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ORIGINAL ARTICLE

Is Subdivision of pT2 Tumors Superior to Lymph Node Metastasis for Predicting Survival of Patients with Gastric Cancer? Review of 224 Patients from Four Centers

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Abstract

Background The prognostic significance of the subclassification of pT2 tumors and the association of these categories with other clinicopathological factors in gastric cancer patients were investigated.

Methods A total of 224 patients with pT2 gastric cancer who had undergone curative gastrectomy and lymph node dissection were retrospectively analyzed. The prognostic role of the subclassification of pT2 tumors was evaluated by univariate and multivariate analysis.

Results Of 224 patients, 75 (33.5%) were classified as having pT2a tumors and 149 (66.5%) as having pT2b tumors. The prevalence of large-sized tumors ($P < 0.003$), lymph node involvement ($P < 0.018$), and lymphatic ($P = 0.016$), blood vessel ($P = 0.001$), and perineural invasion ($P = 0.001$) was significantly higher for pT2b tumors than for pT2a tumors. The rate of recurrence for pT2a cancers was significantly lower than that for pT2b cancers ($P = 0.001$).Median overall survival (OS) times and three-year OS of patients with a pT2b tumor were significantly worse than for patients with a pT2a tumor ($P < 0.001$).When patients were analyzed according to lymph node involvement, the prognosis of patients with $pT2aN_1$ cancers was significantly better than that of patients with $pT2bN_1$ ($P < 0.001$). Multivariate analysis indicated that the pT2 subdivision was an independent prognostic factor for OS ($P = 0.006$), as were pN stage, clinical stage, and recurrence.

Conclusion Our results showed that subclassification of pT2 tumors into pT2a or pT2b was an important prognostic indicator for patients with pT2 gastric cancers who underwent curative gastrectomy. In the TNM staging system, subdivision of pT2 tumors should be undertaken routinely to detect gastric cancer patients who have a poor

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prognosis and to define patients more accurately in terms of their mortality after curative resection in accordance with the new 2010 AJCC TNM staging classification. This may also help as a guide to more appropriate therapy for tumors with subserosal invasion (old pT2b or new pT3).

Keywords Gastric cancer · pT2 subcassification · Lymph node metastasis · Prognosis

Introduction

Despite the improved prognosis for gastric cancer as a result of early diagnosis, radical operations, and the development of adjuvant therapy, it is still the second most common cause of cancer-related deaths worldwide [1, 2]. Identification of prognostic factors in patients with gastric cancer is essential for predicting outcome and for identifying optimum therapeutic strategies. In many studies the number of metastatic lymph nodes (pN stage) and the depth of the primary tumor (pT stage) have been indicated as the most reliable prognostic factors for patients with radically resected gastric cancer [3, 4]. Recently, new prognostic indicators have been documented as a result of advances in molecular and histochemical studies [5].

Advanced gastric cancer is defined when the tumor invades the muscularis propria or subserosa; this is classified as pT2 [6]. pT2 tumors make up 10–38% of all gastric cancers, although pT1 and pT3 tumors are the most frequent categories in gastric cancer patients who have had curative gastrectomy [3, 7]. pT2 tumors are thought of as an intermediate stage of prognosis between early and serosal gastric cancer. The 2002 American Joint Committee on Cancer (AJCC) TNM staging system subclassified pT2 gastric cancer into type pT2a (invasion of the muscularis propria) and type pT2b (invasion of the subserosa) [6]. Although few reports have supported the prognostic significance of pT2 subclassification [7–10], a consensus has not been reached on its clinical importance. Lymph node metastasis [7–9, 11], and the rate of recurrence and mortality [7, 9] have been found to be significantly lower for pT2a tumors than for pT2b tumors. Moreover, although the rate of occurrence of the pN1 stage was similar, that of pN2 and pN3 was higher in pT2b tumors than in pT2a tumors [7]. Nevertheless, in 2010, the AJCC TNM staging system was modified and the old pT2b tumors were renamed pT3 [12].

In this study, we investigated the value of the subclassification of pT2 tumors, compared with the pN stage, as a prognostic factor for patients with gastric carcinoma who had undergone a radical gastrectomy. Furthermore, correlation of the subdivision of the pT2 category with the other clinicopathological factors and the effect of this subclassification on survival were also evaluated.

