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ORIGINAL ARTICLE

Is surgery alone sufficient for treating T1 gastric cancer with extensive lymph node metastases?

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Abstract

Background Whether or not surgery alone is sufficient for treating patients with pathological stage T1N2M0 (Stage IIA), T1N3a/bM0 (Stage IIB/IIIB), and T3N0M0 (Stage IIA) gastric cancer who were not indicated for adjuvant treatment according to the Japanese gastric cancer treatment guideline remains unclear.

Methods We retrospectively reviewed the clinical records of 236 patients who had been diagnosed with pT1N2-3b/pT3N0 gastric cancer and undergone R0 gastrectomy with lymph node dissection between January 2000 and December 2012 at the National Cancer Center Hospital, Japan.

Results The 5-year recurrence-free survival (RFS) rates (95% confidence interval [CI]) of the patients with pathological (p) T1N2-3b and T3N0 cancer were 73.9% (63.1–84.7) and 89.5% (84.0–95.0), respectively. The only significant prognostic factors for the survival identified by a multivariate Cox regression analysis in patients with pT1N2-3 cancer were the pN stage (N3a/N2: hazard ratio [HR] 2.940, 95% CI 1.314–5.577; N3b/N2: HR 8.688, 95% CI 3.096–24.382) and tumor diameter ($<30/\geq 30$ mm) (HR 2.919; 95% CI 1.351–6.304). We divided the patients with pT1N2-3 gastric cancer into 3 risk categories (high, moderate, low) using these 2 significant prognostic factors and found that the 5-year RFS rates were significantly different among the 3 risk groups (low risk, 93.0%; moderate risk, 66.7%; high risk, 25.0%; $P<0.001$).

Conclusions pT3N0 and large pT1N2 with a diameter ≥ 30 mm had an excellent prognosis, while pT1N2-3 with at least N3a/b or a tumor diameter <30 mm showed a relatively poor prognosis. These patients may be candidates for adjuvant chemotherapy.

Keywords Gastric cancer · T1 tumor · Adjuvant chemotherapy

Introduction

A recent global estimate revealed that gastric cancer is the fifth-most common cancer worldwide, with 951,600 new cases reported in 2012 [1]. Patients with stage II or III gastric cancer often develop tumor recurrence, even after complete curative resection.

Adjuvant chemotherapy aims to eradicate micro-metastatic tumor cells. The optimal target of adjuvant chemotherapy is patients for whose prognosis is limited only by surgery alone and adjuvant chemotherapy is expected to be effective. According to the Japanese guideline [2], stage II/III disease, except for pT1N2-3b and pT3N0, are targets for adjuvant chemotherapy as a standard treatment after surgery, as established by the ACTS-GC phase III study [3].

pT1N2-3b and pT3N0 are excluded from the above indication based on the JCOG8801 phase III study comparing adjuvant chemotherapy with mitomycin and fluorouracil to surgery alone [4]. In that trial, adjuvant chemotherapy was considered "over treatment" for pT1N + or pT2-3N0, because the prognosis was excellent with surgery alone, because no additional survival benefit over surgery alone was expected with adjuvant chemotherapy. In that trial, however, the subgroups of pT1N + and pT2-3 were not examined. It, therefore, remains unclear whether or not pT1N2-3b and pT3N0 have a good prognosis with surgery alone.

Based on these previous findings, we explored the unfavorable subgroup with a poor prognosis who might

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be candidates for adjuvant chemotherapy among pT1N2-3b/pT3N0 for which surgery alone is a current standard treatment.

Materials and methods

Patients

We retrospectively reviewed the clinical records of 236 patients who had been diagnosed with pT1N2-3b/pT3N0 gastric cancer and had undergone R0 gastrectomy with lymph node dissection between January 2000 and December 2012 at the National Cancer Center Hospital, Japan. The patients were followed up until death or for 5 years, whichever came first. The flow diagram of the patients registered for this study is shown in Fig. 1.

