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Prognostic impact of lymph node micrometastasis in patients with gastric cancer

(胃癌におけるリンパ節微小転移の予後に及ぼす影響**)**

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ORIGINAL ARTICLE

Prognostic impact of lymph node micrometastasis in patients with gastric cancer

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Abstract

Purpose The clinical significance of lymph node micrometastasis (LNMM) remains controversial in gastric cancer (GC). In this study, we investigated the prognostic impact of LNMM in patients with GC.

Methods A total of 624 patients with pathologically lymph node metastasis-negative (pN0) and N1 status (pN1) who underwent gastrectomy between 2004 and 2018 were enrolled in this retrospective study. The diameter of tumor cell clusters in metastatic lymph nodes was measured in 120 patients with pN1 GC.

Results Patients with lymph node tumors < 1500 μm in diameter (LNMM) had a significantly better prognosis than those with tumors ≥ 1500 μm in diameter ($p = 0.012$; log-rank test). Cox's proportional hazards model revealed that LNMM ($p = 0.016$), several dissected lymph nodes ($p = 0.049$), and the provision of adjuvant chemotherapy ($p = 0.002$) were independent prognostic factors for the overall survival of patients with pN1 GC. There was no significant difference in the overall survival between patients with LNMM who received chemotherapy and those who did not ($p = 0.332$).

Conclusions LNMM is associated with a favorable prognosis and maybe an independent prognostic marker in patients with pN1 GC. LNMM in GC may be considered a factor preventing adjuvant chemotherapy.

Keywords Micrometastasis · Gastric cancer · Lymph node metastases

Introduction

Gastric cancer (GC) is a leading cause of cancer-related death worldwide [1]. Generally, lymph node metastasis (LNM) is a strong prognostic factor in GC, and patients with node-positive GC have a poorer prognosis than those with node-negative GC [2–4]. Even in node-positive GC, radical LN dissection may improve the prognosis; therefore, radical LN dissection is performed for curative surgery in patients with GC without distant metastases [5]. Adjuvant chemotherapy after radical gastrectomy significantly improves the prognosis of patients with locally advanced GC, as revealed by the ACTS-GC trial, CLASSIC study, and START trial [6]. Based on these results, the fourth version of the Japanese Gastric Cancer Treatment Guidelines recommends adjuvant chemotherapy after gastrectomy for advanced GC patients with serosa invasion or LNM [6].

Certainly, chemotherapy is a useful tool for improving the prognosis, but it also has side effects, such as drug toxicity. Therefore, studies to stratify the indication for adjuvant chemotherapy may be useful for facilitating the establishment of tailor-made therapies for patients with GC.

Among cases with LNM, those with small tumor size in the metastatic LN are reported as having lymph node micrometastasis (LNMM) [7]. Based on the results of previous studies, the Union for International Cancer Control (UICC) considers that single tumor cells or cell clusters with a maximum size of ≤ 200 μm in LNs have low-grade biological behavior and have been defined as "isolated tumor cells" (ITCs) [7]. ITCs are not considered LNM, and they are recommended to be listed as pN0 (i+) [7, 8]. The UICC also

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defines LNM with a tumor size of ≤ 2000 μm in metastatic LNs as micrometastasis [7]. However, many institutes do not include LNMM in their clinical classification, so its clinical significance remains controversial.

Some researchers have reported that LNMM is a strong indicator of a poor prognosis; however, they used quantitative polymerase chain reaction (PCR) and immunohistochemistry to define LNMM, indicating that they demonstrated the prognostic impact of occult metastasis [9, 10]. Furthermore, with respect to adjuvant chemotherapy, little research has been performed on the benefits of chemotherapy for patients with LNMM GC [11].

In the present study, we examined the clinical significance and prognostic impact of LNMM using the most general and simple method of measuring the size of a metastatic tumor in the dissected LN. Furthermore, we explored the prognostic benefit of LNMM in GC patients who received adjuvant chemotherapy.