Patients and Methods

This study included a total of 224 patients with pT2 gastric cancer who had undergone radical resection with a lymph node dissection at the Dr Lutfi Kirdar Kartal Education and Research Hospital, the Marmara University Medical Faculty, the Haydarpasa Numune Education and Research Hospital, and the Kocaeli University Medical Faculty between 1998 and 2009. Patients in the pT2 category were subclassified as type pT2a (involving muscularis propria) or type pT2b (involving subserosa) and further classifications according to the 1997 UICC TNM staging classification for gastric cancer [6] were made for lymph node involvement (N_0, no metastasis; N_1, 1 to 6 metastatic lymph nodes; N_2, 7 to 15 metastatic lymph nodes; N_3, $>$ 15 metastatic lymph nodes) and for distant metastasis, stage grouping, and tumor grade. The clinicopathological findings were determined according to the Japanese Classification of Gastric Carcinoma (JCGC) [13]. All pathological slides were re-evaluated to confirm the depth of invasion and nodal status by a pathologist (DY, with 15 years of experience in gastrointestinal pathology) who was an expert in matters of gastric cancer.

The eligibility criteria consisted of a histologically confirmed R_0 gastric resection, which was defined as no macroscopic or microscopic residual tumor and a postoperative survival expectancy longer than three months. Patients with distant metastases and peritoneal metastases at diagnosis were excluded from the study. The following patient characteristics were obtained from patients' charts after written informed consent had been obtained from patients or their relatives: age, gender, resection type, tumor location, histopathology, tumor stage, tumor size, histological grade, lymph node involvement, depth of tumor invasion, lymphatic vessel and blood vessel invasion, resection margins, Borrmann classification, Lauren classification, adjuvant chemotherapy and radiation therapy type, responses to treatment, and survival. The Local Ethics Committee of our hospital approved the study.

The metastatic lymph node ratio (MLR) was also analyzed in this study. It was defined as the ratio of metastatic lymph nodes to the total number of dissected lymph nodes and was determined by the best cutoff approach in terms of the log-rank statistics: MLR 0, 0%; MLR 1, 1–9%; MLR 2, 10–25%, and MLR 3, >25%.

A total of 150 patients (67%) with lymph node metastasis received adjuvant chemoradiotherapy (CRT) with 5-fluorouracil 425 mg/m^2 per day, plus leucovorin 20 mg/m^2 per day, for five days, followed by 4500 cGy of

radiation at 180 cGy per day, given five days per week for five weeks, with modified doses of fluorouracil and leucovorin on the first four and the last three days of radiotherapy, within four weeks after surgery. Ten patients (6.2%) with pN(+) did not receive adjuvant CRT, either because of refusal or poor ECOG performance status. Adjuvant chemoradiotherapy was not given to the 64 of the 224 patients (29%) without lymph node metastasis.

Statistical Analysis

All data were analyzed using SPSS 17.0 software (SPSS, Chicago, IL, USA). The clinicopathological factors of pT2a and pT2b tumors were compared by use of the chi-squared test and Fisher's exact test. Survival analysis and curves were established according to the Kaplan–Meier method and compared by the log-rank test. Disease-free survival (DFS) was defined as the time from curative surgery to disease progression or recurrence, or to the date of death or loss of follow-up. Overall survival (OS) was described as the time from diagnosis to the date of the patient's death or loss of follow-up. Univariate and multivariate analyses to assess the significance of pT2 subdivision and other clinicopathological features as prognostic factors were performed by use of the Cox proportional hazards model. Multivariate P values were used to characterize the independence of these factors. The 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. All P values were two-sided in tests and P values less than 0.05 were considered to be statistically significant.

Results

Eighty-three patients (37%) were female and 141 (63%) were male, with a median age of 58.5 years (range 28–82 years). One hundred and twenty-six patients were aged 60 years or younger (56.3%). Of the study group, 75 patients (33.5%) had pT2a tumors and 149 (66.5%) had pT2b tumors. Postoperatively, 63 patients (28%) were classified as stage I, 94 (42%) as stage II, 51 (23%) as stage III, and 16 (7%) as stage IV. Most of the patients ($n = 106$, 47%) had moderately differentiated tumors. The median number of dissected and metastatic lymph nodes was 21 (range 15–73) and 4 (range 0–33), respectively. The primary tumor location was in the upper third of the stomach in 47 patients (21%), in the middle third in 78 (34%), and in the lower third in 95 (43%); in four patients (2%) the tumor involved the stomach diffusely. On the basis of number of lymph node metastases, 64 patients (29%) were classified as pNo, 97 (43%) as pN_1, 47 (21%) as pN_2, and 16 (7%) as pN_3. Furthermore, 64 patients (29%) were classified as MLR 0, 35 (15%) as MLR 1, 49 (22%) as MLR 2, and 76 (34%) as MLR 3 according to the MLR classification.