Postoperative therapy and follow-up

Outpatient follow-up involved a physical examination and blood tests, including a tumor marker evaluation, every 3 months for the first 2 years postoperatively. Chest and abdominal computed tomography were performed every 6 months for the first 3 years and then annually until 5 years postoperatively.

Clinical and pathological factors

The 8th edition of the Union for International Cancer Control (UICC) tumor-node-metastasis classification of gastric carcinoma was used for the tumor staging [5]. We reviewed the following clinical and pathological factors: age, gender, tumor location, maximum tumor diameter, macroscopic type according to the Borrmann classification, histological type, pathological T factor, pathological N factor, pathological stage, and adjuvant chemotherapy (yes/no). The histopathological diagnosis was determined by experienced pathologists. Resected specimens were examined and diagnosed according to the Japanese Classification of Gastric Carcinoma 15th edition [6] and were classified into stages according to the UICC classification 8th edition.

Statistical analyses

All statistical analyses were performed using the SPSS statistical software program (ver. 24; SPSS Inc., Chicago, IL, USA). The Chi-squared test and Student's *t* test were used for the statistical analyses. The recurrence-free survival (RFS) was defined as the period between surgery and the occurrence of an event, any recurrence, or death, whichever came first. The data for the patients who did not experience an event were treated as censored cases on the date of the final observation. The RFS curves were calculated using the Kaplan–Meier method and compared by the log-rank test.

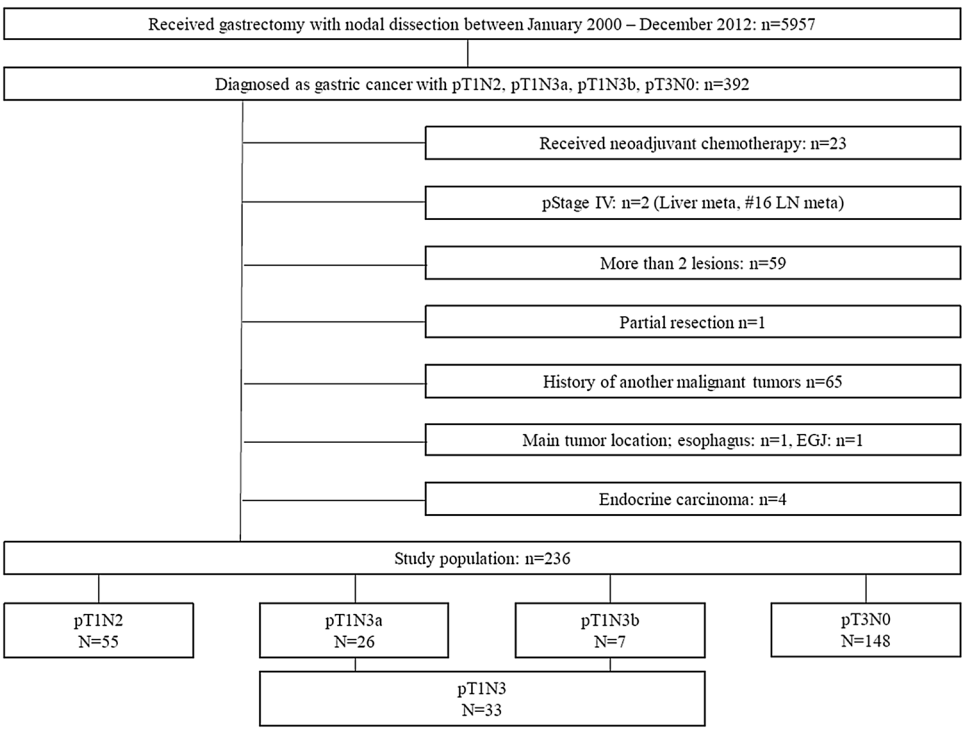

Fig. 1 Study flow for the 5957 patients who underwent gastrectomy for gastric cancer between January 2000 and December 2012

Cox's proportional hazard model was used to perform the univariate and multivariate analyses. A p value of 0.05 was defined as denoting statistical significance.

