ONKOLOGIE

Original Article · Originalarbeit

Onkologie 2010;33:676–682
DOI: 10.1159/000322215

Published online: November 26, 2010

The Effect of Tumor Size on Overall Survival in Patients with pT3 Gastric Cancer: Experiences from 3 Centers

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Keywords
Gastric cancer · pT3 tumor · Survival · Tumor size

Summary
Background: Although a number of studies have investigated whether tumor diameter is a prognostic factor in gastric cancer, no consensus was reached on its clinical importance. In this study, we aimed to determine the effect of tumor size on survival in patients with pT3 gastric cancer. **Patients and Methods:** A total of 232 patients with pT3 gastric cancer, who underwent curative gastrectomy with D2 lymph node dissection, were retrospectively analyzed. Receiver operating characteristics analysis showed that the cutoff value for tumor size was 8 cm. On the basis of this cutoff point, patients were divided into 2 groups: small-size tumors (SST, ≤8 cm) and large-size tumors (LST, >8 cm). The prognostic significance of tumor size and the relationship between tumor size and other prognostic factors were evaluated. **Results:** LST was detected in 44% of patients. Resection type, tumor site, lymph node metastasis, tumor differentiation, lymphatic vessel invasion, and blood vessel invasion were correlated with tumor size. The median survival of patients with SST was significantly better than that of patients with LST (107 vs. 18.2 months; $p < 0.001$). Multivariate analysis indicated that tumor size was an independent prognostic factor ($p = 0.001$; hazard ratio (HR): 0.43) as were resection type and blood vessel invasion. **Conclusions:** Our results show that tumor size is an important prognostic indicator in patients with pT3 gastric cancer, who underwent curative gastrectomy, and that the rate of LST increased with aggressiveness and stage of disease. Tumor size may be a useful and reliable prognostic factor for detection and staging in patients with gastric cancer, who have a poor prognosis after curative resection.

Schlüsselwörter
Magenkarzinom · pT3-Tumor · Überleben · Tumorgröße

Zusammenfassung
Hintergrund: Obwohl mehrere Studien untersucht haben, ob der Tumordurchmesser ein Prognosefaktor beim Magenkarzinom ist, konnte kein Konsensus bezüglich seiner klinischen Bedeutung erzielt werden. Ziel der vorliegenden Studie ist es, die Auswirkung der Tumorgröße auf das Überleben von Patienten mit einem pT3-Magenkarzinom zu bestimmen. **Patienten und Methoden:** Insgesamt wurden 232 Patienten mit einem pT3-Magenkarzinom, bei denen eine kurative Gastrektomie mit D2-Lymphknotenresektion durchgeführt worden war, retrospektiv analysiert. Die ROC (receiver operating characteristics)-Analyse ergab einen Cutoff-Wert für die Tumorgröße von 8 cm. Auf der Basis dieses Cutoff-Wertes wurden die Patienten in 2 Gruppen aufgeteilt: kleine Tumoren (small-size tumors (SST), ≤8 cm) und große Tumoren (large-size tumors (LST), >8 cm). Die prognostische Signifikanz der Tumorgröße sowie das Verhältnis zwischen Tumorgröße und anderen Prognosefaktoren wurden bestimmt. **Ergebnisse:** LST wurden bei 44% der Patienten festgestellt. Resektionstyp, Tumorlokalisation, Lymphknotenmetastasen, Tumordifferenzierung, Lymphgefäßinvasion und Blutgefäßinvasion wurden mit der Tumorgröße in Beziehung gesetzt. Das mittlere Überleben der Patienten mit SST war signifikant besser als das der LST-Patienten (107 vs. 18,2 Monate; $p < 0,001$). Die multivariate Analyse ergab, dass sowohl die Tumorgröße ($p = 0,001$; Hazard Ratio (HR): 0,43) als auch der Resektionstyp und die Blutgefäßinvasion unabhängige Prognosefaktoren sind. **Schlussfolgerungen:** Unsere Ergebnisse zeigen, dass die Tumorgröße ein wichtiger prognostischer Indikator bei Patienten mit einem pT3-Magenkarzinom nach kurativer Gastrektomie ist, und dass die LST-Rate mit wachsender Aggressivität und Erkrankungsstadium ansteigt. Die Tumorgröße könnte ein nützlicher und verlässlicher Prognosefaktor für die Detektion und das Staging von Patienten mit Magenkarzinomen sein, bei denen nach erfolgter kurativer Resektion eine schlechte Prognose besteht.

