1) sm: 22 (45.5)	NR	NR	Infiltration of dendritic cells	NR	NR
Iriyama [54]	1989, Japan	m: 82 (4.9) sm: 84 (16.7)	Yes	NR	Histological type	NR	NR
Korenaga [55]	1988, Japan	m: 75 (13.3) sm: 79 (26.6)	NR	NR	DNA ploidy	NR	NR

*erb*B-2, Protein encoded by the c-*erb*B-2 gene (also known as HER2/neu); LN, lymph node; m, gastric cancer limited to the mucosa; NR, not reported; PCNA, proliferating cell nuclear antigen; sm, gastric cancer limited to the submucosa; MMP, matrix metalloproteinase; VEGF, vascular endothelial growth factor

[a] Patients with and without lymph node metastases were matched for age and sex

[b] The 102 most recent consecutive cases were also subjected to a careful pathologic examination to determine the extent of submucosal invasion

[c] p53 expression was investigated in the 14 primary lesions with lymph node metastases and 14 randomly selected primary lesions without nodal involvement

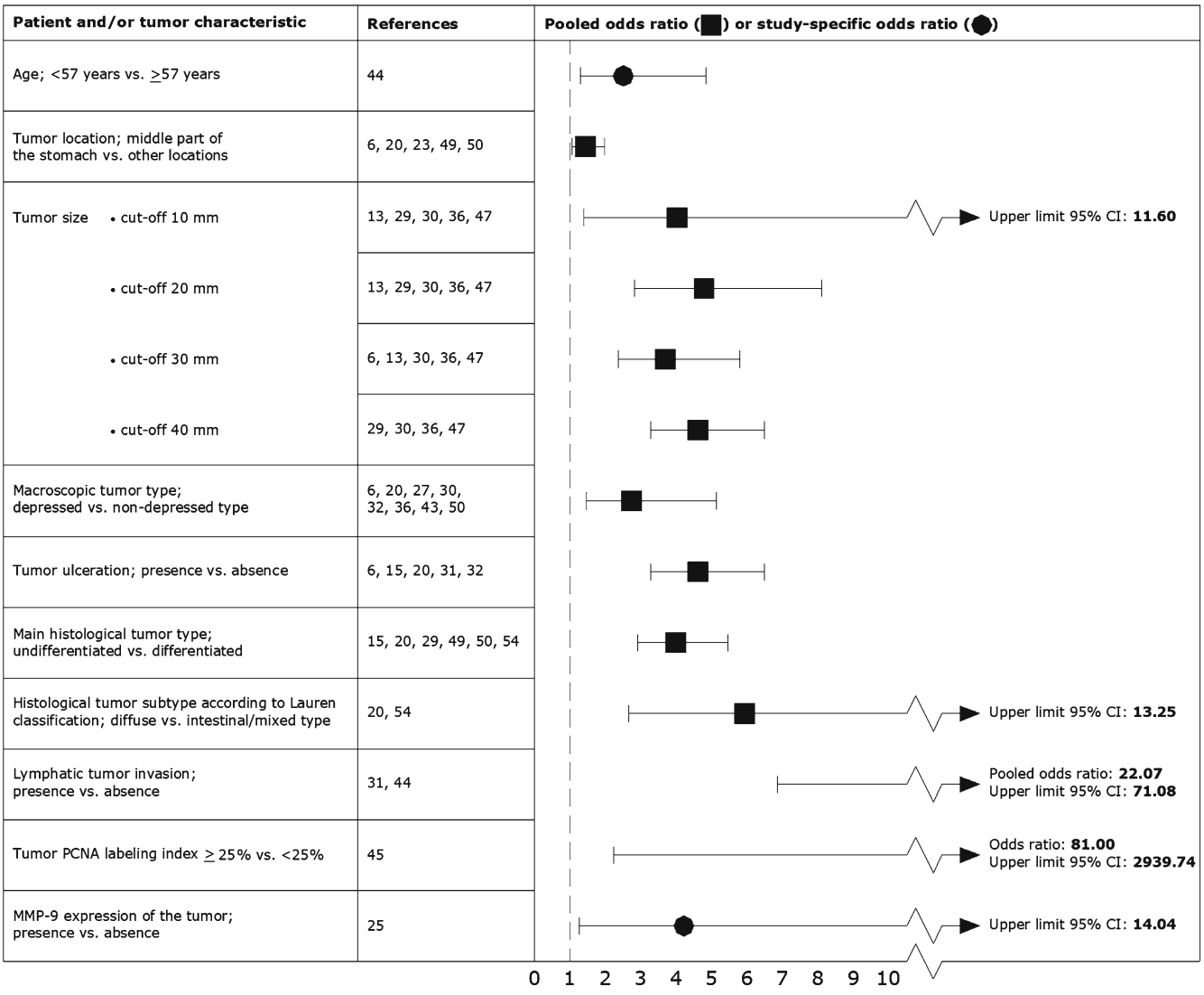

Fig. 1. Forest plot of variables significantly associated with lymph node (LN) metastasis in gastric cancer limited to the mucosa. *PCNA*, Proliferating cell nuclear antigen (an auxiliary protein of the DNA polymerase-delta); *MMP*, matrix metalloproteinase; *CI*, confidence interval

