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ORIGINAL ARTICLE

Venous Invasion Is a Risk Factor for Recurrence of pT1 Gastric Cancer with Lymph Node Metastasis

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Abstract

Background Postoperative adjuvant therapy for early gastric cancer (EGC) has not been widely studied, and there are differing indications for postoperative adjuvant therapy between Western and Asian countries. Japanese gastric cancer treatment guidelines do not recommend adjuvant chemotherapy for EGC, but it is unclear whether surgery alone is the most appropriate treatment.

Methods This is a single-center retrospective study of 1001 consecutive patients who underwent radical gastrectomy for pT1 gastric cancer between 1999 and 2013 at the Wakayama Medical University Hospital.

Results Recurrence was observed in 12 patients, nine of whom as the result of hematogenous metastasis. In all patients with pT1 gastric cancer ($n=1001$), lymph node metastasis was identified as an independent predictive factor for recurrence (hazard ratio [HR] = 10.910, $P=0.002$). In patients with pT1N + gastric cancer, however, the 5-year disease-specific survival (DSS) rate was still high, 90.8%. In patients with pT1N + gastric cancer ($n=97$), the presence of venous invasion (pT1N + v +) was identified by univariate and multivariate analyses as an independent risk factor for recurrence (HR = 4.791, $P=0.032$). In patients with venous invasion, the 5-year DSS rate was significantly lower than that in those without venous invasion (79.3% vs. 95.2%, $P=0.018$).

Conclusions Long-term prognosis of patients with EGC with lymph node metastasis is good, but venous invasion is associated with a higher risk of recurrence. Selective application of postoperative adjuvant chemotherapy for pT1N + v + gastric cancer may efficiently improve prognosis among patients with EGC.

Keywords Early gastric cancer · Lymph node metastasis · Venous invasion · Recurrence

Introduction

Gastric cancer was recently shown to be the fifth most common cancer worldwide and the third most deadly. Globally, there were an estimated 783,000 gastric cancer-related deaths in 2018.[1] The mortality rate of gastric cancer has decreased owing to the eradication of *Helicobacter pylori*.[2] Meanwhile, the detection rate of early gastric cancer (EGC) is increasing owing to more widespread screening with upper gastrointestinal endoscopy.[3] EGC is defined as an adenocarcinoma confined to the mucosa or submucosa (T1), regardless of the presence of lymph node metastasis. The recurrence rate of pathological T1 (pT1) gastric cancer after curative resection is low, and reported rates range between 1.4 and 7.0%.[4] Recurrence does occur, however, and there have been reports of a higher risk of recurrence in cases of EGC with lymph node metastasis.[5–8].

The Japanese Gastric Cancer Treatment Guidelines 2018 (fifth edition) recommend observation without adjuvant chemotherapy after curative resection in patients with pT1 gastric cancer, regardless of the presence of lymph node metastasis.[9] Meanwhile, in the National Comprehensive Cancer Network (NCCN) Guidelines (Version 4, 2021 Gastric Cancer), for any T, N + gastric cancer, adjuvant chemotherapy and chemoradiotherapy are recommended if less than D2 lymph node resection, and chemotherapy is recommended for patients who underwent D2 resection.[10] Disparities in gastric cancer survival rates among different racial and ethnic groups have been reported,[11] so simple comparison of previous studies is inappropriate. In Japan, the prognosis of patients with EGC with lymph node metastasis (pT1N + gastric cancer) is comparatively good, and the 5-year overall survival rate of patients with pT1N1–2 gastric cancer is 85.5%.[12] The standard treatment

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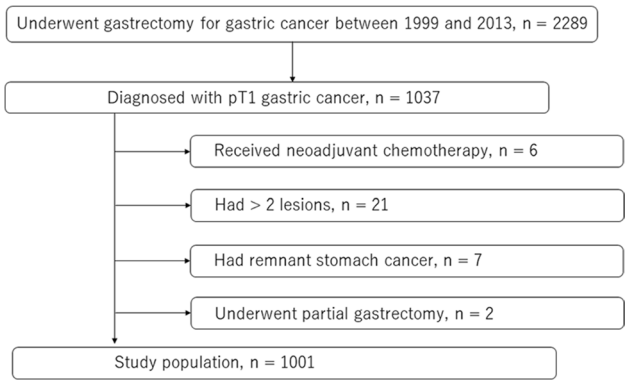

Fig. 1 Flow diagram of the enrollment of 2289 patients who underwent gastrectomy for gastric cancer between 1999 and 2013

for pT1N + gastric cancer in Japan is surgery alone, although postoperative recurrence is to some extent encountered in daily clinical practice.