Significant differences were detected between pT2a and pT2b tumors in respect of age, tumor size, clinical stage, pN stage, MLR, Lauren classification, blood vessel and lymphatic vessel invasion, perineural invasion, and the presence of recurrence. The prevalence of large-sized tumors ($P < 0.001$) and lymph node involvement ($P < 0.001$), and the presence of blood vessel ($P = 0.001$), lymphatic vessel ($P = 0.016$), and perineural ($P = 0.038$) invasion was significantly higher for pT2b than for pT2a tumors. Patients who were older than 60 years frequently had a T2b tumor ($P = 0.03$) and the prevalence of diffuse and mixed histological types was commonly seen in patients with pT2b compared with pT2a cancers ($P = 0.002$). The relationship between subgroups of pT2 tumors and clinicopathological factors is summarized in Table 1.

At the median follow-up of 26 months (range 6.5–128 months), the three-year OS rate and the median OS interval were 60.6% and 67.2 months, respectively. The median OS time and three-year OS rate for patients with pT2a tumors were better than those for patients with pT2b tumors (117 months and 89% vs. 33.2 months and 46.2%, respectively; $P < 0.001$; Fig. 1). In the univariate analysis for all patients, age, pT2 category, pN stage, MLR, clinical stage, blood vessel invasion, perineural invasion, and the presence of recurrence were significant prognostic factors. For patients with a pT2a tumor, the univariate analysis indicated that surgery type ($P = 0.04$), blood vessel invasion ($P = 0.007$), and the presence of recurrence were important prognostic indicators (Table 2). On the other hand, when the univariate analysis was carried out for patients with a pT2b tumor, lymph node metastasis, MLR, clinical stage, blood vessel invasion, and recurrence were found to be important prognostic factors. Table 3 shows the findings of univariate analysis for patients with pT2b cancer.

When patients were analyzed according to lymph node involvement, the prognosis of patients with pT2aN0 cancers was better than that for patients with T2bN0 tumors (three-year OS; 90% vs. 77%; $P = 0.04$; Fig. 2). Moreover, the three-year OS rate and the median OS time of patients with pT2bN1 were significantly worse than those of patients with pT2aN1 (90.8% vs. 48.7% and not reached vs. 33.7 months; $P < 0.001$; Fig. 3). Because there were so few patients with pT2aN2 or N3 tumors, survival analysis could not be performed with regard to N2 or N3 tumors.

A multivariate analysis with the Cox proportional hazards model was performed in order to further evaluate all of the significant prognostic factors that were found in the univariate analysis for patients with a pT2 gastric cancer.

Table 1 Relationship between subgroups of pT2 tumor and clinicopathological factors in patients who had curative gastrectomy

Factor	T2a (*n* (%))	T2b (*n* (%))	*P* values
All patients	75 (33.5)	149 (66.5)	
Gender			0.88
Male	48 (64)	93 (62.4)	
Female	27 (36)	56 (37.6)	
Age (year)			0.03
≤ 60	50 (66.7)	76 (51)	
> 60	25 (33.3)	73 (49)	
Tumor site			0.43
Upper	12 (16)	35 (23.5)	
Middle	25 (33.3)	53 (35.6)	
Lower	36 (48)	59 (39.6)	
Diffuse	2 (2.7)	2 (1.3)	
Surgery type			0.17
Proximal	12 (16)	21 (14)	
Distal	36 (48)	55 (37)	
Total	27 (36)	73 (49)	
Tumor size			<0.001
≤ 3 cm	30 (40)	22 (15)	
≤ 6 cm	30 (40)	66 (44)	
> 6 cm	15 (20)	61 (41)	
Tumor differentiation			0.08
Well differentiated	9 (12)	7 (5)	
Moderately differentiated	37 (49)	69 (46)	
Poorly differentiated	29 (39)	73 (49)	
Borrmann classification			0.22
Type I	5 (6.8)	14 (9.4)	
Type II	34 (45.3)	73 (48.9)	
Type III	28 (37.3)	54 (36.2)	
Type IV	8 (10.6)	8 (5.5)	
Lauren classification			0.002
Intestinal	52 (69.3)	70 (47)	
Diffuse	18 (24)	61 (41)	
Mixed	5 (6.7)	18 (12)	
pN stage			<0.001
N0	32 (42.7)	32 (22)	
N1	37 (49.3)	60 (40)	
N2	3 (4)	44 (30)	
N3	3 (4)	13 (8)	
MLR			<0.001
0	32 (42.7)	32 (21.5)	
1	13 (17.3)	22 (14.8)	
2	18 (24)	31 (20.8)	
3	12 (16)	64 (43)	
Clinical stage			<0.001
I	32 (42.7)	31 (21)	
II	35 (46.7)	59 (40)	
III	5 (6.6)	46 (31)	
IV	3 (4)	13 (8)	
Lymphatic vessel invasion			0.016
Absence	37 (49)	48 (30.4)	
Presence	38 (51)	101 (69.6)	
Blood vessel invasion			0.001
Absence	41 (54.6)	47 (31.5)	
Presence	34 (45.4)	102 (68.5)	
Perineural invasion			0.038
Absence	43 (56)	48 (30.4)	
Presence	32 (44)	101 (69.6)	
Recurrence			0.001
Absence	62 (82.7)	90 (60)	
Presence	13 (17.3)	59 (40)	

