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ORIGINAL ARTICLE

Oncological outcomes in patients with pT1N0–3 or pT2–3N0 gastric cancer after curative resection without adjuvant chemotherapy

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Abstract

Purpose The survival outcomes of pT1N0–3 or pT2–3N0 gastric cancer after curative resection are favorable without adjuvant chemotherapy. However, some patients develop recurrence and details of these recurrences remain unclear. This study aimed to evaluate the prognostic factors in patients with pT1N0–3 or pT2–3N0 gastric cancer.

Methods We retrospectively reviewed the medical records of 1219 patients with pT1N0–3 or pT2–3N0 gastric cancer who underwent curative gastrectomy without neoadjuvant or adjuvant chemotherapy between April 2007 and March 2012 at Cancer Institute Hospital.

Results This cohort included 895 pT1N0, 73 pT1N1, 23 pT1N2, 6 pT1N3, 130 pT2N0, and 92 pT3N0 patients. The 5-year overall survival (OS) and 5-year relapse-free survival (RFS) for pT1N0–3 and pT2–3N0 gastric cancer were 98.9% (95% CI 98.1–99.4) and 97.7% (95% CI 96.7–98.4), respectively. Age (HR 3.56, 95% CI 2.10–6.03) and lymphovascular involvement (hazard ratio (HR) 2.98, 95% CI 1.76–5.04) were independent prognostic factors in a multivariate analysis for RFS. The 5-year RFS for patients aged ≥75 years or with lymphovascular involvement were 94.4% (95% CI 89.8–97.0) and 95.1% (95% CI 92.5–96.8), respectively.

Conclusion The survival outcomes of pT1N0-3 and pT2-3N0 were excellent, even in patients with aged >75 years or lymphovascular involvement which were risk factors. However, the sample size of T1N3 gastric cancer is small, so larger sample size and risk factor analysis are required.

Keywords Gastric cancer · Surgery alone · Lymphovascular involvement · Mode of recurrence

Introduction

Gastric cancer is the fifth most common malignancy in the world, and the third most common cause of cancer death worldwide [1]. Radical gastrectomy with regional lymph node dissection is the main treatment strategy in Japan for resectable gastric cancer [2]. In addition, The Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) demonstrated that adjuvant chemotherapy improved the survival benefit after radical gastrectomy for pathologically confirmed Stage II or III gastric cancer excluding early gastric cancer with lymph node metastasis and pathological T3N0 cancer [3]. After publication of that trial, 1-year administration of S-1 as adjuvant chemotherapy became the standard treatment for pathological Stage II or III gastric cancer excluding early gastric cancer with lymph node metastasis and pathological T3N0 cancer [2].

The survival outcomes were excellent in patients with Stage I and in some patients with Stage II or III (T1N2–3 or T3N0) gastric cancer; therefore, the current Japanese gastric cancer treatment guidelines do not recommend any adjuvant chemotherapy [2]. However, there are some patients who experience recurrence from this category of gastric cancer after curative surgery. The risk factors for recurrence in this cohort are still unclear because there has been little evaluation of survival outcomes and risk factors for recurrence in a patient population with a low incidence of recurrence for whom adjuvant chemotherapy is not indicated. The aim of this study was to evaluate the prognostic factors in patients with T1N0–3 or T2–3N0 gastric cancer.

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Materials and methods

This study was a retrospective, single-institution study. The data of patients who underwent R0 gastrectomy for primary gastric cancer at the Cancer Institute Hospital, Tokyo, between April 2007 and March 2012 were retrospectively reviewed from our prospective database. The following were exclusion criteria: patients with remnant gastric cancer, gastric tube cancer, or other malignancies. In addition, patients who received neoadjuvant or adjuvant chemotherapy were also excluded. Twenty-one patients were excluded because of use of adjuvant chemotherapy, out of which 10 were T1N3, 6 were T1N2, 3 were T3N0, and 1 each was T1N1 and T2N0. Adjuvant chemotherapy was administrated by physician's choice or patient's wish. Our study population consisted of 1219 patients with pT1, pT2N0, or pT3N0 gastric cancer according to eighth edition of the TNM classification (Fig. 1). This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and was approved by the Institutional Review Boards (no. 2018-1005). All patients signed informed consents for the analysis.