The study was conducted with the approval of the Institutional Review Board of the National Cancer Center (No. 2017-077).

Results

Background characteristics and pathological findings of the patients

The number of patients who underwent gastrectomy with nodal dissection during the study period was 5957, of which 392 were classified as having pT1N2-3b or T3N0 disease. Patients with remnant gastric cancer, postoperative confirmation of stage IV disease, a history of neoadjuvant chemotherapy, a history of partial resection, a history of other malignant disease, tumors located in the esophagus or esophagogastric junction, or tumors diagnosed as endocrine carcinoma were excluded. A total of 236 (T1N2, $n=55$; T1N3a, $n=26$; T1N3b, $n=7$; T3N0, $n=148$) patients met the eligibility criteria and were enrolled in this study. The median follow-up period was 86.0 months (range 1–191 months).

Table 1 shows the background characteristics and pathological findings of the patients with T1N2-3b and T3N0. The T1 tumor group had a high proportion of women and undifferentiated cancer; the proportion of women (39/88; 44.3%) was close to half, and the proportion of undifferentiated cancer (61/88; 69.3%) was more than twice that of differentiated cancers (27/88; 30.7%).

The prognosis

Recurrence was observed in 11 patients (7.4%) of the T3N0 group and 25 patients (28.4%) of the T1N2-3 group (T1N2, 9/55; T1N3a, 10/26; T1N3b, 6/7). The 5-year RFS rates (95% confidence interval [CI]) of the patients with stages T1N2-3 and T3N0 cancer were 73.9% (63.1–84.7) and 89.5% (84.0–95.0), respectively (Fig. 2a).

Analyses to identify the unfavorable subset in pT1N2-3

Because pT3N0 had an excellent prognosis with surgery alone, we tried to identify an unfavorable subset among pT1N2-3b cases. Each clinicopathological factor in patients with pT1N2-3b was categorized, as shown in Table 2, and both univariate and multivariate analyses identified pathological N stage (N3a/N2: hazard ratio [HR] 2.940, 95% CI 1.314–5.577; N3b/N2: HR 8.688, 95% CI 3.096–24.382) and tumor diameter (<30 vs. ≥30 mm) (HR 2.919, 95% CI

Table 1 Background characteristics and pathological findings of the patients: T1N2-3b and T3N0

Variables	pT1N2-3b $n=88$	pT3N0 $n=148$
Age		
<70	65	105
≥70	23	43
Gender		
Male	49	99
Female	39	49
Surgical procedures		
TG	12	45
DG	51	84
PG	3	7
PPG	22	12
Lymph node dissection		
D1+	81	57
D2	7	91
Site of tumor		
Upper third	8	44
Middle third	49	60
Lower third	31	44
Tumor diameter (mm)		
<30	18	24
≥30 to 50<	28	48
≥50	42	76
Macroscopic type		
0	87	62
I	1	5
II	0	49
III	0	27
IV	0	1
V	0	4
Histological type		
Differenteitated	27	64
Undifferentiated	61	84
UICC 8th		
Tumor invasion		
T1a (mucosa)	14	0
T1b (submucosa)	74	0
T3 (sub serosa)	0	148
Pathological N factor		
N0	0	148
N2	55	0
N3a	26	0
N3b	7	0
Lymphatic invasion		
ly0	28	86
ly1	38	56
ly2	21	5
ly3	1	1
Vascular invasion		

Table 1 (continued)

Variables	pT1N2-3b $n=88$	pT3N0 $n=148$
v0	73	98
v1	11	35
v2	4	9
v3	0	6
Adjuvant chemotherapy		
Yes	18	8
No	70	140

UICC Union for International Cancer Control, *TG* total gastrectomy, *DG* distal gastrectomy, *PG* proximal gastrectomy, *PPG* pylorus preserving gastrectomy

1.351–6.304) as significant prognostic factors. The 5-year RFS rate of the T1N2-3b cancer patients with a pathological tumor diameter < 30 mm was 44.4% (9.97–78.8), whereas that of the patients with a pathological tumor diameter ≥ 30 mm was 81.4% (71.1–91.7) ($P=0.006$; Fig. 2b). The significant difference in the RFS depending on the tumor size remained even after patients were stratified to T1N2 and T1N3a/b (Fig. 2c, d).