MLR, metastatic lymph node ratio

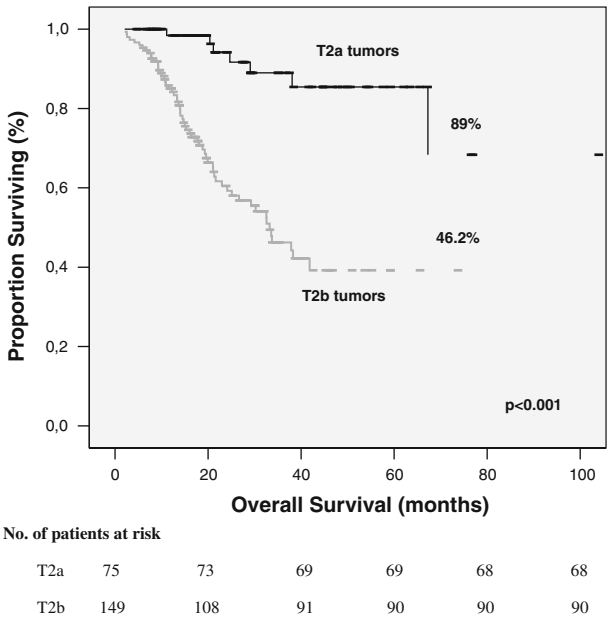


Fig. 1 Three-year overall survival curves of patients with pT2b (median 33.2 months) were significantly worse than those of patients with pT2b (median 117 months)

This showed that the subclassification of the pT2 stage was an independent prognostic factor ($P = 0.006$, HR: 4.87 for T2b vs. T2a; 95% CI: 1.56–15.1), as were pN stage, clinical stage and the presence of a recurrence (Table 4). Thereafter, the multivariate analysis was carried out on the basis of the pT2 subdivision, and this showed that recurrence was the only independent prognostic indicator in pT2a gastric cancers (X^2: 32.7, $P < 0.001$, HR: 17.52; 95% CI: 7.04–43.59). However, for patients with a pT2b tumor, pN stage, clinical stage, and recurrence were found to be independent prognostic indicators in multivariate analysis.

Table 2 Univariate analysis of patients with pT2a gastric tumor for overall survival (OS) according to clinicopathological factors

Factor	Three-year OS rate (%)	Log rank (χ^2 value)	*P* values
Gender		1.27	0.26
Male	83.7		
Female	100		
Age (year)		0.45	0.50
≤ 60	87.7		
> 60	93.3		
Tumor size		2.70	0.25
≤ 3 cm	100		
≤ 6 cm	89.9		
> 6 cm	70		
Tumor site		4.86	0.18
Upper	NA		
Middle	94.7		
Lower	91		
Diffuse	NA		
Surgery type	NA	5.29	0.04
Proximal	95.5		
Distal	87.5		
Total			
Tumor differentiation		1.40	0.49
Well differentiated	NA		
Moderately differentiated	91.5		
Poorly differentiated	83.1		
Borrmann classification		0.78	0.85
Type I	NA		
Type II	86.3		
Type III	89.8		
Type IV	NA		
Lauren classification		1.36	0.24
Intestinal	90.2		
Diffuse	81.8		
Mixed	NA		
pN stage		3.82	0.28
N0	90		
N1	90.8		
N2	NA		
N3	NA		
MLR		2.41	0.49
0	90		
1	NA		
2	90.9		
3	87.5		
Clinical stage		1.46	0.69
I	90		
II	90.3		
III	NA		
IV	NA		
Lymphatic vessel invasion		0.69	0.40
Absence	87		
Presence	87.4		
Blood vessel invasion		7.39	0.007
Absence	100		
Presence	75.8		
Perineural invasion		0.05	0.94
Absence	91.7		
Presence	87.5		
Recurrence		20.1	<0.001
Absence	97.3		
Presence	58.9		