Staging systems

Clinical and pathological findings regarding the tumor depth and nodal status were defined according to the eighth edition of the TNM classification. The tumors were histologically classified into three groups: papillary and tubular adenocarcinomas were classified as differentiated type; poorly differentiated adenocarcinomas, signet ring cell carcinomas, and mucinous adenocarcinomas were classified as undifferentiated type; and the other histologic types were classified as special type.

Data collection

The clinical and pathological data in our database included sex; age; the clinical depth of the primary tumor and the nodal status; the location, size, macroscopic type, histological type, and depth of the primary tumor; the number and location of the dissected lymph nodes; and the number and location of metastatic lymph node. Relapse-free survival (RFS) was determined between the date of the operation and the first documented recurrence or death from any cause. Overall survival (OS) was determined between the date of the operation and death from any cause. If patients did not meet any of the endpoints by March 31, 2018, they were censored at the time of last contact.

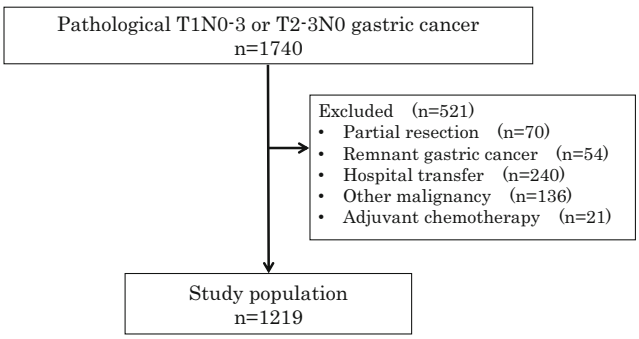

Fig. 1 Schema of patients with pathological T1N0-3 or T2-3N0 gastric cancer who underwent curative gastrectomy without adjuvant or neoadjuvant chemotherapy

Surgical procedures

The surgical procedure was determined according to the Japanese gastric cancer treatment guidelines at the time. Generally, laparoscopic gastrectomy was conducted for clinical Stage I gastric cancer. Open gastrectomy with D2 lymphadenectomy was performed in the patients with cT2–4 or clinically node-positive status. D1+ lymphadenectomy was conducted for cT1N0 gastric cancer.

Follow-up

The patients with Stage I cancer were examined at outpatient visits every 6 months for the first 3 years after surgery, and then they were seen every year until the fifth year. The patients with Stage II or III cancer were examined every 3 months for the first 2 years, and then they were seen every 6 months until the fifth year. Physical examination and blood tests were performed at every visit. Abdominal computed tomography (CT) or ultrasonography was performed every 6 months for the first 3 years and every year for the next 2 years in patients with Stage II or III cancer. The patients with Stage I cancer underwent abdominal CT every year.

Statistical analysis

Survival curves for 5-year RFS and 5-year OS were estimated using the Kaplan–Meier method. Multivariate analysis for RFS was performed using Cox proportional hazards model, and the variables were selected by the stepwise method using the Bayesian information criterion (BIC). Patient characteristics were evaluated by Fisher's exact test. The level of significance was set to $p < 0.05$ and all statistical tests were two-sided. All statistical analysis was performed with EZR version 1.36 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [4].

Results

Patient characteristics

A total of 1219 patients were eligible for this study. The clinicopathological characteristics of 1219 patients are shown in Table 1. Briefly, the median age of the patients was 63 years (interquartile range [IQR] 55–70), with a male-to-female ratio of approximately 2:1. The proportion of differentiated and undifferentiated tumor types was approximately even; five patients were diagnosed with special type tumors, including carcinoid tumor, endocrine cell carcinoma, and hepatoid adenocarcinoma. Gastric cancer was classified as pT1 in 997 patients and as pT2 or pT3 in 222 patients. The most frequently performed operation was distal gastrectomy, followed by total gastrectomy, pylorus-preserving gastrectomy, and proximal gastrectomy. Laparoscopic gastrectomy was performed in 911 patients (74.7%).