No randomized trials have yet clarified whether postoperative chemotherapy increases the survival of patients undergoing resection for EGC with lymph node metastasis. Postoperative adjuvant therapy has been used in some cases, but the most appropriate regimen and duration of treatment remain unclear. Analysis of the risk factors in pT1 and pT1N + gastric cancer to determine which patients have a high risk of recurrence may therefore help to identify the groups that require postoperative chemotherapy. Unnecessary anticancer therapy might be reduced in patients with EGC, and the curability of EGC may be further improved.

This study aims to investigate the long-term prognosis of patients with EGC and to identify the groups at high risk of recurrence among patients with pT1N + gastric cancer.

Methods

Patients

Clinicopathologic data were retrospectively evaluated of the 1001 patients who underwent curative gastrectomy with radical lymph node dissection and were diagnosed with pT1 gastric cancer between January 1999 and December 2013 at the Wakayama Medical University Hospital. Patients with prior gastric surgery, double primary malignancies, neoadjuvant chemotherapy, and R1 or R2 surgical margins were excluded. The study was approved by the Wakayama Medical University Hospital Human Ethics Review Committee (Approval Number 3277) in accordance with the Declaration of Helsinki. It was registered on the University Hospital Medical Information Network Clinical Trials Registry (UMIN000045382). Figure 1 depicts the patient enrollment.

Patient Characteristics and Clinicopathologic Data

Data were obtained on clinical characteristics such as age, surgical techniques, the method of approach (open or laparoscopic), surgical procedures, lymph node dissection, tumor location, maximum tumor size, macroscopic type, histologic type, lymphatic invasion, venous invasion, pathological N factor, and adjuvant chemotherapy. For all gastric cancer patients, contrast-enhanced computed tomography (CT) is performed to evaluate the primary tumor, lymph node metastasis, and distant metastasis, and endoscopic ultrasound (EUS) is performed to evaluate tumor depth. During surgical treatment, D2 dissection was performed in patients with suspected T2 invasion by preoperative upper gastrointestinal endoscopy or possible lymph node metastasis by contrast-enhanced CT, D1 + dissection in patients diagnosed with EGC by preoperative examination and D1 dissection in patients with severe comorbidity. Histological types were reviewed according to the World Health Organization classification and

Table 1 Characteristics of 1001 patients with pT1 gastric cancer

Variables		No. of patients (%)
Age, median, years		67 (27–96)
Sex	Male/female	676 (67.5)/325 (32.5)
Surgical method	Total/subtotal	126 (12.6)/875 (87.4)
Lymph node dissection	D1/D1 + /D2	208 (20.8)/526 (52.5)/267 (26.7)
Differentiation	Differentiated/undifferentiated	664 (66.3)/337 (33.7)
Tumor depth	T1a(m)/T1b(sm1)/T1b(sm2)	474 (47.4)/110 (11.0)/417 (41.6)
Lymph node metastasis	Present/absent	97 (9.7)/904 (90.3)
Lymphatic invasion	Present/absent	218 (21.8)/783 (78.2)
Venous invasion	Present/absent	111 (11.1)/890 (88.9)
Stage(TNM classification 8th edition)	IA/IB/IIA/IIB/IIIB	904 (90.3)/63 (6.3)/25 (2.5)/7 (0.7)/2 (0.2)
Adjuvant chemotherapy	+/−	16 (1.6)/985 (98.4)