The RFS was then stratified using the N factor (1.0 points for N2, 2.9 points for N3a, and 8.7 points for N3b) and tumor diameter (1.0 points for ≥ 30 mm and 3.2 points for < 30 mm) according to the HR, as these had been calculated as significant independent factors in the multivariate analysis in the T1N2-3b group. The 5-year RFS was stratified to 6 sub-categories by the total score for the N factor and tumor diameter (Table 3). The prognosis was inversely correlated with the total score; however, the reliability of these sub-categories was limited due to the small number of patients included in several sub-categories (Table 3). We, therefore, combined several sub-categories and re-classified the risk category as follows: high risk (sub-categories of 6.1 points, 9.7 points and 11.8 points), moderate risk (sub-categories of 3.9 points and 4.2 points), and low risk (sub-category of 2.0 points). The 5-year RFS in the low-risk ($N=43$), moderate-risk ($N=33$), and high-risk ($N=12$) groups were 93.0% (85.4–100.0), 66.7% (50.6–82.8), and 25.0% (0.5–49.5), respectively ($P<0.001$) (Fig. 3).

Recurrence patterns

Among all T1N2-3b patients, 28.4% (25/88) developed recurrence. The most frequent site was bone ($n=8$, 9.1%) followed by lymph node ($n=7$, 8.0%) and peritoneum ($n=7$, 8.0%), liver ($n=4$, 4.5%), and lung ($n=1$, 1.1%). In contrast, 7.4% (11/148) of the T3N0 patients developed recurrence primarily at the liver in 5 (3.4%) followed by anastomotic site in 3 (2.0%), peritoneum in 2 (1.4%), and lymph node in 1 (0.7%). The moderate-to-high-risk group of T1 tumors showed a high rate of recurrences of 46.7% (21/45) predominantly to the distant organs in 26.7% (12/45), peritoneum in 13.3% (6/45), and lymph nodes in 8.9% (4/45).

Discussion

In the present study, we attempted to identify the unfavorable subset of pT1N2-3b/pT3N0 for which the current standard treatment is surgery alone. While pT3N0 had an excellent prognosis, there was some room for improvement with pT1N2-3b. In particular, patients who had at least N3a/b or tumors < 30 mm in diameter had a poor prognosis. These findings suggested that pT1N3a/b or small pT1N2 tumors may be candidates for adjuvant chemotherapy.

The present study showed that tumor size of < 30 mm had a poor prognosis in pT1N2-3b, which may be paradoxical considering the findings of the previous reports, wherein the prognosis was shown to be poorer with larger tumors [7, 8]. However, those previous reports examined cases of advanced cancer in which peritoneal recurrence was dominant. The exposed surface on the serosa is quite large, so peritoneal recurrence is frequent, as was reported previously. It is, therefore, unsurprising that large cancer more often shows a poor prognosis. However, the present cohort comprised T1 gastric cancer, which does not invade the peritoneal surface. Indeed, hematogenous recurrences were the most frequent pattern in this study. Aoyama et al. [9] previously reported that the 5-year RFS rate of pT1N2-3 gastric cancer patients with tumor diameters of < 30 mm was 60.0%, whereas that in those with tumor diameters of ≥ 30 mm was 88.9% ($P=0.0248$). However, the number of patients with T1N2-N3 disease was small ($n=28$) in that study, which makes the results less reliable than those obtained in the present study. A similar paradoxical survival relationship has been reported for a number of different cancers, such as breast, colon, prostate, and pancreatic cancers [10–13]. Wo et al. [10] examined breast cancer patients with ≥ 4 positive nodes and reported that T1a tumors (size ≤ 0.5 cm) showed a poorer prognosis than T1b tumors (size > 0.5 cm and ≤ 1.0 cm). Muralidhar et al. [11–13] analyzed colon, prostate, and pancreatic cancer patients with node-positive disease and found that small tumors had a poorer prognosis than large tumors. These similar findings across various carcinomas suggest that small tumors associated with lymph node metastasis represent more biologically aggressive cancers and acquire metastatic potential earlier than large tumors. In general, large tumor is well -known risk factor for lymph node metastasis, even in T1 tumors. Therefore, it must be an unusual situation when a tumor < 30 mm in diameter has multiple lymph node metastases. Considering these, T1N2-3b tumors with diameter < 30 mm have strong