invasion, tumors with a proliferating cell nuclear antigen (PCNA) labeling index of more than 25%, and MMP-9 positive tumors (Fig. 1). Among the studies investigating the variable "tumor ulcerations", more than moderate heterogeneity was identified ($I^2 = 55.8\%$).

Submucosal cancer

In patients with submucosal cancer, there was no significant association between age (for various cutoff values), family history of gastric cancer, macroscopic tumor type, tumor ulceration, tumor type according to the Lauren classification, tumor growth pattern, presence of fibrosis near the tumor, tumor stroma, infiltration of dendritic cells, DNA ploidy, p53 overexpression, GCP-like glandular proliferation of the tumor, vascular endothelial growth factor (VEGF)-D expression, *erb*B-2 expression, and presence of LN metastasis.

Variables significantly associated with LN metastasis were: female sex, tumor location in the lower part of the stomach, larger tumor size, undifferentiated tumors, increasing depth of submucosal invasion, lymphatic tumor invasion, vascular tumor invasion, increased submucosal vascularity, tumors with a PCNA labeling index of more than 25%, tumors with a gastric mucin phenotype, and VEGF-C-positive tumors (Fig. 2). Among the studies investigating the variables "main histological tumor type (differentiated vs undifferentiated tumors)" and "vascular tumor invasion", more than moderate heterogeneity was identified (with an I^2 of 82.5% and 51.3%, respectively).