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Introduction

Despite the incidence of gastric cancer having decreased significantly over the past few decades, it still remains a major public health issue as the second leading cause of cancer death worldwide [1, 2]. Although the incidence rate has declined, the prognosis of patients with gastric cancer has not improved much. The radical nature of the surgery, as measured by the width of tumor-free margins and the extent of lymphadenectomy, has been indicated to have a definitive prognostic significance as complete surgical resection of gastric tumors in combination with regional lymph node dissection is the only currently available curative therapy [3, 4]. A correct definition of poor prognostic factors may help to guide more aggressive adjuvant treatment protocols postoperatively [5, 6].

It is well documented that the number of metastatic lymph nodes (pN stage) and the depth of the primary tumor (pT stage) are the most reliable prognostic factors for patients with radically resected gastric cancer [7–9]. Recently, new prognostic indicators have been documented following advances in molecular and histochemical studies [10, 11]. Because these indicators are not available preoperatively, they do not contribute any additional information for surgeons. However, tumor size can not be measured easily by imaging studies before surgery. The prognostic significance of tumor size has previously been shown in gastric cancer as well as in breast cancer and lung cancer [12, 13]. pT3 gastric cancer makes up 40% of all gastric cancers and may be present at a large size. Recently, Liu et al. [14] indicated that tumor diameter is a reliable prognostic indicator in patients with pT3 gastric cancer.

In the present study, we investigate the value of tumor size as a prognostic factor for patients with pT3 gastric carcinoma, who underwent curative D2 resection. In addition, the association of tumor size with other clinicopathological factors and the effect of tumor diameter on survival are also analyzed.

Patients and Methods

A total of 232 patients with pT3 gastric cancer, who had undergone curative gastrectomy and D2 lymph node dissection at the Dr Lutfi Kirdar Kartal Education and Research Hospital, Kocaeli University, Medical Faculty and Haydarpasa Numune Education and Research Hospital between October 2004 and March 2009, were retrospectively evaluated. All patients underwent either distal partial gastrectomy, proximal partial gastrectomy, or total gastrectomy with D2 lymph node dissection with curative intent. The eligibility criteria consisted of histologically confirmed R0 gastric resection which was defined as no macroscopic or microscopic residual tumor and a postoperative survival expectancy of > 3 months. Patients with distant metastases, peritoneal metastases, and positive surgical margin at diagnosis were excluded from the study.

Patient characteristics regarding age, gender, resection type, tumor location, histopathology, pT stage, tumor size, histological grade, lymph node involvement, lymphatic vessel invasion (LVI), blood vessel invasion (BVI) and perineural invasion (PNI), resection margins, Borrmann classification, Lauren classification, adjuvant chemotherapy and radiation therapy, responses to treatment, and survival were obtained from the patients' charts.

The primary tumor was identified as pT3 stage according to the American Joint Committee on Cancer (AJCC) TNM staging classification for gastric cancer [15]. Lymph node involvement was also classified with respect to the AJCC TNM classification (pN0, no metastasis; pN1, 1–6 metastatic lymph nodes; pN2, 7–15 metastatic lymph nodes; pN3, > 15 metastatic lymph nodes). Moreover, the clinicopathological findings and D2 lymph node dissection were determined according to the Japanese Classification of Gastric Carcinoma (JCGC) [16]. Depth of invasion and nodal status were evaluated by a pathologist who is an expert in matters of gastric cancer. The tumor size was measured according to the following procedures. Firstly, the resected stomach was cut open along the greater or the lesser curvature so that the entire mucosa could be seen clearly. The opened specimen was affixed to a flat board with the mucosal side up, and fixed with 10% formalin solution. Finally, the maximum diameter of the tumor (indicator for tumor size) was examined and recorded macroscopically as accurately as possible.