MLR, metastatic lymph node ratio; NA, not applicable

Log rank test—a test for comparing two (or more) sets of survival times. The data consist of the completed lifetimes of individuals who have died and the current ages of those still living

The results of the multivariate analysis are listed for the pT2 subgroups in Tables 5 and 6.

Recurrent disease was detected in 72 (32.1%) of the patients. The rate of recurrence for patients with T2a cancers was significantly lower than for patients with T2b cancer (18% vs. 82%, $P = 0.001$). The most frequently relapsing sites were the liver and peritoneum (30.4% and 21.4%, respectively). After recurrent disease was detected, 55 of 72 patients (76.3%) were treated with second-line chemotherapy whereas 16 patients (22.2%) were treated with best supportive care alone. In addition, re-operation was performed for one patient (1.5%) with a local recurrence.

Discussion

In this study, the prevalence of large-sized tumors, lymph node involvement, and lymphatic, blood vessel, and perineural invasion was significantly lower in patients with pT2a tumors than in those with pT2b tumors. In addition, the rate of recurrence for patients with T2b cancer was significantly higher than that for patients with T2b cancer. Using multivariate analysis, we found that the subdivision of pT2 tumors was an independent prognostic factor for patients with stage pT2 gastric cancer who had undergone radical surgery, and this was in addition to the already known important clinicopathological prognostic indicators such as pN stage, clinical stage, and the presence of recurrence. The only independent prognostic factors that were found were the presence of recurrence in patients with pT2a tumors and pN stage, the clinical stage and the

Table 3 Univariate analysis of patients with pT2b gastric tumor for overall survival (OS) according to clinicopathological factors

Factor	Three-year OS rate (%)	Log rank (χ^2 value)	*P* values
Gender		0.11	0.73
Male	45.1		
Female	48.1		
Age (year)		3.01	0.08
≤ 60	55.7		
> 60	36.8		
Tumor size		1.04	0.59
≤ 3 cm	NA		
≤ 6 cm	41.6		
> 6 cm	50.9		
Tumor site		2.18	0.53
Upper	49		
Middle	42.3		
Lower	51.3		
Diffuse	NA		
Surgery type		0.79	0.62
Proximal	33.8		
Distal	53.9		
Total	46.2		
Tumor differentiation		1.32	0.51
Well differentiated	NA		
Moderately differentiated	50.8		
Poorly differentiated	40.8		
Borrmann classification		2.66	0.44
Type I	NA		
Type II	43.5		
Type III	57		
Type IV	NA		
Lauren classification		0.08	0.92
Intestinal	46		
Diffuse	52.6		
Mixed	NA		
pN stage		9.73	0.02
N0	77.1		
N1	48.7		
N2	31.4		
N3	NA		
MLR		13.89	0.003
0	77.1		
1	NA		
2	50.1		
3	27.3		
Clinical stage		13.67	0.003
I	84		
II	48.4		
III	28.3		
IV	NA		
Lymphatic vessel invasion		1.93	0.16
Absence	52.7		
Presence	41.7		
Blood vessel invasion		6.45	0.01
Absence	65.9		
Presence	40.9		
Perineural invasion		1.68	0.19
Absence	49.8		
Presence	44.8		
Recurrence		89	<0.001
Absence	88		
Presence	11.5		

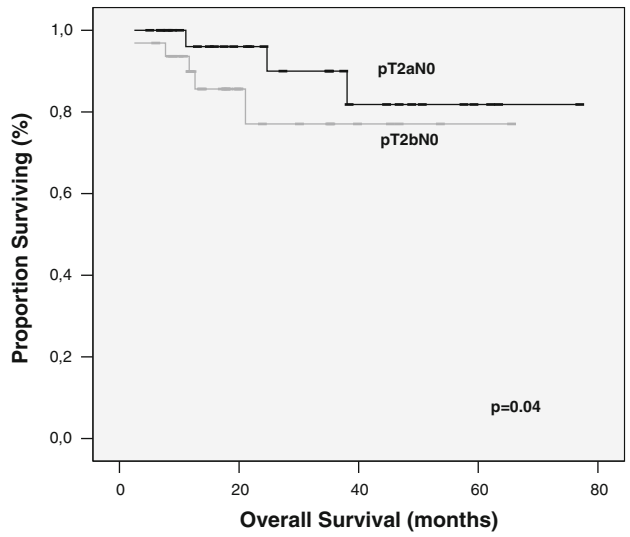
MLR, metastatic lymph node ratio; NA, not applicable