Recurrence and survival

The clinicopathological features of the 23 patients (1.9%) who experienced recurrence are shown in Table 2. The most common site of recurrence was the lymph nodes (47.8%), followed by the liver (17.4%), peritoneum (17.4%), lung (13.0%), bone (4.3%), and locoregional recurrence (4.3%) (Table 2). One patient had a simultaneous recurrence in distant lymph nodes and peritoneum. The lymph node recurrence was found in paraaortic, hepatic hilar, supraclavicular, mediastinal, and locoregional lymph nodes. Of the 11 cases of lymph node recurrence, D2 dissection was performed in 3 cases. Of the two cases of locoregional lymph node recurrence, one was D1+ dissection and one was D2 dissection. The most frequent recurrence route in patients with pT1 gastric cancer was lymphatic metastasis (six patients, 54.5%), followed by hematogeneous metastasis (three patients, 27.3%), peritoneal, and local recurrence (one patient, 9.1%), whereas the most frequent recurrence route in patients with pT2-3N0 gastric cancer were hematogenous and lymphatic metastasis (five patients, 38.5%), followed by peritoneal recurrence (three patient, 23.1%). The median time between operation and recurrence was 30.1 months (IQR 13.3–50.5 months). The recurrence was found 5 years after surgery in five patients (21.7%), and four of these patients had early gastric cancer. The relationship between the mode of the recurrence and the timing of the recurrence is shown in Table 3. Hematogenous metastasis was significantly more common within 3 years after curative surgery ($p = 0.001$), whereas lymphatic node recurrence was seen more often after the third year after curative surgery ($p = 0.039$).

After the median follow-up period of 62.4 months, the 5-year RFS and 5-year OS were 97.7% (95% CI 96.7–98.4) and 98.9% (95% CI 98.1–99.4), respectively. The 5-year RFS

Table 1 Clinicopathological features and surgical procedures

Characteristics	No. of patients (n=1219)
Age*	63 (55, 70)
Sex	
Male	793 (65.1)
Female	426 (34.9)
Macroscopic type	
0	1048 (86.0)
1	19 (1.6)
2	76 (6.2)
3	69 (5.7)
5	7 (0.6)
Histological type	
Differentiated type	527 (43.2)
Undifferentiated type	687 (56.4)
Special type	5 (0.4)
Diameter (mm)*	30 [20, 45]
Type of gastrectomy	
Distal gastrectomy	676 (55.5)
Proximal gastrectomy	28 (2.3)
Total gastrectomy	199 (16.3)
Pylorus-preserving gastrectomy	316 (25.9)
Lymphadenectomy	
<D2	874 (71.7)
≧D2	345 (28.3)
pT factor (JC-15/TNM-8)	
pT1a	454 (37.2)
pT1b	543 (44.5)
pT2	130 (10.7)
pT3	92 (7.5)
pN factor (JC-15/TNM-8)	
pN0	1117 (91.6)
pN1	73 (6.0)
pN2	23 (1.9)
pN3a	6 (0.5)
TNM classification (JC-15/TNM-8)	
T1N0	895 (73.4)
T1N1	73 (6.0)
T1N2	23 (1.9)
T1N3	6 (0.5)
T2N0	130 (10.7)
T3N0	92 (7.5)
Lymphovascular involvement	
Yes	789 (64.7)
No	430 (35.3)

JC-15 Japanese Classifications 15th edition, *TNM-8* the Union for International Cancer Control 8th edition and American Joint Committee on Cancer 8th edition

* Values are median (inter-quartile range)

Table 2 Clinicopathological features and surgical procedures of patients with recurrence