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 test: MLR 0, 0%; MLR 1, 1–9%; MLR 2, 10–25%; MLR 3, > 25%.

In total, 193 patients (83.2%) received adjuvant chemoradiotherapy (CRT) with 5-fluorouracil 425 mg/m^2 per day, plus leucovorin 20 mg/m^2 per day for 5 days, followed by 4,500 cGy of radiation at 180 cGy per day, given 5 days per week for 5 weeks, with modified doses of fluorouracil and leucovorin on the first 4 and the last 3 days of radiotherapy, within 4 weeks after surgery. However, 39 patients (16.8%) did not receive adjuvant CRT because they refused or had a poor ECOG performance status.

Statistical Analysis

Statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA) software. The relationships between tumor size and other clinicopathological factors were analyzed by the chi-squared test and Fisher's exact test. Survival analysis and curves were established according to the Kaplan-Meier method and compared with 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 the patient being lost to follow-up. Overall survival (OS) was described as the time from diagnosis to the date of the patient's death or him/her being lost to follow-up. Univariate analyses to assess the significance of tumor diameter and other clinicopathological features as prognostic factors were carried out, then the multivariate analysis with the Cox proportional hazards model was performed in order to further evaluate all of the significant prognostic factors which were found in the univariate analysis for patients with pT3 stage gastric carcinoma. 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. The receiver operating characteristics (ROC) analysis was performed for detection of a cutoff value of tumor size, which predicted survival. All p values were two-sided in tests, and p values less than 0.05 were considered to be statistically significant.

Results

A total of 232 patients with pT3 tumors, who underwent curative surgery for gastric cancer, were retrospectively analyzed. Of those, 72 patients (31%) were women and 160 (69%) were men, with a median age of 59 years (range, 26–87 years); 128 patients were equal to or younger than 60 years (55.2%).

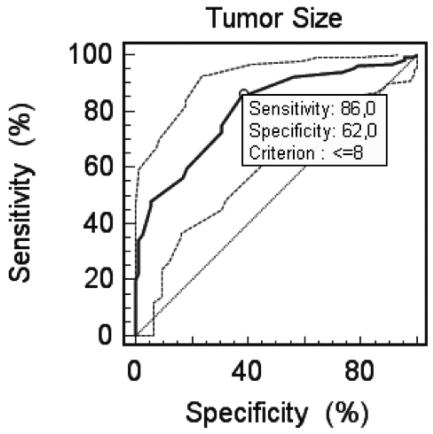

Fig. 1. ROC (receiver operating characteristics) curve shows sensitivity and specificity for a tumor size cutoff value of 8 cm were 86% and 62%, respectively (area under the curve = 0.703, p = 0.0001) in the prediction of survival in pT3 gastric cancer patients.

Postoperatively, 36 patients (15.5%) were classified as stage II, 74 (31.9%) as stage IIIA, 76 (32.8%) as stage IIIB, and 46 (19.8%) as stage IV. The majority of patients (n = 114, 49.1%) had poorly differentiated tumors. The median number of dissected and metastatic lymph nodes was 28 (range, 25–67) and 6 (range, 0–62), respectively. In addition, 37 patients (15.9%) were classified as pNo, 76 (32.8%) as pN1, 73 (31.5%) as pN2, and 46 (19.8%) as pN3 according to the number of lymph node metastases. Based on the MLR classification, 38 patients (16.4%) were classified as MLR 0, 12 (5.2%) as MLR 1, 39 (16.8%) as MLR 2, and 143 cases (61.6%) as MLR 3.

The mean and median tumor sizes were 7.5 + 3.1 cm and 7 cm (range, 3–18 cm), respectively. The ROC analysis indicated that sensitivity and specificity in the prediction of survival with a cutoff value of 8 cm tumor size after gastric surgery were 86% and 62%, respectively (area under the curve (AUC) = 0.703, p = 0.0001) (fig. 1). Based on this tumor size cutoff point, patients were divided into 2 groups as follows: small-size tumors (SST; size ≤ 8 cm) and large-size tumors (LST; size > 8 cm). Thereafter, LST was detected in 102 of the 232 patients (44%).