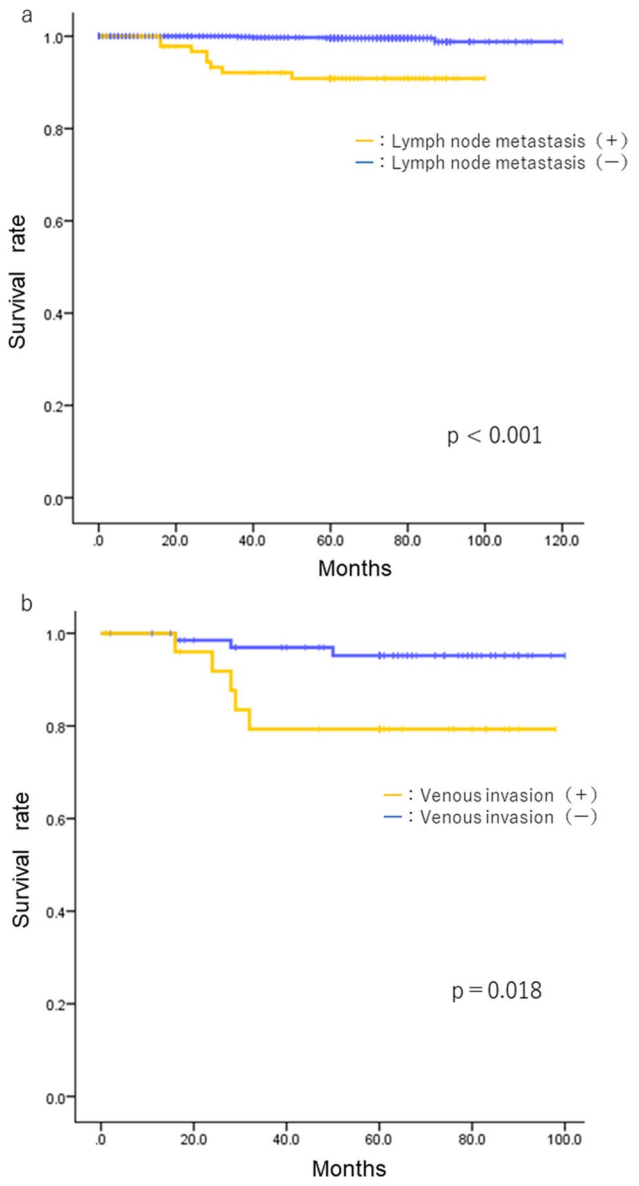

Fig. 2 **a** Kaplan–Meier estimates of disease-specific survival (DSS) rates in patients with pT1 gastric cancer. Analysis of 5-year DSS in each group divided according to the presence of lymph node metastasis. Patients with early gastric cancer (EGC) with lymph node metastasis exhibited a significantly poorer DSS than patients with EGC without lymph node metastasis (5-year DSS rate, 90.8% vs. 99.6%; $P < 0.001$). **b** Kaplan–Meier estimates of disease-specific survival (DSS) rates in patients with pT1N + gastric cancer. Analysis of DSS in each group was divided according to the presence of venous invasion. Patients with pT1N + v + gastric cancer exhibited a significantly poorer DSS than patients with pT1N + v − gastric cancer (5-year DSS rate, 79.3% vs. 95.2%; $P = 0.018$)

categorized into differentiated and undifferentiated types. Pathological stages were determined according to the eighth edition of the Union for International Cancer Control/American Joint Committee on Cancer classification system.[13].

Follow-up and Adjuvant Chemotherapy

Tumor recurrence was identified according to standard clinical practices. Patients were evaluated every 3 or 6 months until 2 years after surgery and then every 6 months thereafter for up to 5 years. Evaluation is comprised of physical examination, laboratory tests, imaging studies (enhanced CT from the chest to the pelvis), and endoscopic examination. The decision to administer chemotherapy was based on the surgeon's or patient's preference because there was no established postoperative adjuvant treatment strategy for pT1N + gastric cancer during the study period. Sixteen patients received postoperative adjuvant chemotherapy, either tegafur/uracil or TS-1. All patients who received postoperative adjuvant chemotherapy had sm invasive gastric cancer with lymph node metastasis.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows (version 24.0; SPSS Inc., Chicago, IL, USA). Univariate and multivariate analyses for factors predictive of tumor recurrence after curative resection for pT1 gastric cancer were performed using a Cox proportional hazards model. Disease-specific survival (DSS) curves were analyzed using the Kaplan–Meier method, with the duration of DSS (in months) calculated as the length of time between the primary surgical treatment and the last follow-up or confirmed date of death from gastric cancer. Statistical significance was set at $P < 0.05$.

Results

Background Characteristics and Pathologic Findings

A total of 1001 patients met the eligibility criteria and were enrolled in this study. Lymph node metastasis was observed in 97 patients (T1N1, $n = 63$; T1N2, $n = 25$; T1N3a, $n = 7$; T1N3b, $n = 2$). Median follow-up period was 67 months (range: 1–120 months). Characteristics of all patients with pT1 gastric cancer are summarized in Table 1.