Materials and methods

Patients

Between January 2004 and December 2018, 868 patients with GC underwent surgery at the University of Yamanashi Hospital. Patients who did not undergo gastrectomy and those without radical LN dissection were excluded, and those with pathologically LNM-negative (pN0) and N1 status (pN1) were enrolled in this retrospective study. LN dissection was performed according to the guidelines of the Japanese Gastric Cancer Association [6]. pN1 indicates that the patients showed metastasis of one or two LNs. The clinicopathological features of each patient were retrieved from the hospital database. The tumor specimens and dissected LNs were obtained during surgery and embedded in paraffin.

All patients underwent double-contrast barium examination, endoscopy, and multidetector-row computed tomography. Follow-up procedures consisted of blood examinations, abdominal ultrasound, and computed tomography, which were performed every 3 to 6 months after surgery. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 1964 Declaration of Helsinki and later versions [12]. Informed consent was obtained from all patients included in the study.

The histological evaluation of LNMM

Following the guidelines [13], the primary tumors were cut crosswise through the center of the tumor, and the retrieved LNs were cut longitudinally on the largest plane through the hilus.

To define LNMM, we reviewed hematoxylin and eosin (HE)-stained specimens of LNs of patients with GC diagnosed with pN1. For all of these LNs, we measured the diameter of the tumor cell clusters using a microscope; these analyses were conducted with a pathologist to obtain a consensus on the results. In two tumor cell clusters where two different diameter values were obtained, we considered the greatest value for the analysis. Based on the diameters of the tumor cell clusters, we set the LNMM cut-off value that most strongly affects the prognosis.

Statistical analyses

Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/foundation/). The clinicopathological variables pertaining to the corresponding patients were analyzed using the χ^2 test or Fisher's exact test. Quantitative results were presented as means ± standard deviation (SD) and evaluated using the Mann–Whitney *U* test. For the survival analysis, Kaplan–Meier survival curves were constructed for groups based on univariate predictors, and differences between the groups were tested using the log-rank test. Univariate and multivariate survival analyses were performed using the likelihood ratio test of the stratified Cox proportional hazards model. Differences were assessed with a two-sided test and considered significant for values with $p < 0.05$.

Results

Clinicopathological characteristics of patients

A total of 624 patients were included in this study. The clinicopathological characteristics of the patients in the present study are summarized in Table 1. The mean patient age was 68.3 (range 35–88) years old, and the male:female ratio was 2.6:1. The number of patients with pN0 and pN1 was 504 and 120, respectively. The median tumor size in the primary tumor was 45 mm (range 10–200 mm), and the median tumor size in the LNs was 2622 μm.

Setting of the LNMM cut-off value that affects the prognosis

The cut-off values of the diameter of tumor cell clusters in LNs were set to < 1000 μm, < 1500 μm, and < 2000 μm, and their clinical significance was examined. Patients with an LN tumor diameter cut-off of < 1500 μm had a significantly better prognosis than those with a cut-off of ≥ 1500 μm, and the 5-year overall survival (OS) was

Table 1 Clinicopathological characteristics of patients in the present study

Age (years) (mean ± SD)	68.3 ± 11.2
Gender *n* (%)	
Male	453 (72.6)
Female	171 (27.4)
Type of procedure *n* (%)	
Total gastrectomy	208 (33.3)
Distal gastorectomy	363 (58.2)
Proximal gastorectomy	31 (5.0)
Others	22 (3.5)
pT stage[a] *n* (%)	
pT1	447 (71.6)
pT2–4	174 (27.9)
pN stage[a] *n* (%)	
pN0	504 (80.8)
pN1	120 (19.2)
lymphatic invasion *n* (%)	
Negative	390 (62.5)
Positive	229 (36.7)
Venous invasion *n* (%)	
Negative	432 (69.2)
Positive	187 (30.0)
Tumor size (mm) (mean ± SD)	38.7 ± 27.2
Histological type[b] *n* (%)	
Differentiated	445 (71.3)
Undifferentiated	171 (27.4)
Macroscopic appearance, *n* (%)	
Localize	197 (31.6)
Diffuse	427 (68.4)
Adjuvant chemotherapy *n* (%)	
Present	93 (15.0)
Absent	529 (84.8)

[a]Disease stage was defined in accordance with the UICC 8th tumor-lymph node-metastases (TNM) classification

[b]Predominant histopathological finding

0.768 and 0.528, respectively ($p = 0.012$; log-rank test). When the cut-off value of the LN tumor diameter was set at < 1000 μm or < 2000 μm, there was no significant difference in the prognosis between the groups above and below the cut-off values.