Significant differences were detected in surgery type, tumor site, lymph node metastasis (pN stage), and LVI and BVI between SSTs and LSTs. SSTs were more frequently localized in lower sites compared with LSTs (p = 0.025). However, LSTs tumors were more frequently found to be of a poorly differentiated type (p = 0.018). Total gastrectomy was more frequently performed for LSTs, while distal gastrectomy was more frequently carried out for SSTs (p = 0.000). The correlations between tumor size and clinicopathological findings are shown in table 1.

At the median follow-up of 23.5 months (range, 6.5–141 months), the 2-year OS rate and the median OS interval were 60.6% and 29.3 months (standard error (SE): 3.4, 95% CI: 22.6–36), respectively. Moreover, the median OS time and 2-year OS rate of patients with SST were better than those of the patients with LST (107 months and 76.9% vs. 18.2 months and 44%, p < 0.001) (fig. 2). In the univariate analysis for all patients, tumor size (≤ 8 cm vs. > 8 cm), lymph node metastasis, MLR, LVI, BVI, and PNI were found to be significant prognostic factors. The results of the univariate analysis for all patients are listed in table 2. For patients with SST, the univariate analysis indicated that Lauren classification, lymph node metastasis, MLR, LVI, and BVI were important prognostic indicators (table 3). On the other hand, when the univariate analysis was performed in patients with LST, we found that lymph node metastasis, MLR, LVI, BVI, and PNI were

Table 1. The relationship between tumor size and clinicopathological factors in patients with gastric cancer, who underwent curative resection

Factors	Tumor diameter ≤ 8 cm, n (%)	Tumor diameter > 8 cm, n (%)	p
Total number of patients	130 (56)	102 (44)	
Gender			0.08
Male	95 (73)	65 (63.7)	
Female	35 (27)	37 (36.3)	
Age, years			0.59
≤ 60	74 (56.9)	54 (52.9)	
> 60	56 (43.1)	48 (47.1)	
Tumor site			0.025
Upper	25 (19.2)	30 (29.4)	
Middle	35 (26.9)	36 (35.2)	
Lower	67 (51.5)	32 (31.3)	
Diffuse	3 (2.4)	4 (4.1)	
Surgery type			0.000
Proximal	16 (18.3)	12 (11.8)	
Distal	64 (49.2)	24 (23.5)	
Total	50 (45.1)	66 (64.7)	
Tumor differentiation			0.018
Well differentiated	20 (15.5)	6 (6)	
Moderately differentiated	56 (43)	36 (35.2)	
Poorly differentiated	54 (41.5)	60 (58.8)	
Borrmann classification			0.36
Type I	6 (4.6)	8 (7.8)	
Type II	59 (45.3)	40 (39.2)	
Type III	62 (47.6)	50 (49)	
Type IV	3 (2.5)	4 (4)	
Lauren classification			0.78
Intestinal	70 (53.8)	49 (48)	
Diffuse	54 (41.5)	44 (43.1)	
Mixed	6(4.7)	9 (8.9)	
pN stage			0.033
N0	22 (16.9)	15 (10.8)	
N1	46 (35.3)	30 (34.4)	
N2	42 (32.3)	31 (29.4)	
N3	20 (15.5)	26 (25.4)	
MLR			0.66
0	22 (16.9)	16 (15.6)	
1	7 (5.5)	5 (5.1)	
2	25 (19.2)	14 (13.7)	
3	76 (58.4)	67 (65.6)	
Lymphatic vessel invasion			0.004
Absence	71 (54.6)	18 (17.7)	
Presence	59 (45.4)	84 (82.3)	
Blood vessel invasion			0.04
Absence	80 (61.5)	26 (25.5)	
Presence	52 (38.5)	76 (74.5)	
Perineural invasion			0.40
Absence	41 (31.6)	38 (33.3)	
Presence	89 (68.4)	64 (62.7)	

MLR = Metastatic lymph node ratio.