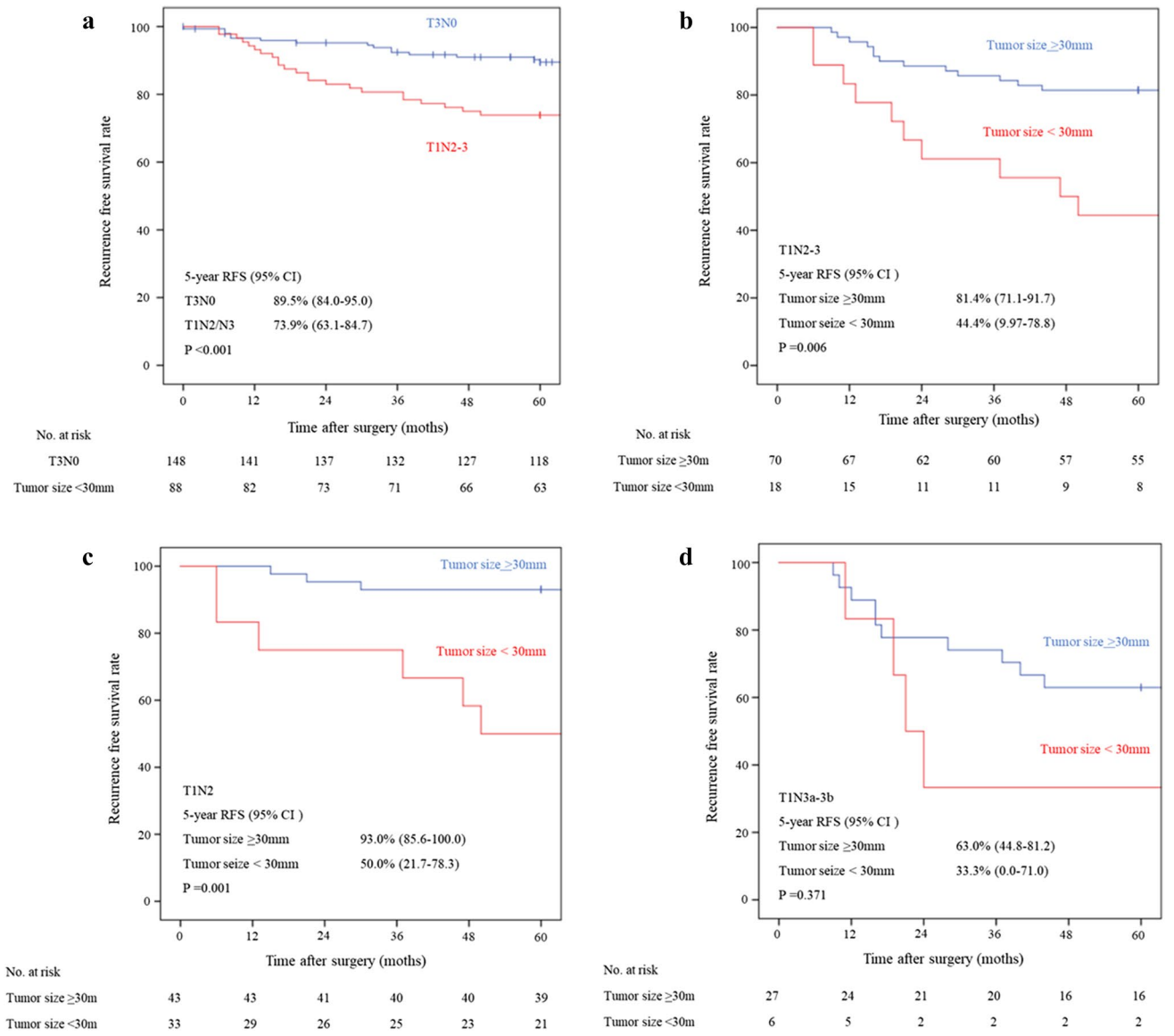

Fig. 2 **a** Recurrence-free survival curve for patients in the T3N0 group and T1N2-3 group ($P < 0.001$). **b** Recurrence-free survival curve for patients in the T1N2-3 group with tumor diameters of < 30 mm and ≥ 30 mm ($P = 0.006$). **c** Results of the subgroup analysis: Recurrence-free survival curve for patients in the T1N2 group with tumor diameters of < 30 mm and ≥ 30 mm ($P = 0.001$). **d** Results of the subgroup analysis: Recurrence-free survival curve for patients in the T1N3a/b group with tumor diameters of < 30 mm and ≥ 30 mm ($P = 0.371$)

malignant potential, because these tumors already have metastatic ability, even in the early phase.

Unsurprisingly, the N factor of N2 or N3a/b was identified as a prognostic factor by a multivariate analysis in the present study. This concept is consistent with the findings of a previous report. Sano et al. [14] reported in the International Gastric Cancer Association staging project that in gastric cancer, there was a significant difference in the survival between N3a and N3b. Notably, they observed this trend in the entire patient cohort as well as in each region. N3a and N3b were designated as separate groups in the stage grouping cluster analysis, and N3b retained a definite survival impact.

In the present study, T3N0 and low-risk T1N2-3 (large pT1N2 with diameter ≥ 30 mm) had an excellent prognosis that was comparable to that of Stage IA/IB disease, while the prognosis for the moderate-risk group (small pT1N2 < 30 mm or large pT1N3a ≥ 30 mm) was comparable to that of Stage II-IIIA disease, and that for the high-risk group (small pT1N3a < 30 mm or pT1N3b) was comparable to that of Stage IIIA–IV disease according to the JGCA nationwide registry [15]. These results strongly suggest that