Prognosis

The 5-year DSS rate of patients with pT1N0 cancer was 99.6% (95% confidence interval [CI] 99.4–99.8), and that of patients with pT1N + cancer was 90.8% (95% CI 87.7–93.9) (Fig. 2a).

Analysis of Risk Factors for Recurrence in pT1 Gastric Cancer

Among patients with pT1 gastric cancer, risk factors for recurrence and subgroups with poor prognosis were analyzed. Univariate analysis revealed that significant

Table 2 Univariate and multivariate analyses of risk factors for tumor recurrence in patients with pT1 gastric cancer

Variables	Univariate analysis			Multivariable analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (≥ 75 years)	1.109	0.966–1.075	0.481			
Sex	2.529	0.554–11.544	0.231			
Open/laparoscopic	2.789	0.755–10.303	0.124			
Total/subtotal gastrectomy	2.365	0.640–8.737	0.197			
Lymph node dissection						
D1/D1 +	0.868	0.168–4.497	0.866			
D1/D2	1.716	0.519–1.716	0.519			
Tumor site (upper/middle·lower)	0.975	0.213–4.450	0.974			
Tumor diameter (> 3 cm)	3.056	0.970–9.628	0.056			
Macroscopic type (0/I–V)	4.247	1.149–15.694	0.030	1.294	0.313–5.351	0.722
Gross type (elevated/non-elevated)	0.893	0.242–3.301	0.866			
Sm2 invasion (+)	7.323	1.603–33.445	0.010	2.479	0.421–14.582	0.315
Differentiation (differentiated)	5.722	0.738–44.334	0.095			
Lymphatic invasion (+)	3.733	1.204–11.580	0.023	0.479	0.114–2.010	0.314
Venous invasion (+)	6.203	1.968–19.548	0.002	3.223	0.831–12.504	0.091
Lymph node metastasis (+)	18.750	5.645–62.237	< 0.001	10.910	2.463–48.321	0.002
Adjuvant chemotherapy (+)	20.165	5.547–74.507	< 0.001	2.743	0.606–12.406	0.190

HR hazard ratio, *CI* confidence interval

predictive factors for recurrence were lymphatic invasion, venous invasion, adjuvant chemotherapy, lymph node metastasis, sm2 (submucosal layer 2) invasion, and macroscopic type other than 0. Multivariate analysis indicated that lymph node metastasis was an independent predictive factor for recurrence (Table 2).

Characteristics of 97 Patients with pT1N + Gastric Cancer

Lymph node metastasis was an independent prognostic factor for pT1 EGC, so we examined the patient population with pT1 plus lymph node metastases in detail.

The characteristics of 97 patients with pT1N + cancer are summarized in Table 3. Of the patients with EGC with lymph node metastasis, 72.2% had differentiated gastric cancer, and 92.8% had submucosal invasive cancer. D1 + lymph node dissection or higher was performed in 88.7% of the cases.

Univariate and Multivariate Analyses of Risk Factors for Tumor Recurrence in Patients with pT1N + Gastric Cancer

The risk factors for recurrence and groups with poor prognosis were analyzed among patients with pT1N + gastric cancer. Univariate analysis suggested the potential prognostic factors related to patients who required total gastrectomy ($P = 0.056$) and those with tumors with venous invasion ($P = 0.029$). Multivariate analyses revealed that only venous invasion (pT1N + v +) was a significant risk factor for the recurrence

Table 3 Characteristics of 97 patients with pT1N + gastric cancer

Variable		No. of patients (%)
Age, median, years		67 (27–88)
Sex	Male/female	58 (59.8)/39 (40.2)
Surgical method	Total/subtotal	15 (15.5)/82 (84.5)
Lymph node dissection	D1/D1 + /D2	11 (11.3)/44 (45.4)/42 (43.3)
Differentiation	Differentiated/undifferentiated	70 (72.2)/27 (27.8)
Tumor depth	T1a(m)/T1b(sm1)/T1b(sm2)	7 (7.2)/10 (10.3)/80 (82.5)
Lymphatic invasion	Present/absent	66 (68.0)/31 (32.0)
Venous invasion	Present/absent	27 (27.8)/70 (72.2)
Stage (TNM classification 8th edition)	IB/IIA/IIB/IIIB	63 (64.9)/25 (25.8)/7 (7.2)/2 (2.1)
Adjuvant chemotherapy	+ / −	16 (16.5)/81 (83.5)

Table 4 Univariate and multivariate analyses of risk factors for tumor recurrence in patients with pT1N + gastric cancer