The 5-year OS rates for the groups above and below the 1000 μm cut-off values were 0.780 and 0.564 ($p = 0.076$; log-rank test), respectively, and those above and below the 2000 μm cut-off values were 0.689 and 0.560 ($p = 0.157$; log-rank test), respectively.

Therefore, in the present study, LNMM was defined as tumor cell clusters within LNs with a diameter < 1500 μm.

Clinicopathological characteristics of patients with LNMM

A representative figure of the tumor cluster in metastatic LNs is shown in Fig. 1. The diameter of the tumor cluster in Fig. 1a was < 1500 μm, and the tumor was classified as a positive LNMM. In contrast, the diameter of the tumor cluster in Fig. 1b was more than 1500 μm, and the tumor was classified as a positive LNM.

The clinicopathological characteristics of pN1 patients with LNMM and positive LNM are summarized in Table 2. Of the 120 patients diagnosed with pN1, 42 (35.0%) were classified as having LNMM, and 78 (65.0%) were classified as having positive LNM on a postoperative pathological examination. Patients with LNMM had a significantly lower pT stage and less microscopic lymphatic invasion than those with positive LNM ($p = 0.002$ and 0.049, respectively). They were also more likely to have smaller primary tumors and macroscopically localized findings than those with positive LNM.

Prognostic impact of LNMM in patients with GC

Figure 2 shows the prognostic impact of LNMM in patients with GC. GC patients with LNMM had significantly higher OS and recurrence-free survival rates than those with positive LNM (log-rank test; $p = 0.012$ and 0.033, respectively). In contrast, there was no significant difference in the prognosis between LNMM and pN0 patients with GC.

Cox's proportional hazards model revealed that LNMM ($p = 0.016$), several dissected LNs ($p = 0.049$), and the provision of adjuvant chemotherapy ($p = 0.002$) were independent prognostic factors for the OS of patients with pN1 GC (Table 3). Regarding the recurrence pattern, no significant difference was found between LNMM and positive LNM in patients with GC ($p = 0.803$).

The prognosis of patients with LNMM GC with and without adjuvant chemotherapy

We examined the benefits of adjuvant chemotherapy for patients with GC and LNMM. Of the 120 patients with pN1 GC, 62 received adjuvant chemotherapy, and 58 did not. In the LNMM group, 24 patients received adjuvant chemotherapy, of whom 17 received S-1 (tegafur, gimeracil, and oteracil potassium combination), and 7 received UFT (a tegafur and uracil combination). In the positive LNM group, 38 patients received adjuvant chemotherapy, of whom 32 received S-1, 3 received S-1 plus paclitaxel, and 3 received UFT. In patients who did not receive adjuvant chemotherapy, the OS was significantly better in LNMM patients than in positive LNM patients ($p = 0.037$). In contrast, in patients who received adjuvant chemotherapy,