Log rank test—a test for comparing two (or more) sets of survival times. The data consist of the completed lifetimes of individuals who have died and the current ages of those still living

presence of recurrence in pT2b cancers. Moreover, when data were analyzed according to lymph node involvement, the prognosis for patients with both pT2aN0 and pT2aN1 was significantly better than that for patients with both pT2bN0 and pT2bN1.

The determination of prognostic factors for patients with gastric cancer is essential for predicting outcome and for identifying appropriate treatment strategies. It is generally accepted that the depth of tumor invasion and lymph node metastasis are the most important prognostic indicators [3, 4]. In 2002, the AJCC further divided pT2 gastric adenocarcinomas into types pT2a and pT2b because of the significantly different survival rates [6]. Sarele et al. [7] indicated that the prevalence of nodal metastasis was significantly lower with pT2a than with pT2b and that five-year survival was significantly greater for patients with pT2a tumors than for those with pT2b tumors. However, the prognostic importance of the pT2 category could not be proved by multivariate analysis. In a large study performed by Park et al. [9] that included 1,118 patients with more than 15 lymph nodes dissected, there was a significant five-year survival advantage for patients with pT2a tumors compared with pT2b patients. In a retrospective large trial, Lu et al. [14] reported significantly higher disease-specific survival for those with pT2a tumors than for those with pT2b tumors, and that prognosis was significantly better for patients with pT2a cancers for those with pT2b cancers at the pN0, pN1, and pN2, but not pN3 stages. Moreover, the authors found that age, tumor location, pT stage, and pN stage were correlated with prognosis in their multivariate analysis.

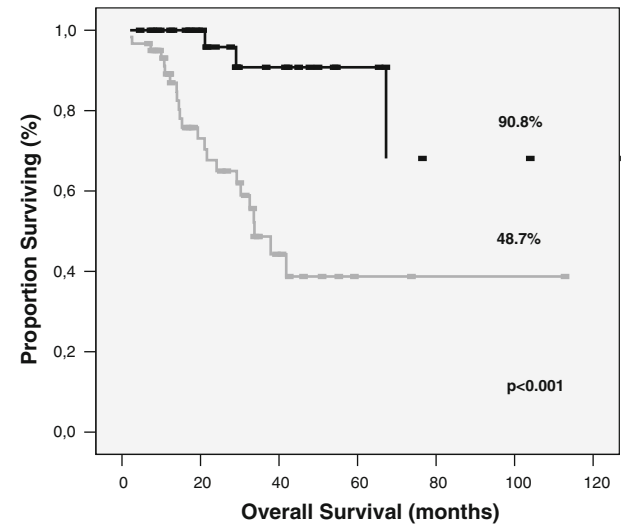
In contrast with the reports mentioned above, Fotia et al. [15] indicated that there was no significant survival



No. of patients at risk

T2aN0	32	31	29	29	29
T2bN0	32	28	27	27	27

Fig. 2 Overall survival curves are shown for pT2a or pT2b gastric cancer patients without lymph node metastasis



No. of patients at risk

T2aN1	37	37	35	35	34	34	34
T2bN1	60	47	38	37	37	37	37

Fig. 3 Comparison of overall survival for pT2aN1 and pT2bN1 patients

advantage for patients with pT2a compared with pT2b gastric cancer. In addition, although Isozaki et al. [11] found a significant survival difference between the pT2 tumor subcategories, the prognostic importance of this category could not be confirmed by multivariate analysis. In a recent study of 192 pT2 gastric cancer patients by Nitti et al. [10], the five-year OS rate was better for patients with pT2a tumors than that for pT2b patients. By multivariate analysis the authors confirmed that the pT stage was an

Table 4 Multivariate analysis of the prognostic factors in all patients with pT2 gastric cancer