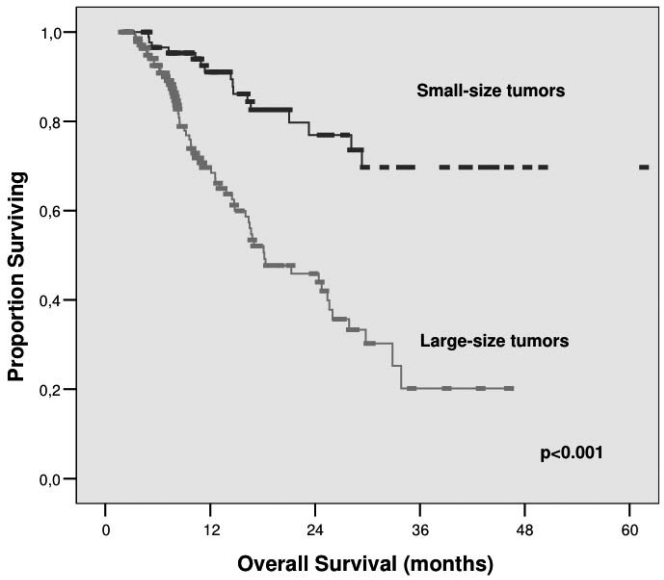

Fig. 2. Overall survival curves of patients with LST (median, 18.2 months) were significantly worse than those of patients with SST (median, 107 months).

important prognostic factors. Table 4 shows the findings of the univariate analysis for patients with LST.

The multivariate analysis indicated that tumor size was an independent prognostic factor (p = 0.001, hazard ratio (HR): 0.33) as was BVI (p = 0.01, HR: 6.44) (table 5). Furthermore, when the multivariate analysis was carried out with respect to tumor size classification, it showed that the Lauren classification was the only independent prognostic indicator in SST (p = 0.009, HR: 0.32). In LST patients, LVI and BVI were found to be independent prognostic indicators in a multivariate analysis (p = 0.002, HR: 0.38 and p = 0.000, HR: 1.82, respectively). The results of the multivariate analysis are summarized for tumor size subgroups in tables 6 and 7.

After the clinical stages of all pT3 patients were divided as stage II, stage IIIA, stage IIIB, or stage IV with respect to tumor size, survival in these stages was compared between SST and LST. We found that 2-year OS rates for stages IIIA, IIIB, and IV in patients with LST were significantly worse than those of patients with SST (p = 0.04, p = 0.031, and p = 0.009, respectively).

The median OS time and 2-year OS rate in patients who received adjuvant CRT (29.8 months and 63.9%) were better than those of patients who did not received it (18.2 months and 47.7%), but these differences were not significant (p = 0.06). Recurrent disease was detected in 97 patients (41.8%). Sixty-seven of the 97 patients (69%) had LST. In the majority of patients (59%), liver and peritoneum were the most common relapse sites. After recurrent disease was detected, 65 patients received second-line chemotherapy, while 32 patients were treated with best supportive care alone.

Table 2. Univariate analysis of the patients' clinicopathological factors for overall survival (OS)

Factors	n (%)	2-year OS rate, %	Log rank X^2 value	p
Gender			0.011	0.91
Male	160 (69)	58.9		
Female	72 (31)	64.6		
Age, years			0.001	0.98
≤ 60	128 (55.2)	59.8		
> 60	104 (44.8)	61.7		
Tumor size, cm			25.5	< 0.001
≤ 8	130 (56)	76.9		
> 8	102 (44)	44.0		
Tumor site			2.85	0.41
Upper	55 (19.2)	60.8		
Middle	71 (26.9)	61.1		
Lower	99 (51.5)	58.0		
Diffuse	7 (2.4)	NA		
Surgery type			2.84	0.24
Proximal	28 (18.3)	54.7		
Distal	88 (49.2)	64.1		
Total	116 (45.1)	58.9		
Tumor differentiation			2.08	0.35
Well differentiated	26 (15.5)	88.5		
Moderately differentiated	92 (43)	57.8		
Poorly differentiated	114 (41.5)	56.1		
Borrmann classification			4.67	0.19
Type I	14 (4.6)	NA		
Type II	99 (45.3)	61.7		
Type III	112 (47.6)	59.2		
Type IV	7 (2.5)	NA		
Lauren classification			1.74	0.18
Intestinal	119 (53.8)	55.8		
Diffuse	98 (41.5)	65.9		
Mixed	15 (4.7)	NA		
pN stage			22.9	0.000
N0	37 (16.9)	80.9		
N1	76 (35.3)	68.9		
N2	73 (32.3)	56.9		
N3	46 (15.5)	25.9		
MLR				
0	38 (16.9)	81.6	12.8	0.005
1	12 (5.5)	NA		
2	39 (19.2)	71.5		
3	143 (58.4)	48.1		
Lymphatic vessel invasion			15.7	0.000
Absence	89 (54.6)	87.6		
Presence	143 (45.4)	51.1		
Blood vessel invasion			22.3	0.000
Absence	106 (61.5)	91.7		
Presence	128 (38.5)	49.3		
Perineural invasion			7.62	0.006
Absence	79 (31.6)	74.3		
Presence	153 (68.4)	54.9		