Age	Gender	Location	Macroscopic type	Histological type	Tumor size (mm)	Type of gastrectomy	Lymph node dissection	T category	N category	Lymphatic invasion	Venous invasion	Time interval (mo)	Recurrence site	Survival
66	M	C	1	tub1	35	PG	D1+	SM	0	1a	1b	30.1	Lymph node	Alive
47	M	C	0	NEC	20	PG	D1+	SM	0	1b	1a	36.8	Lymph node	Dead
70	M	L	0	tub1	45	DG	D1+	SM	0	1a	0	75.6	Lymph node	Dead
72	F	L	0	tub2	31	DG	D1+	SM	0	1a	1a	6	Lymph node	Dead
63	M	L	0	tub2	60	DG	D1+	SM	0	1a	0	38.7	Lymph node	Alive
73	M	L	0	tub2	18	DG	D1+	SM	0	0	0	70.1	Lymph node	Alive
72	M	L	0	tub2	20	DG	D1+	SM	0	1a	1b	13.3	Liver	Alive
65	M	M	0	tub2	25	TG	D1+	SM	1	0	0	84	Locoregional	Alive
81	M	M	2	pap	20	DG	D1+	SM	1	1b	1b	13.3	Liver	Dead
68	M	L	2	muc	75	DG	D2	SM	2	1b	0	63.1	Peritoneum	Dead
58	M	L	0	sig	85	DG	D1+	SM	3a	1b	0	24.3	Bone	Alive
74	M	L	3	tub1	115	DG	D2	MP	0	0	1a	13	Liver	Alive
84	M	U	3	por1	59	TG	D2	MP	0	1a	1c	2.9	Liver	Dead
65	M	M	0	por2	30	DG	D1+	MP	0	1b	1a	46.8	Lymph node	Dead
77	M	M	1	tub2	40	DG	D2	MP	0	1c	1a	42.3	Lymph node	Alive
84	M	U	2	tub1	35	TG	D2	MP	0	0	1b	10.6	Lymph node	Dead
70	M	C	0	tub1	28	TG	D2	MP	0	1a	1b	16.6	Lung	Dead
65	M	U	0	tub1	56	TG	D2	MP	0	1c	1b	38.1	Peritoneum	Dead
77	M	C	3	tub2	85	TG	D2	SS	0	1a	1b	18.3	Lung	Dead
72	M	M	0	por2	32	DG	D1+	SS	0	1a	0	97.6	Lymph node	Alive
64	M	C	0	por2	15	TG	D2	SS	0	1b	0	11.9	Lung	Dead
75	M	M	1	por1	96	TG	D2	SS	0	1a	1a	54.1	Peritoneum	Dead
35	M	U	0	por2	30	DG	D1+	SS	0	0	0	28.7	Lymph node Peritoneum	Dead

Table 3 The relationship between pattern of recurrence and timing of recurrence

	<36 months	> 36months	*p* value
Hematogeneous	8	0	0.001
Lymphatic	3	8	0.039
Peritoneal	1	3	0.371
Local	0	1	0.478

according to pStage were 98.6% (95% CI 97.5–99.2) for stage IA, 96.1% (95% CI 92.3–98.0) for stage IB, 94.7% (95% CI 88.5–97.6) for stage IIA, and 83.3% (95% CI 27.3–97.5) for stage IIB. Figure 2a and b shows the 5-year OS and 5-year RFS curves in each TNM classification.

On multivariate analysis for RFS using the BIC stepwise method, multiple factors, such as age, sex, tumor size, macroscopic type, histological type, depth of primary tumor, and lymphovascular involvement, were included. Age (hazard ratio (HR) 3.56, 95% CI 2.10–6.03) and lymphovascular involvement (HR 2.98, 95% CI 1.76–5.04) were significant (Table 4). Figure 2c and d shows the 5-year RFS stratified by lymphovascular involvement or age. The 5-year RFS for patients with lymphovascular involvement and age ≥75 years were 95.1% and 94.4%, respectively.

Discussion

Our study presents three findings about survival outcomes and mode of recurrence in patients with T1N0–3 or T2–3N0 gastric cancer after radical gastrectomy. First, the 5-year RFS are excellent, at over 90% even in patients with pStage II gastric cancer except for T1N3. Second, age and lymphovascular involvement were independent risk factors for recurrence in this cohort. Third, we showed a relationship between the timing of the recurrence and the mode of the recurrence. These findings might be useful for managing pT1N0–3 or T2–3N0 gastric cancer after radical gastrectomy.