Factor	Wald	*P*	HR	95% CI
Age (years)		0.08		
≤ 60	2.97		0.60	0.19–1.10
> 60	2.52		0.47	0.32–1.12
pN stage		0.02		
N0	4.79		0.12	0.02–0.80
N1	4.21		0.12	0.01–1.00
N2	3.82		0.34	0.14–1.13
N3	2.97		0.40	0.21–1.19
T2 subclassification		0.006		
T2a	6.56		0.24	0.08–0.72
T2b	7.45		4.87	1.56–15.1
MLR		0.20		
0	1.63		3.35	0.34–4.12
1	0.03		1.31	
2	0.46		0.68	
3	0.24		1.22	
Clinical stage		0.002		
I	9.59		17.73	2.87–35.1
II	2.09		0.13	0.09–2.04
III	0.65		2.03	0.36–11.4
IV	0.71		1.22	0.22–2.01
Blood vessel invasion		0.68		
Absence	0.16		0.77	0.21–2.77
Presence	1.75		1.75	0.76–4.03
Perineural invasion		0.25		
Absence	1.30		0.54	0.19–1.53
Presence	2.38		1.66	0.87–3.19
Recurrence		<0.001		
Absence	48.5		45.47	15.53–133.1
Presence	51.5		1.33	1.01–3.42

HR, hazards ratio; CI, confidence interval; MLR, metastatic lymph node ratio

Table 5 Multivariate analysis of the prognostic factors in patients with T2a gastric cancer

Factor	Wald	*P*	HR	95% CI
pN stage	0.28	0.59	1.50	0.33–6.76
Surgery type	0.04	0.82	0.79	0.09–6.61
Blood vessel invasion	0.05	0.94	0.21	0.07–1.17
Recurrence	5.21	0.02	0.71	0.07–1.32

HR, hazards ratio; CI, confidence interval

Table 6 Multivariate analysis of the prognostic factors in patients with T2b gastric cancer

Factor	Wald	*P*	HR	95% CI
pN stage	5.20	0.02	0.39	0.02–0.69
MLR	0.21	0.64	1.13	0.67–1.91
Clinical stage	9.28	0.002	12.81	4.38–20.11
Blood vessel invasion	0.05	0.94	1.03	0.38–2.76
Recurrence	32.7	<0.001	17.52	7.04–43.59

HR, hazards ratio; CI, confidence interval; MLR, metastatic lymph node ratio

independent prognostic factor. In our study we found there was a statistically significant difference with regard to OS between patients with pT2a and those with pT2b tumors. The median OS time and three-year OS rate of patients with pT2a cancer (117 months and 89%, respectively) were better than those of patients with pT2b cancer (33.2 months and 46.2%, respectively, $P < 0.001$). In addition, univariate analysis showed that age, pT2 category, pN stage, MLR, clinical stage, blood vessel invasion, perineural invasion, and the presence of recurrence were significant prognostic factors for all patients. For patients with pT2a tumors, univariate analysis indicated that surgery type, blood vessel invasion, and the presence of recurrence were important prognostic indicators. However, when univariate analysis was performed for patients with pT2b tumors, lymph node metastasis, MLR, clinical stage, blood vessel invasion, and recurrence were found to be important prognostic factors.

Sarela et al. [7] reported that there was no survival difference between patients with pT2aN0 and pT2bN0 and those with pT2aN1 and pT2bN1 disease in a subgroup analysis. Furthermore, they found by multivariate analysis that the pN stage and tumor site are the only prognostic factors, but not the pT2 subdivision. In the light of these results, they decided that the subclassification of pT2 tumors for gastric cancer patients who had undergone radical gastrectomy did not provide any additional information when accurate lymph node staging had been carried out [7]. In our study, the prognosis of patients with pT2aN0 cancers was significantly better than that for patients with T2bN0 tumors (3-year OS; 90% vs. 77%, $P = 0.04$). In addition, when patients with N1 were evaluated, three-year OS and the median OS time for patients with pT2bN1 tumors were significantly worse than those for patients with pT2aN1 ($P < 0.001$). But, patients with N2 or N3 tumors were not analyzed, because there were so few cases with N2 or N3 tumors in our population. Nitti et al. [10] also showed that five-year survival of patients with pT2a and pT2b tumors was significantly different for patients with and without lymph node metastasis. The authors reported that patients with pT2aN0 disease had a similar OS rate as those with pT2aN1 disease; nevertheless, in pT2b tumors OS for patients with lymph node metastasis was significantly lower than for patients without node metastasis. Our results were thus compatible with the study of Nitti et al.