MLR = Metastatic lymph node ratio; NA = not applicable.

Discussion

In the present study, we found that tumor size and BVI are independent prognostic indicators for patients with pT3 stage gastric cancer, who had undergone curative gastrectomy. The Lauren classification in SST patients and LVI and BVI in LST

Table 3. Univariate analysis of patients with small-size gastric tumors for overall survival (OS) according to clinicopathological factors

Factors	n (%)	2-year OS rate, %	Log rank χ^2 value	p
Gender			0.17	0.67
Male	95 (73)	64.6		
Female	35 (27)	71.3		
Age, years			1.08	0.29
≤ 60	74 (56.9)	67.6		
> 60	56 (43.1)	65.0		
Tumor site			4.39	0.22
Upper	25 (19.2)	72.4		
Middle	35 (26.9)	76.7		
Lower	67 (51.5)	57.4		
Diffuse	3 (2.4)	NA		
Surgery type			4.96	0.08
Proximal	16 (18.3)	59.1		
Distal	64 (49.2)	59.8		
Total	50 (45.1)	78.5		
Tumor differentiation			0.79	0.67
Well differentiated	20 (15.5)	80.9		
Moderately differentiated	56 (43)	65.5		
Poorly differentiated	54 (41.5)	58.5		
Borrmann classification			0.70	0.87
Type I	6 (4.6)	NA		
Type II	59 (45.3)	68.0		
Type III	62 (47.6)	58.3		
Type IV	3 (2.5)	NA		
Lauren classification			4.41	0.036
Intestinal	70 (53.8)	57.8		
Diffuse	54 (41.5)	75.8		
Mixed	6 (4.7)	NA		
pN stage			16.9	0.001
N0	22 (16.9)	81.6		
N1	46 (35.3)	72.9		
N2	42 (32.3)	64.3		
N3	20 (15.5)	33.0		
MLR			9.8	0.021
0	22 (16.9)	81.6		
1	7 (5.5)	NA		
2	25 (19.2)	73.9		
3	76 (58.4)	58.7		
Lymphatic vessel invasion			4.45	0.035
Absence	71 (54.6)	85.4		
Presence	59 (45.4)	59.4		
Blood vessel invasion			6.24	0.012
Absence	80 (61.5)	88.4		
Presence	52 (38.5)	58.5		
Perineural invasion			3.29	0.06
Absence	41 (31.6)	83.2		
Presence	89 (68.4)	61.2		

MLR = Metastatic lymph node ratio; NA = not applicable.

Table 4. Univariate analysis of patients with large-size gastric tumor for overall survival (OS) according to clinicopathological factors