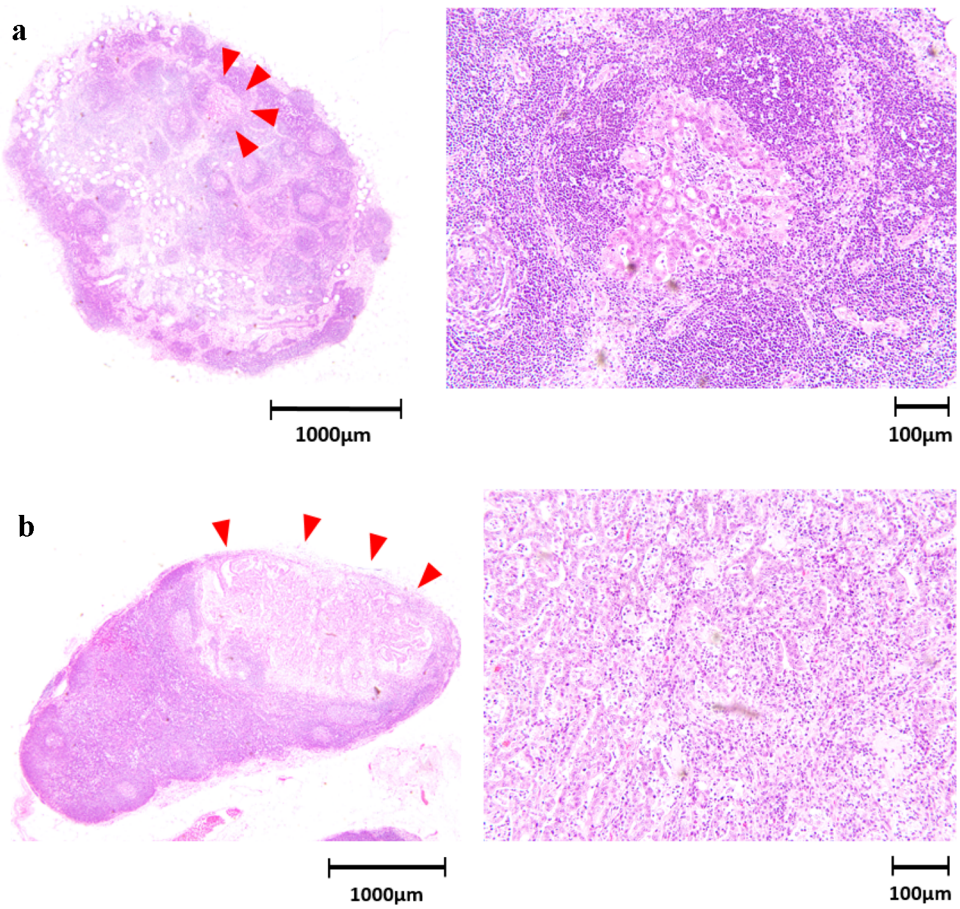

Fig. 1 Representative photomicrographs of LNMM (**a**) and positive LNM (**b**) stained with hematoxylin and eosin. The red arrowheads indicate tumor cell clusters in metastatic LNs. LNMM, lymph node micrometastasis; *LNM* lymph node metastasis

there were no significant differences in the OS in LNMM and positive LNM patients ($p = 0.211$). In the GC patients with LNMM, there was no significant difference in the OS between patients who received chemotherapy and those who did not ($p = 0.332$) (Fig. 3a). In contrast, among positive LNM patients, those who received chemotherapy had a significantly higher OS rate than those who did not ($p = 0.003$) (Fig. 3b).

Discussion

The present study demonstrated the possibility that LNMM might be useful for the further stratification of conventional staging systems that only reflect the number of metastatic LNs. We detected LNMM without immunohistochemical staining or PCR. The method of measuring the tumor size in LNs using HE staining is very simple, and we were able to accurately detect tumor cell clusters in metastatic LNs with the help of a professional pathologist to make a diagnosis of LNMM.

Several previous studies have reported micrometastasis in GC cases; its clinical potential has been investigated, and previous prospective multicenter trials have demonstrated the clinical safety and efficacy of sentinel LN navigation surgery in patients with GC [14]. Regarding the evaluation method for intraoperative sentinel LN, RT-PCR or the OSNA method can reportedly detect micrometastasis more sensitively than an intraoperative diagnosis using frozen sections [15, 16].