Variable	Univariate analysis			Multivariable analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (≥ 75 years)	1.379	0.278–6.852	0.694			
Sex	5.308	0.653–43.171	0.119			
Open/laparoscopic	3.678	0.454–29.974	0.222			
Total/subtotal gastrectomy	4.054	0.966–17.008	0.056	3.867	0.920–16.254	0.065
Lymph node dissection						
D1/D1 +	0.366	0.033–4.052	0.413			
D1/D2	1.036	0.120–8.984	0.974			
Tumor site (upper/middle·lower)	2.714	0.547–13.464	0.222			
Tumor diameter (> 3 cm)	2.465	0.497–12.222	0.269			
Macroscopic type (0/I–V)	1.620	0.326–8.054	0.555			
Gross type (elevated/non-elevated)	1.293	0.309–5.412	0.725			
Sm2 invasion	1.529	0.188–12.434	0.619			
Differentiation (differentiated)	3.085	0.379–25.088	0.292			
Lymphatic invasion (+)	1.507	0.304–7.465	0.616			
Venous invasion (+)	4.940	1.180–20.685	0.029	4.791	1.143–20.082	0.032
N stage ≥ 2	1.858	0.465–7.310	0.381			
Adjuvant chemotherapy (+)	3.004	0.718–12.571	0.132			

HR hazard ratio, *CI* confidence interval

of pT1N + gastric cancer ($P = 0.032$), and odds ratio was 4.791 (95% confidence interval, 1.143–20.082) (Table 4). Characteristics of pT1N + gastric cancer patients according to venous invasion are summarized in Table 5. Postoperative adjuvant chemotherapy in both v + group and v − group was less than 20%, and the number of recurrences was 4 cases each groups.

DSS analysis by Kaplan–Meier method showed that the group of patients with pT1N + v + cancer had a significantly shorter survival time than the other groups. The 5-year DSS rate in this group was 79.5% (95% CI 71.3–87.7), which was significantly lower than that in the group without venous invasion (pT1N + v −, 95.3%) (Fig. 2b, P = 0.018). In this study, D1, D1 +, and D2 lymph node dissection was performed for pT1N + GC, and there was no significant difference between these dissection ranges (the 5-year DSS rate: D1, 87.5%; D1 +, 95.5%; D2, 86.3%; data not shown).

Recurrence Patterns

Regarding the recurrence pattern, nine patients had hematogenous metastases (seven with liver metastases, two with bone metastases), one patient had peritoneal dissemination, and two patients had distant lymph node metastases. Hematogenous metastasis was observed in 75% of the patients (58% liver metastasis), whereas lymph node metastasis was observed in 16.7% of the patients (Table 6).

Discussion

Lymph node metastasis has been considered to be the most important risk factor for EGC recurrence.[5–8], The prognosis of patients with EGC is good, however, even if there is lymph node metastasis.[4] In this study, the 5-year DSS rate of pT1N + gastric cancer was 90.8%, indicating good prognosis. Administering adjuvant chemotherapy to all patients with pT1N + gastric cancer therefore constitutes an overtreatment. Identification of the patient population that requires adjuvant chemotherapy is therefore necessary.

Venous invasion was identified in this study as an independent risk factor for the recurrence of pT1N + gastric cancer. In comparison to pT1N + gastric cancer with and without venous invasion using the Kaplan–Meier method, the 5-year DSS rate of the pT1N + v + group was 79.3%, a considerably poorer prognosis than that in the pT1N + v − group, which had a rate of 95.2%.

Regarding recurrence patterns, EGC has less peritoneal dissemination recurrence and a higher frequency of hematogenous metastasis than advanced gastric cancer.[12] The low number of lymph node recurrences owing to adequate local control with lymph node dissection and reduced peritoneal recurrence owing to limited invasion into the submucosal layer may be factors contributing to the increased rate of hematogenous metastasis in EGC. The presence of venous

Table 5 Characteristics of pT1N + gastric cancer patients according to venous invasion