Table 2 Univariate and multivariate Cox proportional hazards analyses of clinicopathological factors in the patients with T1N2-3b

Variables	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age						
< 70	1.000					
≥ 70	1.407	0.634–3.125	0.401			
Tumor diamter (mm)						
≥ 30	1.000			1.000		
< 30	2.790	1.293–6.023	0.009	3.187	1.460–6.957	0.006
Histological type						
Differentiated	1.000					
Undifferentiated	1.357	0.581–3.167	0.481			
Surgical approach						
PPG	1.000					
DG	0.847	0.342–2.101	0.721			
PG	1.005	0.123–8.195	0.996			
TG	1.444	0.458–4.553	0.531			
Lymph node dissection						
D1+	1.000					
D2	1.951	0.584–6.516	0.318			
UICC 7th						
Tumor invasion						
T1a (mucosa)	1.000					
T1b (submucosa)	1.369	0.475–3.948	0.561			
Pathological N factor						
N2	1.000			1.000		
N3a	2.910	1.301–6.510	0.009	2.940	1.314–6.577	0.009
N3b	7.405	2.683–20.435	< 0.001	8.688	3.096–24.382	< 0.001
Lymphatic invasion						
Negative	1.000					
Positive	0.933	0.436–1.995	0.858			
Vascular invasion						
Negative	1.000					
Positive	1.117	0.426–2.931	0.822			
Adjuvant chemotherapy						
No	1.000					
Yes	2.257	1.022–4.985	0.044			

UICC Union for International Cancer Control

Table 3 Relationship between total score of hazard ratio and 5-year recurrence-free survival rate

Tumor size (score)	N factor (score)	Total score (number of the patients)	5-year RFS (%)
30 < (1.0)	N2 (1.0)	2.0 (43)	93.0
30 < (1.0)	N3a (2.9)	3.9 (21)	76.2
< 30 (3.2)	N2 (1.0)	4.2 (12)	50.0
< 30 (3.2)	N3a (2.9)	6.1 (5)	40.0
30 < (1.0)	N3b (8.7)	9.7 (6)	16.7
< 30 (3.2)	N3b (8.7)	11.9 (1)	0.0

RFS recurrence-free survival

surgery alone is sufficient for T3N0 and low-risk T1N2-3, but adjuvant chemotherapy should be considered for moderate- and high-risk T1N2-3.