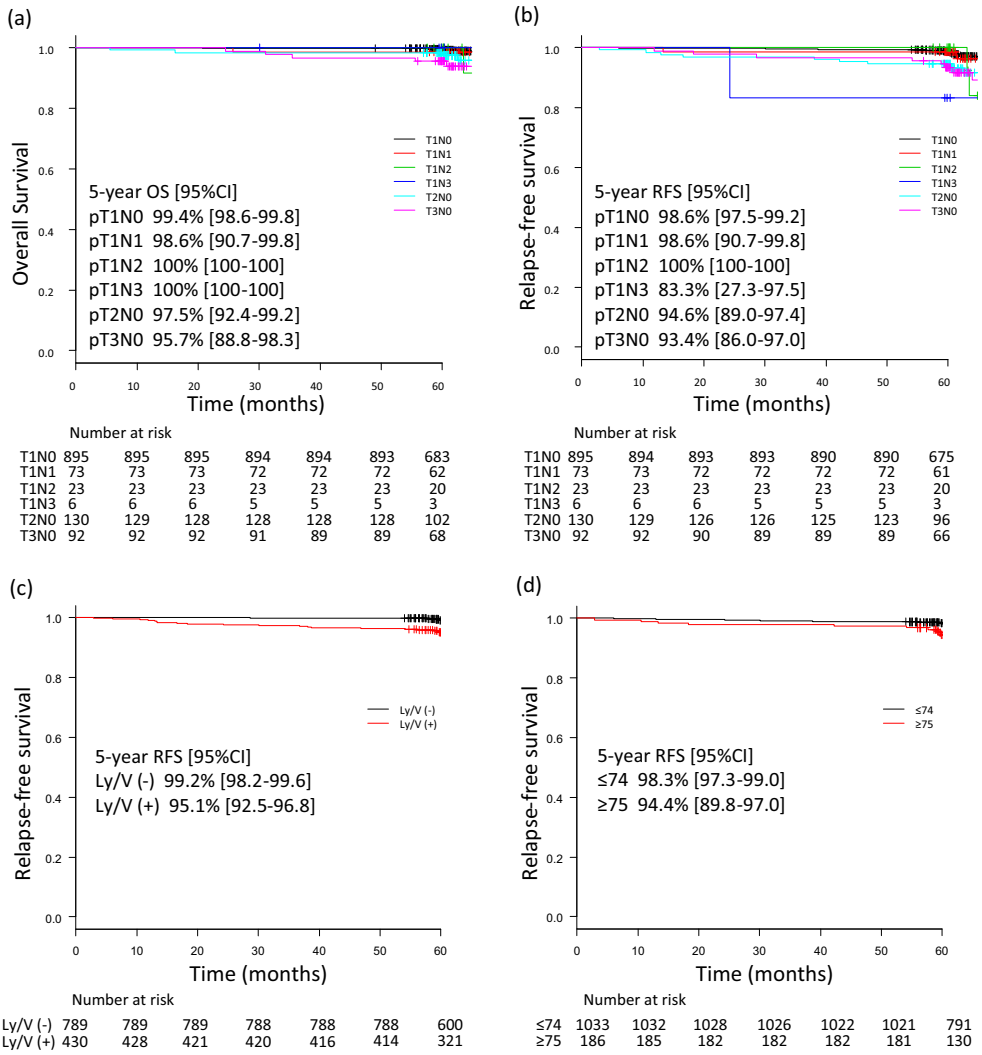

Fig. 2 Kaplan–Meier estimates of overall survival (**a**) and relapse-free survival (**b**) according to TNM classification, and relapse-free survival according to lymphovascular involvement (**c**) and age (**d**)

Table 4 Univariable analysis and multivariable analysis by stepwise method to identify the risks of relapse-free survival