In another study, micrometastasis was detected using immunohistochemical findings as an additional test for GC patients diagnosed as node-negative using HE specimens. However, the prognostic impact of LNMM is still controversial. Wang et al. demonstrated the predictive effect of cadherin-17 for LNMM and reported that the 5-year OS rate was significantly higher in patients with GC who had micrometastases with LN tumors ≤ 2000 μm than in those who had LNM with LN tumor sizes > 2000 μm [17].

Conversely, certain researchers have suggested that micrometastasis does not affect the prognosis of patients. Kim et al. and Morgagni et al. showed that the presence of nodal micrometastasis did not correlate with the survival in patients with GC [18, 19]. The discrepancy in these results may be due to differences in methodologies. such as immunostaining, and differences in the number of LN slides evaluated. These studies examined the clinical significance of micrometastasis detected by additional immunostaining of

Table 2 Clinicopathological characteristics of LNMM in patients with pN1 gastric cancer

	LNMM	Positive LNM	*p* value
Age, *n*			
< 60	8	8	0.259
60 ≤	34	70	
Gender, *n*			
Male	31	58	1.000
Female	11	20	
pT stage[a], *n*			
pT1	22	18	0.002
pT2–4	20	60	
Dissected LN < 15			
Present	5	13	0.597
Absent	37	65	
Lymphatic invasion, *n*			
Negative	7	4	0.049
Positive	35	74	
Venous invasion, *n*			
Negative	15	24	0.683
Positive	27	54	
Tumor size (mm), *n*			
< 45	23	32	0.180
45 ≤	19	46	
Histological type[b], *n*			
Differentiated	29	62	0.264
Undifferentiated	13	16	
Macroscopic appearance, *n*			
Localize	25	36	0.184
Diffuse	17	42	
Adjuvant chemotherapy, *n*			
Present	24	38	0.445
Absent	18	40	

LNM Lymph Node Metastasis, *LNMM* Lymph Node Micrometastasis

[a]Disease stage was defined in accordance with the UICC 8th tumor-lymph node-metastases (TNM) classification

[b]Predominant histopathological finding

p Values are from $\chi 2$ test or Fisher's exact test and were significant at < 0.05

Significant values are given in boldface

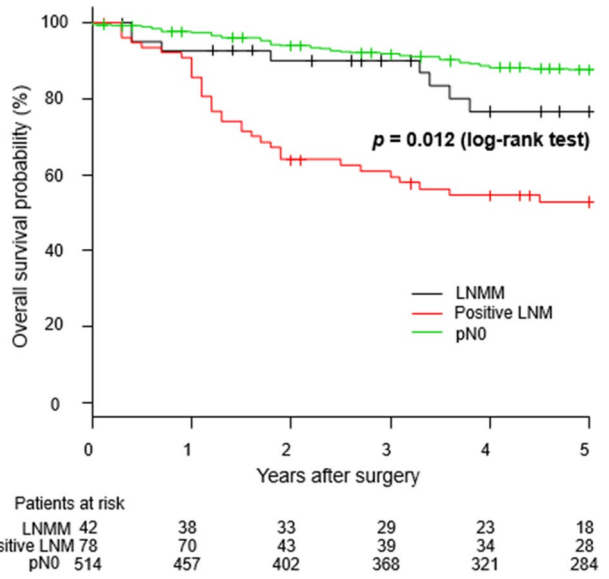

Fig. 2 The overall survival in pN1 GC patients with LNMM and positive LNM. The overall survival rates of LNMM were significantly higher than those of positive LNM in patients with GC. GC, gastric cancer; LNMM, lymph node micrometastasis; *LNM* lymph node metastasis

cytokeratin or cadherin-17 in patients diagnosed as pathologically node-negative by HE-stained specimens.

In the present study, we investigated the prognostic impact of small tumor size on metastatic LNs among patients pathologically diagnosed with N1 based on HE-stained specimens. In our simple evaluation method, the tumor size in metastatic LNs has a prognostic impact. GC patients with LNMM had a significantly better prognosis than those with positive LNM, and there was no significant difference in the prognosis from those with pathologically node-negative disease.