Several prognostic factors, for example pN stage [7, 9, 11, 14], age [16] and macroscopic appearance [17] have previously been documented in pT2 gastric cancer patients. In the multivariate analysis of our study, the pT2 subdivision was found to be an independent prognostic factor, as were pN stage, clinical stage, and the presence of recurrence, in pT2 gastric cancer patients who had undergone a curative resection, and this is compatible with the previous literature [9, 10, 14]. However, a higher hazard ratio was obtained for the pT2 category than the pN category of the AJCC/UICC classification (4.87 vs. 0.12). Therefore, the prognostic significance of the subclassification pT2 may be important, especially in patients without accurate lymph node staging.

In this study the pT2 subclassification was significantly correlated with age, tumor size, clinical stage, pN stage, MLR, Lauren classification, blood vessel and lymphatic vessel invasion, perineural invasion, and the presence of recurrence. In other words, patients with pT2b tumors tended to have large-sized and advanced stage tumors and had more lymph node metastasis, blood vessel, lymphatic vessel, and perineural invasion than patients with pT2a tumors. Patients who were older than 60 years frequently had T2b tumors and a prevalence of diffuse and mixed histological types was more commonly seen in patients with pT2b than in those with pT2a cancers. The Lauren-intestinal histological type was particularly associated with pT2a cancers. This finding may be related to tumor biology. Thus, our results were comparable with literature results with regard to pN stage [7, 9, 10, 14], MLR [10] tumor size [7–9, 14], lymphatic vessel invasion [8], and age [9]. However, we found that blood vessel and perineural invasion, and Lauren classification were closely associated with the pT2 category, which is in contrast with the literature [8–10, 14]. When the multivariate analysis was performed according to the pT2 category, it was found that only the prevalence of recurrence affected prognosis in patients with pT2a tumors. Furthermore, pN stage, clinical stage and the prevalence of recurrence were found to be prognostic factors in the pT2b group by multivariate analysis. OS was poor for pTb tumors with lymph node metastasis, irrespective of other clinicopathological prognostic factors. This situation may be attributed to the fact that pT2b tumors had more node involvement than pT2a tumors in pT2 gastric cancer patients. Our results differ from those in previous reports [7–10, 14] because multivariate analysis was performed separately according to pT2 subdivision.

In the light of all these findings, the subclassification of pT2 tumors was found to provide additional information for the staging of patients with pT2 gastric cancer. pT2b

tumors resemble pT3 cancers and differ from pTa tumors. Therefore, this subclassification may be important for treatment decisions, and for pT2b tumors treatment strategies could be conducted in the same way as for pT3 cancers. Although previous studies on the association of the pT2 subclassification with patient survival have been inconsistent and a consensus has not been reached about its clinical importance to date, this controversy concluded with new AJCC classification in 2010. This new edition of AJCC TNM classification is contained numerous changes compared with the 2002 classification [12]. In the new version, old pT2b tumors (tumor penetrates subserosal connective tissue) were replaced as pT3. Thus, our results were compatible with 2010 TNM classification. On the other hand, we staged our patients with 2002 AJCC TNM version, because our study was retrospective. If the patients with pT2bN0 (new pT3N0) tumors receive appropriate treatment options, they may survive longer.

The retrospective nature of our study was an important limitation and might have affected our results. The other limitations of this study were the small sample size and short follow-up time. Although our results should be confirmed by prospective studies and compared with the new version of the TNM staging system for gastric cancer, we believe that they contribute to the literature because our results were compatible with the new TNM version and distinct prognostic factors were detected for both pT2a and pT2b (new pT3) tumors by multivariate analysis, in contrast with previous studies.

In conclusion, our study indicates that subdivision of pT2 tumors into pT2a or pT2b (new pT3 classification) is an important prognostic indicator for patients with pT2 gastric cancer without distant metastasis who had undergone R_0 radical surgery. Moreover, pN stage, clinical stage, and the presence of recurrence are independent prognostic factors for pT2 gastric cancer patients, and the ratio of lymph node involvement, advanced stage disease, and recurrent disease increases with pT2b disease. In the TNM staging system, subdivision of pT2 tumors should be undertaken routinely to detect patients with gastric cancer who have a poor prognosis and also to identify patients more accurately in terms of their mortality after curative resection in accordance with the new 2010 AJCC TNM staging classification; this may also help as a guide for more appropriate therapy for tumors with subserosal invasion (old pT2b or new pT3).

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