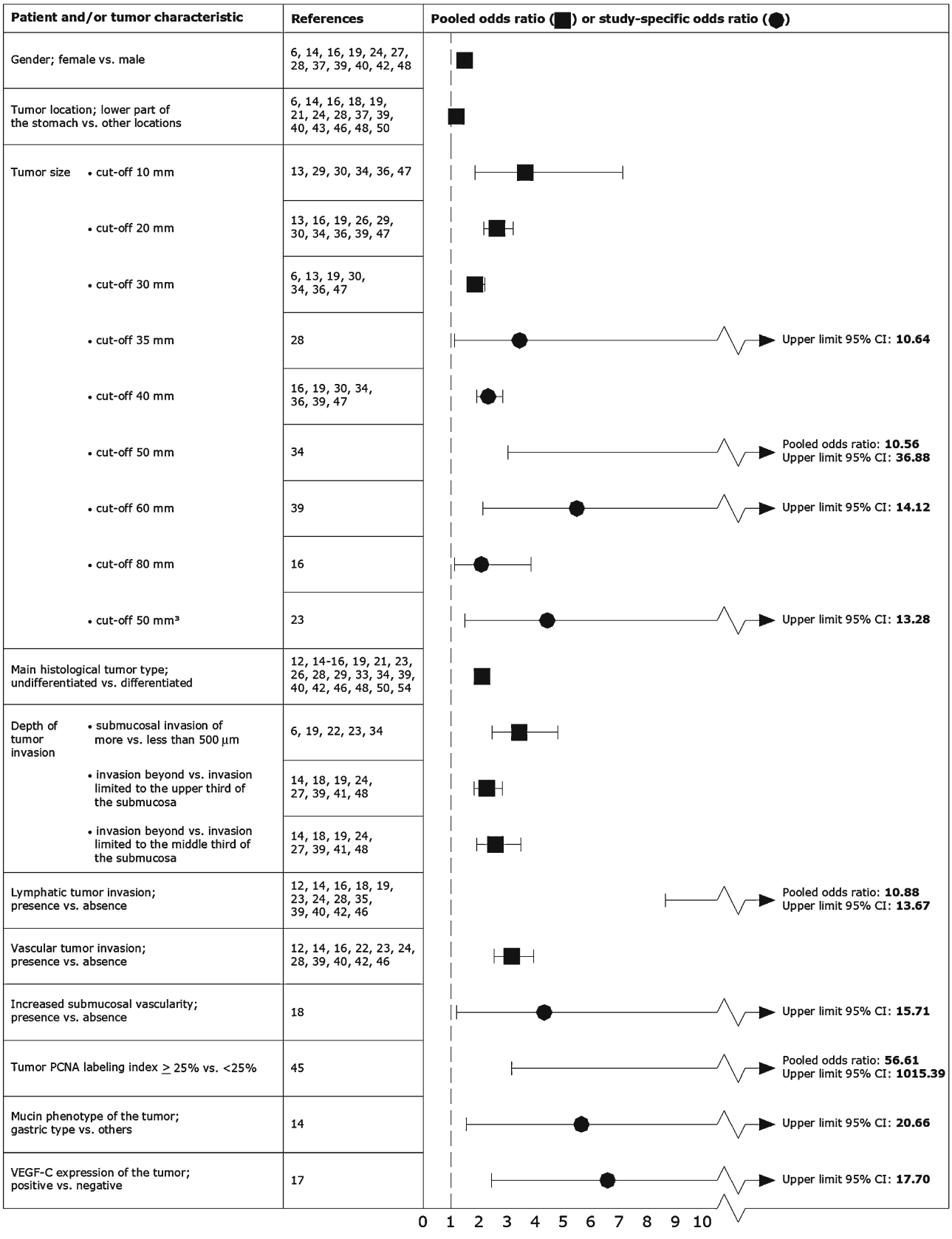

Fig. 2. Forest plot of variables significantly associated with LN metastasis in gastric cancer limited to the submucosa. *PCNA*, Proliferating cell nuclear antigen (an auxiliary protein of the DNA polymerase-delta); *VEGF*, vascular endothelial growth factor

Discussion

The overall risk of LN metastasis in mucosal gastric cancer is only about 3.2% (see Results). In submucosal cancer, the risk of LN metastasis is approximately 19.2% (see Results). To date, no imaging modality has been proven to be consistently accurate in assessing LN metastasis in EGC. Endoscopic ultrasonography (EUS) mainly depends on LN echogenicity, morphology, and size as criteria to define malignancy. Reported sensitivities and specificities of EUS to detect LN metastases in gastroesophageal carcinomas vary widely, between 59.5% and 97.2%, and between 40.0% and 100% [56]. Computed tomography (CT), another anatomical imaging modality, mainly uses LN size as a criterion to define malignancy. Using a 64-section multidetector-row CT scanner, a recent study found a sensitivity and specificity of 84.2% (95% CI, 62.4–94.5) and 84.0% (95% CI, 65.4–93.6) [57]. Still, differentiating between benign and metastatic LNs may be unreliable when LN size is used as a criterion [58, 59]. ^{18}F-fluoro-2-deoxyglucose positron emission tomography, a functional imaging modality based on the increased glycolytic rate of malignant cells [60], has also been shown to be insufficiently accurate in assessing LN status in gastric cancer; although reported specificities vary between 90.0% and 97.0%, reported sensitivities vary between only 34.0% and 64.6% [61–63]. The accuracy of other functional imaging modalities, including magnetic resonance imaging (MRI) with ultrasmall particles of superparamagnetic iron oxide [64] and diffusion-weighted MRI [65], still has to be investigated in large patient cohorts. Laparoscopic sentinel node (SN) biopsy is another promising tool to more accurately determine nodal status in EGC patients. The SN concept is based on the premise that tumor cells will preferentially metastasize to the first draining LN in the regional lymphatics, the SN. After identifying the SN (by use of a radionucleotide tracer and/or dye), and laparoscopic biopsy, LN metastasis is confirmed or ruled out by histological examination. A disadvantage of laparoscopic SN biopsy, however, is its invasiveness. Although studies on laparoscopic SN biopsy have shown its potential [66–69], various technical and material limitations still have to be overcome. Also, the reliability of laparoscopic SN biopsy has yet to be determined by multicenter prospective clinical trials [70].