Regarding the cut-off value, when the cut-off was set at 1500 μm, the prognosis of LNMM patients was significantly better than that of positive LNM patients. Furthermore, LNMM was selected as an independent prognostic factor for patients with pN1 GC as well as the presence of postoperative chemotherapy. Further verification may be needed in the future to confirm the appropriate cut-off values. However, we showed that the tumor size in metastatic LNs may have a strong impact on the prognosis.

Regarding adjuvant chemotherapy, advanced GC patients with serosa invasion or LNM are indicated for such treatment in many institutions [20–22]. However, in the clinical setting, there is some debate as to whether or not adjuvant chemotherapy is actually necessary for early GC with LN metastasis and whether or not it should be performed for patients with pN1 advanced GC with severe comorbidities [23, 24]. The presence of surrogate markers that can stratify the prognosis and predict the benefits of adjuvant chemotherapy is of great importance in providing treatment to such patients. Adjuvant chemotherapy did not significantly improve the OS in GC patients with LNMM, but GC patients with positive LNM enjoyed a significant improvement in the OS with adjuvant chemotherapy. Adjuvant chemotherapy did not improve the prognosis of patients with LNMM GC because the prognosis of LNMM GC was relatively favorable. Patients with LNMM GC have a 5-year survival rate of approximately 80%; therefore, the benefits of adjuvant chemotherapy may be minimal. In Japan, almost all institutes comply with the Gastric Cancer Treatment Guidelines

Table 3 Cox proportional hazard model for 5-year overall survival in patients with pN1 gastric cancer

Variable	Univariate HR (95% CI)	*p* value	Multivariate HR (95% CI)	*p* value
Age, 60 ≤ vs. ≺ 60	2.80 (0.86–9.07)	0.087	–	–
Gender, male vs. female	1.13 (0.57–2.24)	0.727	–	–
pT2–4 vs. pT1	1.55 (0.80–3.02)	0.195	–	–
Dissected LN, ≺ 15 vs. 15 ≤	2.05 (1.01–4.17)	0.047	2.04 (1.00–4.16)	0.049
Lymphatic invasion, positive vs. negative	1.86 (0.45–7.71)	0.391	–	–
Venous invasion, negative vs. positive	1.01 (0.54–1.88)	0.987	–	–
Tumor size (mm), 45 ≤ vs. ≺ 45	1.45 (0.79–2.67)	0.232	–	–
Pathological type, undifferentiated vs. differenciated	1.17 (0.60–2.26)	0.650	–	–
Macroscopic appearance, localize vs. diffuse	1.01 (0.56–1.84)	0.966	–	–
Adjuvant chemotherapy, absent vs. present	2.66 (1.44–4.94)	0.002	2.61 (1.40–4.85)	0.002
Positive LNM vs. LNMM	2.46 (1.18–5.12)	0.016	2.46 (1.18–5.14)	0.016

CI confidence interval, *LNM* Lymph Node Metastasis, *LNMM* Lymph Node Micrometastasis

Significant values are given in boldface.