	Univariable		Multivariable	
	HR (95%CI)	*p* value	HR (95%CI)	*p* value
Age		<0.001		<0.001
<75	1 (reference)		1 (reference)	
≥75	4.1 (2.44–6.90)		3.56 (2.10–6.03)	
Sex		0.020		
Male	1 (reference)			
Female	0.47 (0.25–0.89)			
Tumor size		0.033		
≤30mm	1 (reference)			
>30mm	1.75 (1.05–2.91)			
Macroscopic type		<0.001		
Type 0	1 (reference)			
Type 1–5	3.07 (1.80–5.23)			
Histological type		0.007		
Differentiated type	1 (reference)			
Undifferentiated type	0.50 (0.30–0.83)			
Depth of primary tumor		<0.001		
T1	1 (reference)			
T2–3	2.50 (1.48–4.23)			
Nodal status		0.249		
N0	1 (reference)			
N1–3	1.55 (0.74–3.25)			
Lymphovascular involvement		<0.001		<0.001
No	1 (reference)		1 (reference)	
Yes	3.36 (2.00–5.66)		2.98 (1.76–5.04)	

Radical gastrectomy without adjuvant chemotherapy is currently the standard treatment in Japan for pT1 and pT2–3N0 gastric cancer [2]. The incidence of recurrence in patients with early gastric cancer has been reported as 1.4–28.4%, although the relapse rates differ depending on the N status of each cohort [5–9]. It was reported that 7.4–12.2% of patients are with T2–3N0 relapse [7–9]. In the current study, the relapse rates for early gastric cancer and T2–3N0 were 1.3% and 5.8%, respectively, which were consistent with the previous reports. We showed age and lymphovascular involvement as independent risk factors for RFS in this cohort. Some other reports also suggested that lymphatic and/or vascular involvement may be an independent prognostic factor in patients with gastric cancer for whom adjuvant chemotherapy is not indicated. Lee et al. demonstrated that the prognosis of patients with node-negative gastric cancer and lymphovascular involvement was significantly worse than that of patients whose cancer did not have lymphovascular involvement [10]. Araki et al. and Terada et al. demonstrated the clinical significance of vascular involvement as a prognostic factor in their investigations of pT2–3N0 gastric cancer and pT1N+ or pT2–3N0 gastric cancer, respectively [7, 8]. These reports are consistent with our findings. However, there do not seem to be candidates for adjuvant chemotherapy, because the 5-year OS and 5-year RFS were excellent even in patients with pT1N0–3 or pT2–3N0 gastric cancer with lymphovascular involvement in the present study. Moreover, a retrospective Japanese multicenter study was conducted to determine the candidates for neoadjuvant chemotherapy in patients with pT1N+ or T2–3N0 gastric cancer. In the multivariate analysis to identify independent prognostic factors before the surgical treatment, age ≥65 years, male sex, and cT2–4 category were associated with worse OS [11]. However, similar to our study, that study concluded that giving neoadjuvant chemotherapy to all patients with cT2–4 gastric cancer seems to be overtreatment, because the 5-year OS in patients with cT2–4 and pT1N+ or pT2–3N0 gastric cancer was 89.6%. Therefore, these results suggest that radical gastrectomy without neoadjuvant or adjuvant chemotherapy is sufficient and appropriate treatment for patients with pT1 or T2–3N0 gastric cancer.

Age was also an independent prognostic factor in our study, and the natural history may affect these results due to the good survival rate of this study. In a study using the nationwide registry of the Japanese Gastric Cancer

Association, patients aged ≥75 years had worse prognosis after curative gastrectomy for pStage I gastric cancer than those aged <75 years, and deaths due to other diseases were frequently seen in those aged ≥75 years; in patients with Stage I gastric cancer aged ≥75 years, 5-year disease-specific survival rates were >90%; however, the 5-year OS rates were <82% [12]. Saka et al. showed that the number of nodes positive for metastasis was an independent risk factor for recurrence after radical gastrectomy in patients with lymph node-positive early gastric cancer [6]. Yura et al. found that pT1N2–3 gastric cancer had worse 5-year RFS than T3N0 gastric cancer by reviewing 236 patients with pT1N2–3 or pT3N0 gastric cancer after curative surgery [9]. In the International Gastric Cancer Association staging project, the survival of patients with N3b cancer was shown to be poorer than that of patients with N3a cancer [13]. Therefore, by introducing pN3a and pN3b into a cluster analysis, they established a new Stage grouping with better stratification than the American Joint Committee on Cancer seventh edition, especially among Stage III subgroups. However, the number of patients with N3a and N3b in our cohort was 6 and 0, respectively. Therefore, the small sample size might affect our survival outcomes of N3, and it is not possible to reach a consistent conclusion.