Because currently available imaging modalities fail to accurately determine nodal status, nodal status in EGC is still predicted by means of the presence or absence of certain tumor characteristics. According to the treatment guidelines of the Japanese Gastric Cancer Association (JGCA), EMR without lymphadenectomy is indicated in differentiated mucosal cancers less than 20 mm in size, and subtotal gastrectomy with D1 lymphadenectomy plus resection of the no. 7 (+8a) LNs is indicated in undifferentiated mucosal cancers, differentiated mucosal cancers 20 mm or more in size, and differentiated submucosal cancers 15 mm or less in size. For other submucosal cancers, the JGCA treatment guidelines indicate subtotal gastrectomy with D1 lymphadenectomy plus resection of the no. 7, 8a, and 9 LNs [5]. These criteria, however, may be too strict and can lead to unnecessary surgery [3, 6]. Gotoda et al. [6] proposed expanded criteria for the endoscopic treatment of EGC; using the variables "histological tumor type", "lymphatic-vascular involvement", "ulcer findings", and "tumor size", they defined (additional) groups of patients with EGC who may also have been eligible for endoscopic tumor resection. However, for patients who did not belong to one of these groups, the risk of LN metastasis was not reported [6]. Furthermore, there may be more predictive variables allowing an even better risk assessment in the individual EGC patient.

The results of the present systematic review and meta-analysis show that variables significantly associated with LN metastasis in mucosal cancer are: age younger than 57 years, tumor location in the middle part of the stomach, larger tumor size, macroscopically depressed tumor type, tumor ulcerations, undifferentiated tumors, diffuse tumor type according to the Lauren classification [9], lymphatic tumor invasion, tumors with a PCNA labeling index of more than 25%, and MMP-9-positive tumors (Fig. 1). Patients with tumor ulcerations also had a significantly higher risk of LN metastasis. However, more than moderate heterogeneity was identified among the studies investigating this variable. An explanation for this heterogeneity may be the interobserver variability between studies for the assessment of tumor ulcerations. Also, none of the studies investigating this variable mentioned whether assessment of this variable was done blinded to LN status. Variables significantly associated with LN metastasis in submucosal cancer are: female sex, tumor location in the lower part of the stomach, larger tumor size, undifferentiated tumors, increasing depth of submucosal invasion, lymphatic tumor invasion, vascular tumor invasion, increased submucosal vascularity, tumors with a PCNA labeling index of more than 25%, tumors with a gastric mucin phenotype, and VEGF-C-positive tumors (Fig. 2). It should be noted that more than moderate heterogeneity was identified among the studies investigating the variables "main histological tumor type (differentiated vs undifferentiated tumors)" and "vascular tumor invasion". This may be explained by interobserver variability between studies and the assessment of these variables unblinded to LN status. Another limitation is that certain variables, such as "PNCA labeling index", "MMP-9 expression", "mucin phenotype", and "VEGF-C expression", were investigated

only by single and relatively small-sized studies. This is also expressed by their wide confidence intervals (see Figs. 1 and 2).

Lymphatic tumor invasion was the strongest univariate predictor for LN metastasis in both mucosal and submucosal gastric cancer. This is not surprising, as the lymphatics are the direct pathway to the LNs. However, the JGCA treatment guidelines are not based on the presence or absence of lymphatic tumor invasion [5]. JGCA treatment guidelines use a tumor size of 20 mm as the cutoff in differentiated mucosal cancer to decide for either endoscopic resection or modified gastrectomy. This was based on the assumption that differentiated mucosal cancer of 20 mm or less has no LN metastasis, and also because 20 mm was the technical upper limit of en-bloc resection at the time the guidelines were composed [5]. However, newer endoscopic resection techniques allow the en-bloc resection of larger lesions [2]. Future studies should assess whether there is a significant difference in LN metastasis risk between different tumor size cutoff values, after applying multivariate analysis to adjust for other variables. Notably, although a large size of carcinoma can contribute to contact between carcinoma cells and a lymphoid vessel, specific enzymes are necessary for the degradation of the vessel wall and for the invasion of the lymphoid vessel. MMPs are considered to be important for the facilitation of tumor invasion and spread [71]. Indeed, MMP-9 was significantly associated with LN metastasis in mucosal cancer [31]. To our knowledge, the relation between MMPs and LN metastasis in submucosal cancer still has to be investigated. It should also be further explored which MMPs (or combinations of MMPs) are most predictive for LN metastasis.