Factors	n (%)	2-year OS rate, %	Log rank χ^2 value	p
Gender			0.001	0.97
Male	65 (63.7)	48.0		
Female	37 (36.3)	57.6		
Age, years			1.46	0.22
≤ 60	54 (52.9)	47.0		
> 60	48 (47.1)	57.8		
Tumor site			2.82	0.41
Upper	30 (29.4)	49.6		
Middle	36 (35.2)	44.6		
Lower	32 (31.3)	59.8		
Diffuse	4 (4.1)	NA		
Surgery type			3.07	0.21
Proximal	12 (11.8)	NA		
Distal	24 (23.5)	76.0		
Total	66 (64.7)	48.4		
Tumor differentiation			1.03	0.59
Well differentiated	6 (6)	NA		
Moderately differentiated	36 (35.2)	44.2		
Poorly differentiated	60 (58.8)	53.9		
Borrmann classification			6.01	0.11
Type I	8 (7.8)	NA		
Type II	40 (39.2)	49.6		
Type III	50 (49)	61.5		
Type IV	4 (4)	NA		
Lauren classification			0.39	0.52
Intestinal	49 (48)	53.0		
Diffuse	44 (43.1)	49.8		
Mixed	9 (8.9)	NA		
pN stage			6.46	0.011
N0	15 (10.8)	80.8		
N1	30 (34.4)	64.9		
N2	31 (29.4)	44.5		
N3	26 (25.4)	28.2		
MLR			9.12	0.028
0	16 (15.6)	82.5		
1	5 (5.1)	NA		
2	14 (13.7)	NA		
3	67 (65.6)	38.7		
Lymphatic vessel invasion			10.6	0.001
Absence	18 (17.7)	93.5		
Presence	84 (82.3)	39.8		
Blood vessel invasion			18.1	0.000
Absence	26 (25.5)	96.2		
Presence	76 (74.5)	36.0		
Perineural invasion			4.82	0.028
Absence	38 (33.3)	71.7		
Presence	64 (62.7)	45.0		

MLR = Metastatic lymph node ratio; NA = not applicable.

patients were found to be independent prognostic factors. Furthermore, significant differences of survival were detected between SST and LST patients with respect to stages IIIA, IIIB, and IV.

Tumor size is included in the staging of diseases such as breast and lung cancer [15]. However, some studies have found tumor size to be an independent prognostic factor [12, 13, 17] while others considered tumor size as an unreliable indicator [18–20]. Thus, the prognostic significance of tumor size in gastric cancer is still under debate. Saito et al. [13] divided the maximum diameter of the tumor by the cutoff point of 8 cm in their study. The authors indicated that tumor size was an independent prognostic factor along with depth of invasion, lymph node metastasis, and LVI. Adachi et al. [12] classified tumor size into 3 subgroups: < 4 cm, < 10 cm, and > 10 cm in diameter, and found that there was an independent

Table 5. Multivariate analysis of prognostic factors in all patients with gastric cancer

Factors	Wald	p	HR	95% CI
pN stage	0.27	0.60	1.20	0.60–2.40
Tumor size (≤ 8 cm vs. > 8 cm)	11.65	0.001	0.33	0.17–0.62
MLR	1.65	0.64	0.24	0.02–2.16
Lymphatic vessel invasion	0.13	0.71	0.75	0.17–3.32
Blood vessel invasion	6.64	0.01	6.44	1.56–26.5
Perineural invasion	0.02	0.86	1.06	0.50–2.27

HR = Hazards ratio; CI = confidence interval; MLR = metastatic lymph node ratio.

Table 6. Multivariate analysis of prognostic factors in patients with small-size gastric cancer

Factors	Wald	p	HR	95% CI
pN stage	0.38	0.53	1.38	0.49–3.87
MLR	1.93	0.58	0.64	0.16–2.53
Lymphatic vessel invasion	0.34	0.55	2.39	0.13–13.9
Blood vessel invasion	0.39	0.52	2.31	0.17–11.7
Lauren classification	6.88	0.009	0.32	0.14–0.75

HR = Hazards ratio; CI = confidence interval; MLR = metastatic lymph node ratio.