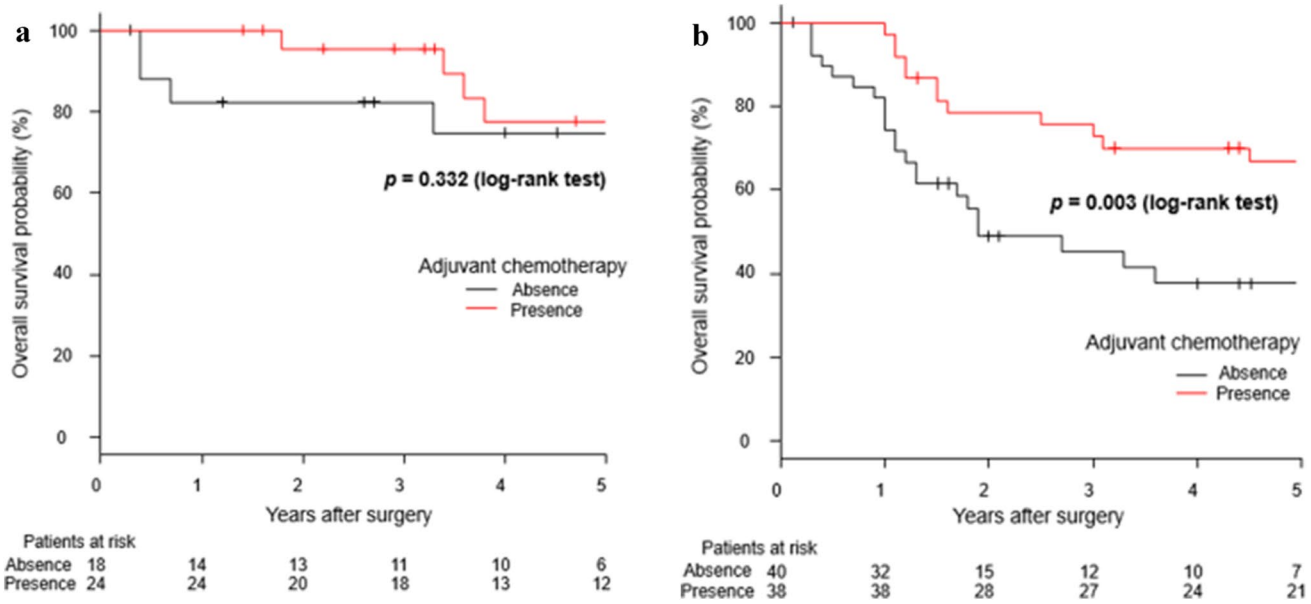

Fig. 3 The overall survival of GC patients with LNMM (**a**) and positive LNM (**b**) according to the presence and absence of adjuvant chemotherapy. *GC* gastric cancer; *LNMM* lymph node micrometastasis; *LNM* lymph node metastasis

of the Japanese Society of Gastric Cancer [6]. That is, LNMM is not a clinicopathological factor. The results of the present study may provide new treatment options for patients with pN1 GC.

Several limitations associated with the present study warrant mention. The study was conducted at a single center with small sample size and had a retrospective design; thus, we were unable to draw any concrete conclusions regarding the prognostic impact of LNMM with a cut-off value of 1500 μm. The tumor depth and size are among the most well-known and strongest prognostic factors in GC. Furthermore, in the present study, patients with deeper or larger tumors tended to have a poorer prognosis than others. However, because of the relatively small sample size due to the limitation of analyzing only pN1 cases, we did not detect a significant difference. Furthermore, the diagnosis of LNMM was made only on slides that cut the LN with the maximum diameter passing through the hilus; therefore, there may be larger tumor cell clusters in other slices of the specimen. However, in the clinical setting, the most commonly used final assessment method of LN metastasis is HE staining with formalin-fixed specimens on the plane of the

maximum dimension of the node containing the hilus. This study aimed to prove that a small tumor size within metastatic LNs was a prognostic biomarker for gastric cancer. Therefore, we feel that a simple and general method of diagnosing LNs with the maximum diameter passing through the hilus is most suitable for this study.

In conclusion, LNMM is associated with a favorable prognosis and may be an independent prognostic marker in patients with pN1 GC. Furthermore, there was no significant difference in the OS between GC patients with LNMM who received chemotherapy and those who did not. Owing to the favorable prognosis associated with LNMM, it may be a factor preventing adjuvant chemotherapy in patients with pN1 GC.

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Authors' contributions AY and KS designed the research. KS performed the research. KS reviewed the surgical pathology. AY and KS analyzed the data. AY and KS wrote the paper. All authors read and approved the final manuscript.

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Data availability All data generated or analyzed during this article are included in this published article. The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Declarations

Conflicts of interest None of the authors have any conflicts of interest to disclose.

Ethics approval This study was approved by the Ethics Committee of the University of Yamanashi Hospital and was performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from the patient for the publication of these findings and accompanying images.

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