Several limitations associated with the present study warrant mention. First, this was a retrospective single-center study, and the number of patients was relatively small. In particular, only seven cases of N3b were included. The reliability of the prognostic value on N3b, therefore, seems limited. Second, the optimal cutoff value was unknown. We looked for the optimal cutoff value by cutting the tumor size at 10, 20, 30, or 40 mm referring *p* value for the survival difference and found that *p* value became significant only when the tumor size was cut at 30 mm.

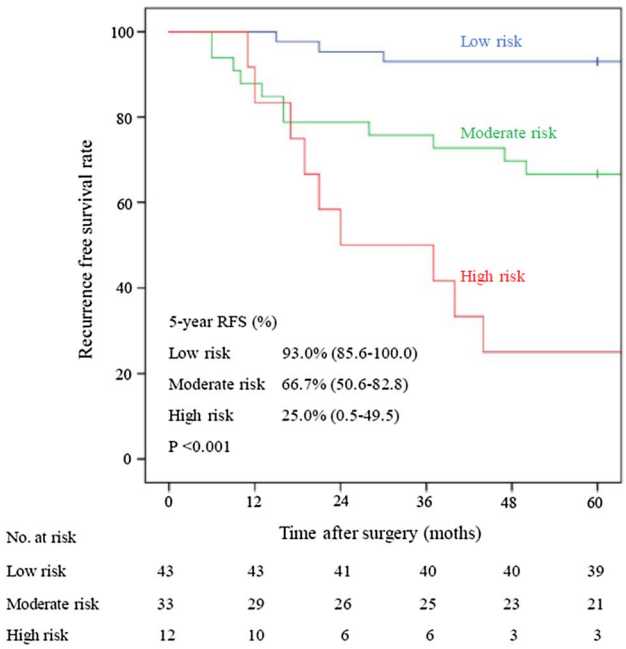

Fig. 3 Recurrence-free survival curve for patients in the T1N2-3 group with low-risk, moderate-risk, and high-risk diseases ($P < 0.001$)

In conclusion, pT3N0 and large pT1N2 with a diameter ≥ 30 mm had an excellent prognosis, while pT1N2-3 with at least N3a/b or a tumor diameter < 30 mm showed a relatively poor prognosis. These patients may be candidates for adjuvant chemotherapy.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interests to declare in relation to this article. This study was conducted with the approval of the National Cancer Center Hospital Ethics Committee (No: 2017-077).