Despite the findings of our univariate analysis, confounding of variables may be present. For instance, lymphatic tumor invasion, vascular tumor invasion, and VEGF-C are all significantly associated with LN metastasis, but tumor angiogenesis and lymphangiogenesis (which may both promote lymphatic and vascular tumor invasion) are also related to VEGF-C. In addition, it is also very likely that the variables "main tumor histology (differentiated vs undifferentiated type)" and "tumor histology according to the Lauren classification" [9] are overlapping. Thus, future studies are needed to assess which variables are significant predictors of LN metastasis after multivariate analysis. These variables can then be used to develop a model that can accurately predict the risk of LN metastasis in an individual patient.

Of note, in 1989 Kampschoer et al. [72] had already developed a computer program to predict the probability of LN metastasis, based on certain histopathological features of the primary tumor. However, the point at which LN dissection should be done, based on this program, is not clear [73]. In addition, the computer program is based only on the preoperative variables "sex", "age", "tumor location", "macroscopic type", "tumor size", "depth of tumor invasion", and "histological type" [72]. For instance, both lymphatic and vascular invasion, which proved to be strongly associated with LN metastasis by our analysis, were not used by the program.

It should also be noted that, in the study of Kampschoer et al. [72], depth of tumor invasion and histological type were assessed by means of double-contrast X-rays and histological analysis of biopsied tissue. Endoscopic ultrasound was performed if results were inconclusive. Kampschoer et al. [72] stated that the preoperative diagnosis and classification were correlated with the surgical findings in 96.5% of cases, and that the extent of invasion could be accurately assessed because of the expertise of the radiologists. In actual practice, however, the accuracy of histopathologic grading using forceps biopsy specimens is only approximately 82.5% when compared to the final histological typing based on the predominant histology of the resected tumor [74]. In addition, it is still unclear whether EUS, the current first-choice imaging modality in T-staging, can accurately differentiate between mucosal and deeper gastric cancer [75]. When biopsy specimens do not reflect the predominant histopathology of the entire tumor and/or the depth of invasion as assessed by EUS is greater than the actual depth, a decision may be made to perform surgery unnecessarily. Endoscopic resection, however, has the ability to provide complete histopathological staging (and assessing all variables) without precluding future surgery [3, 76]. Therefore, in all patients who are suspected of having EGC or in cases in which the biopsy-based histopathologic typing or EUS-determined depth of invasion is thought to be unreliable, endoscopic resection should be performed as the first step. Then, after evaluating the resected specimen, one can weigh the risks of LN metastasis against the risk of surgery.

Although the majority of the studies included in the present systematic review and meta-analysis were performed in Japan, it is likely that the results of this meta-analysis are generalizable, because the clinicopathological features of gastric cancer in Japan and Western countries do not seem to differ [77]. Of the included studies, 16% performed D2 or more extensive lymphadenectomy in all patients. D1 lymphadenectomy includes the removal of level 1 LNs only, whereas D2 lymphadenectomy adds the removal of level 2 LNs [8]. Although metastasis to level 2 LNs is rare, occurring in only 0.4% of patients with mucosal cancer and in 4.9% of patients with submucosal cancer [78], some skip metastases may have been missed in patients who

underwent less than D2 lymphadenectomy. Another limitation of the included studies is that all but one did not assess patient and/or tumor characteristics blinded to LN status, and vice versa, which may have introduced bias.

In conclusion, the present systematic review and meta-analysis identified several variables that are associated with LN metastasis in EGC. These variables should be included in future research, in order to assess which of these variables remain as significant predictors of LN metastasis.

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