For early gastric cancer treated by curative surgery, lymphatic metastasis was the most frequent site of recurrence in the present study. Saka et al. reported that in patients with early gastric cancer with positive lymph nodes, 37% of the first recurrence sites were lymph nodes. Terada et al. also found that 70% of recurrences in patients with T1N2–3 gastric cancer were lymphatic metastases. These results are compatible with our findings. Interestingly, the 11 patients with lymph node recurrence in our study were all pathologically N0 patients; however, lymphovascular involvement was seen in 10 of these patients (90.9%). Thus, cancer cells infiltrated into the lymphatic or vascular channels in these patients, and the presence of micrometastasis to the regional lymph nodes might be reasonable for this paradoxical mode of recurrence. Nakajo et al. evaluated the clinical significance of micrometastasis to the regional lymph nodes in patients with T1–2N0 gastric cancer by examining the presence of tumor cells in the lymph nodes using immunohistochemical staining with anti-cytokeratin AE1/AE3 monoclonal antibody [14]. Occult lymph node metastasis was seen in 20.9% of their patients with T1–2N0 gastric cancer, and the prognosis of those with micrometastasis was significantly worse than that of those without micrometastasis.

Next, we found an association between the mode of the recurrence and the timing of the recurrence; hematogenous metastasis was common within 3 years of radical surgery and lymph node recurrence was common more than 3 years after radical surgery. Araki et al. reported that 83% of liver metastasis was seen within 2 years in patients with T2–3N0 gastric cancer [7]. In a study on recurrence in node-positive early gastric cancer, the median time between surgery and the detection of lymph node recurrence was 39 months, whereas the median time between surgery and the detection of liver metastasis was 8 months [6]. This relationship has also been reported in patients with pStage II or III gastric cancer. In that report, liver and lymph node metastasis reached a plateau 3 years after radical gastrectomy [15]. Those results support our findings. However, the timing of the lymph node recurrence was different. The differences in residual tumor volume according to pStage may have influenced this discrepancy. In addition, visceral metastases may have been easily diagnosed using imaging, compared with peritoneal dissemination. These results suggested that hematogenous metastasis should be carefully monitored within 3 years after surgery and recurrences or symptoms other than those for hematogenous metastasis should be given attention after the third year of the follow-up period. Additionally, the usefulness of magnetic resonance imaging for liver metastasis has been reported, so magnetic resonance imaging may be beneficial if liver metastasis is suspected [16, 17].

There are several limitations to the current study. This was a single-center, retrospective study with a small sample size. Although it comprised one of the largest sample sizes, the number of patients with pT1N3 gastric cancer was only six, which made the survival outcomes of pT1N3 gastric cancer less reliable. A multi-institutional prospective study should be performed to overcome these limitations. Next, lymphovascular involvement was diagnosed by hematoxylin and eosin staining alone, so minor lymphovascular involvement may have been overlooked. However, this situation was similar to those at other institute; therefore, our results reflect real-world situations.

Conclusion

In conclusion, the survival outcomes of pT1N0-3 and pT2-3N0 were excellent, even in patients with aged >75 years or lymphatic involvement which were risk factors. However, the sample size of T1N3 gastric cancer is small, so larger sample size and risk factor analysis are required.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00423-021-02084-1.

Authors' contributions Writing - original draft preparation, Shusuke Yagi; writing - review and editing, Souya Nunobe. All authors read and approved the final manuscript.

Availability of data, material, and code All patients provided informed consents for the analysis.

Declarations

Ethics approval and consent to participate This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and was approved by the Institutional Review Boards (no. 2018-1005). All patients signed informed consents for the analysis

Consent for publication Patients signed informed consent regarding publishing their data.

Conflict of interest The authors declare no competing interests.

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