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359–E386. https://doi.org/10.1002/ijc.29210 **(Epub 2014/09/16; PubMed PMID: 25220842)**.
2. Japanese Gastric Cancer A. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer. 2017;20(1):1–19. https://doi.org/10.1007/s10120-016-0622-4. **(Epub 2016/06/28; PubMed PMID: 27342689; PubMed Central PMCID: PMCPMC5215069)**.
3. Shinichi Sakuramoto Mitsuru Sasako, Toshiharu Yamaguchi, Taira Kinoshita, Masashi Fujii, Atsushi Nashimoto, Hiroshi Furukawa, Toshifusa Nakajima, Yasuo Ohashi, Hiroshi Imamura, Masayuki Higashino, Yoshitaka Yamamura, Akira Kurita, Kuniyoshi Arai, for the ACTS-GC Group. Adjuvant Chemotherapy for Gastric Cancer with S-1, an Oral Fluoropyrimidine. N Engl J Med. 2007;357:1810–20.
4. Nakajima T, Nashimoto A, Kitamura M, Kito T, Iwanaga T, Okabayashi K, et al. Adjuvant mitomycin and fluorouracil followed by oral uracil plus tegafur in serosa-negative gastric cancer: a randomised trial. Lancet. 1999;354(9175):273–7. https://doi.org/10.1016/s0140-6736(99)01048-x.
5. UfIC Control. TNM classification of Malignant Tumors. 8th ed. New York: Wiley; 2017.
6. Association JGC. Japanese classification of gastric carcinoma. 15th ed. Tokyo: Kanehara Publisher; 2017.
7. Saito H, Osaki T, Murakami D, Sakamoto T, Kanaji S, Oro S, et al. Macroscopic tumor size as a simple prognostic indicator in patients with gastric cancer. Am J Surg. 2006;192(3):296–300. https://doi.org/10.1016/j.amjsurg.2006.03.004 **(Epub 2006/08/22; PubMed PMID: 16920421)**
8. Liu X, Xu Y, Long Z, Zhu H, Wang Y. Prognostic significance of tumor size in T3 gastric cancer. Ann Surg Oncol. 2009;16(7):1875–82. https://doi.org/10.1245/s10434-009-0449-x **(Epub 2009/04/18; PubMed PMID: 19373514)**
9. Aoyama T, Yoshikawa T, Fujikawa H, Hayashi T, Ogata T, Cho H, et al. Exploratory analysis to find unfavorable subset of stage II gastric cancer for which surgery alone is the standard treatment; another target for adjuvant chemotherapy. Int Surg. 2014;99(6):835–41. https://doi.org/10.9738/INTSURG-D-13-00176.1**(Epub 2014/12/02; PubMed PMID: 25437596; PubMed Central PMCID: PMCPMC4254249)**.
10. Wo JY, Chen K, Neville BA, Lin NU, Punglia RS. Effect of very small tumor size on cancer-specific mortality in node-positive breast cancer. J Clin Oncol. 2011;29(19):2619–27. https://doi.org/10.1200/JCO.2010.29.5907**(Epub 2011/05/25; PubMed PMID: 21606424; PubMed Central PMCID: PMCPMC3139369)**.
11. Vinayak M, Ryan DN, David PR, Theodore SH, Paul LN, Jennifer YW. Association between very small tumor size and increased cancer-specific mortality in node-positive colon cancer. Dis Colon Rectum. 2016;59(3):187–93.
12. Muralidhar V, Mahal BA, Nezolosky MD, Beard CJ, Feng FY, Martin NE, et al. Association between very small tumour size and increased cancer-specific mortality after radical prostatectomy in lymph node-positive prostate cancer. BJU Int. 2016;118(2):279–85. https://doi.org/10.1111/bju.13248**(Epub 2015/08/04; PubMed PMID: 26235660)**.
13. Muralidhar V, Nipp RD, Mamon HJ, Punglia RS, Hong TS, Ferrone C, et al. Association between very small tumor size and decreased overall survival in node-positive pancreatic cancer. Ann Surg Oncol. 2018. https://doi.org/10.1245/s10434-018-6832-8**(Epub 2018/10/10; PubMed PMID: 30298331)**.
14. Sano T, Coit DG, Kim HH, Roviello F, Kassab P, Wittekind C, et al. Proposal of a new stage grouping of gastric cancer for TNM classification: International Gastric Cancer Association staging project. Gastric Cancer. 2017;20(2):217–25. https://doi.org/10.1007/s10120-016-0601-9**(Epub 2016/02/22; PubMed PMID: 26897166; PubMed Central PMCID: PMCPMC4992472)**.
15. Nashimoto A, Akazawa K, Isobe Y, Miyashiro I, Katai H, Kodera Y, et al. Gastric cancer treated in 2002 in Japan: 2009 annual report of the JGCA nationwide registry. Gastric Cancer. 2013;16(1):1–27. https://doi.org/10.1007/s10120-012-0163-4 **(Epub 2012/06/26; PubMed PMID: 22729699; PubMed Central PMCID: PMCPMC3549249)**.