Variables	V + (*n* = 27)	V − (*n* = 70)	*P* value
Age, median, years	67 (40–87)	67 (27–88)	
Sex			0.648
Male	15 (55.6)	43 (61.4)	
Female	12 (44.4)	27 (38.6)	
Surgical method			1.000
Total gastrectomy	4 (14.8)	11 (15.7)	
Subtotal gastrectomy	23 (85.2)	59 (82.3)	
Lymph node dissection			0.912
D1	6 (22.2)	5 (7.2)	
D1 +	8 (29.6)	36 (51.4)	
D2	13 (48.2)	29 (41.4)	
Differentiation			0.024
Differentiated	24 (88.9)	46 (65.7)	
Undifferentiated	3 (11.1)	24 (34.3)	
Tumor depth			0.064
T1a(m)	0 (0)	7 (10)	
T1b(sm1)	0 (0)	10 (14.3)	
T1b(sm2)	27 (100)	53 (75.7)	
Lymphatic invasion			0.007
Present	24 (88.9)	42 (60)	
Absent	3 (11.1)	28 (40)	
Stage (TNM classification 8th edition)			0.395
IB	15 (55.6)	48 (68.6)	
IIA	10 (37)	15 (21.4)	
IIB	1 (3.7)	6 (8.6)	
IIIB	1 (3.7)	1 (1.4)	
Adjuvant chemotherapy			0.765
Present	5 (18.5)	11 (15.7)	
Absent	22 (81.5)	59 (84.3)	
Recurrence			0.148
Present	4 (14.8)	4 (5.7)	
Absent	23 (85.2)	66 (94.3)	

invasion in advanced gastric cancer has been reported as a risk factor for hematogenous metastasis[14]. Furthermore, venous invasion was shown to be a risk factor for hematogenous metastasis in EGC with lymph node metastasis. EGC with lymph node metastasis already has a high rate of positive lymphatic invasion (68%), and venous invasion involved in distant metastasis is expected to be an important risk factor for the recurrence. Reduction of recurrence in EGC depends on the prevention of postoperative hematogenous metastasis. Postoperative adjuvant therapy therefore has a good possibility of reducing the risk of recurrence in such patients. We compared the 5-year DSS of patients with pT1N1 gastric cancer and those with pT1N2–3b gastric cancer and found no significant differences between the two groups (pT1N1, 93.2%; pT1N2–3b, 86.6%; data not shown). The 5-year DSS rate of patients with pT1N2–3b gastric cancer was higher than that of patients with pT1N + v + gastric cancer (79.5%). This study shows the possibility that even multiple lymph node metastases are not a crucial risk factor for poor prognosis if lymph node dissection is appropriately performed during surgical treatment. However, the number of pN3a-b cases was very small (9 cases), and recurrence in pN3a-b was as high as 2/9 (22.2%), compared to 4/59 (6.8%) for pN1 and 2/25 (8%) for pN2 (Table 6). It has been reported that the risk of recurrence of pT1N3a-b is high[15], and further accumulation of multiple lymph node metastasis cases is needed.

Table 6 Pattern of recurrence

Stage	No. of cases (%)	Recurrence site
T1bN0	4/438 (0.9)	H2, B1, L1
T1bN1	4/59 (6.8)	H4
T1bN2	2/25 (8)	H1, P1
T1bN3a–b	2/9 (22.2)	B1, L1

H hepatic metastasis, *B* bone metastasis, *L* lymph node metastasis, *P* peritoneal metastasis

This study had several limitations; it was a single-center retrospective study, and there was no standardization of patient background, surgical treatment, or postoperative adjuvant therapy. Second, owing to the small number of recurrences, the analysis might be statistically insufficient. Large-scale prospective trials are needed to improve the outcomes of patients with pT1N + gastric cancer who require adjuvant therapy and to investigate appropriate treatment regimens.

Conclusion

Among patients with EGC, those with pT1N + v + gastric cancer have a high risk of recurrence from distant metastasis and require careful follow-up. Postoperative adjuvant therapy to prevent hematogenous metastasis may be beneficial for patients with pT1N + v + gastric cancer.

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Author Contribution AT designed the study and wrote the initial draft of the manuscript. AT and TO contributed to data interpretation and critical revision of the manuscript. All the other authors (MK, KH, TG, JK, ST, NF, TN, and HY) contributed to data collection and interpretation and critical review of the manuscript. All authors have read and approved the final version of the manuscript and have agreed to be accountable for all aspects of the study, ensuring that any queries related to the accuracy or integrity of any part of the work are answerable.

Declarations

Ethics Approval and Consent to Participate This study was approved by the Wakayama Medical University Institutional Review Board. All procedures were undertaken in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent to be included in the study, or the equivalent, was obtained from all patients.

Conflict of Interest The authors declare no competing interests.

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