Table 7. Multivariate analysis of the prognostic factors in patients with large-size gastric cancer

Factors	Wald	p	HR	95% CI
pN stage	0.06	0.79	1.13	0.43–3.00
MLR	0.61	0.89	0.47	0.07–3.16
Lymphatic vessel invasion	9.32	0.002	0.38	0.13–3.9
Blood vessel invasion	14.89	0.000	1.82	0.89–3.58
Perineural invasion	0.93	0.33	1.65	0.59–4.57

HR = Hazards ratio; CI = confidence interval; MLR = metastatic lymph node ratio.

effect of tumor size on the survival of patients with gastric cancer. In the study by Guiliani et al. [17], the maximum diameter of the gastric tumor was categorized by the cutoff points of 2.5 and 5 cm, which was of independent prognostic significance. Wang et al. [21] divided the maximum tumor size into 4 subgroups: < 2 cm, < 3 cm, < 5 cm, and > 5 cm, using the method of minimizing the estimated average expected distance objective function in gastric cancer patients. They showed that tumor size was a non-negligible independent prognostic indicator for patients with gastric cancer. Furthermore, a positive association of tumor size with lymph node status and depth of invasion was indicated by log-linear model results. In light of all these findings, the authors concluded that tumor size provided powerful information on the aggressiveness and outcome of gastric cancer.

In the present study, cases of pT3 gastric cancer without distant metastasis and positive surgical margins were also analyzed, because pT3 gastric tumors are responsible for more than 40% of gastric cancer cases and commonly present at a large size [12, 13, 17]. In patients with pT3 gastric carcinoma, we found that there was a statistically significant difference with respect to OS between patients with SSTs and those with LSTs. The median survival time and 2-year survival rate of patients with SST (107 months and 76.9%) were better than those of patients with LST (18.2 months and 44%, $p < 0.001$). In addition, the univariate analysis showed that lymph node metastasis, MLR, LVI, BVI, and PNI were significant prognostic indicators for all patients. In patients with SST, univariate analysis indicated that the Lauren classification, lymph node metastasis, MLR, LVI, and BVI were important prognostic factors. On the other hand, when the univariate analysis was performed in patients with LST, we found that lymph node metastasis, MLR, LVI, BVI, and PNI were important prognostic factors. In a recent study by Liu et al. [14], tumor size was analyzed in 273 patients with pT3 gastric cancer, who underwent curative D2 gastrectomy. The authors categorized the maximum tumor diameter into 2 groups according to the approximate mean tumor size (< 6 cm and > 6 cm). They showed that tumor size was correlated with histological type, LVI, BVI, and resection type. The survival of the SST group was better than that of the LST group. In addition, in the multivariate analysis, lymph node status, MLR, and tumor size were found to be independent prognostic indicators.

In the multivariate analysis of the present study, tumor size was found to be an independent prognostic factor, as was BVI, in pT3 gastric cancer patients who underwent radical resection, which is compatible with the study by Liu et al. [14]. Therefore, one may think that the prognostic significance of tumor size is important, especially in locally advanced disease, because pT3 gastric tumors are responsible for more than 40% of gastric cancer cases and commonly present with a large size. However, unlike in the study of Liu et al. [14], we calculated a cutoff point for tumor size with respect to the ROC analysis. These results indicated a cutoff point for the tumor diameter of 8 cm. Moreover, tumor size was significantly associated with surgery type, tumor site, lymph node metastasis, tumor differentiation, LVI, and BVI for SSTs and LSTs. Large tumors tended to be poorly differentiated, and total gastrectomy was more frequently carried out for LSTs, while distal gastrectomy was performed for SSTs. However, SSTs were more often located in the distal third of the stomach. Although distal gastric tumors present as SSTs, proximal tumors usually get diagnosed earlier than distal tumors. In the Turkish population, gastroscopy is frequently performed because of dyspeptic symptoms, so gastric cancer can be diagnosed at an early stage even if located in the distal third of the stomach. Thus, our results were comparable with the results of Liu et al. [14]. However, a relationship between lymph node status and tumor size was not indicated in their study.

In light of these findings, tumor size was found to provide additional information for the staging of patients with pT3 gastric cancer, which was important for deciding whether tumor size could be included in a gastric cancer staging system. When the multivariate analysis was performed according to the tumor size group, it was found that only the Lauren classification affected prognosis in the SST group. Especially Lauren intestinal histological type is associated with smaller

tumors. This result may be related to tumor biology. Our results are compatible with the literature. In addition, LVI and BVI were found to be prognostic factors in the LST group by multivariate analysis. OS was poor in the LST group with LVI and BVI, and were independent from other clinicopathological prognostic factors. This situation may be attributed to an advanced tumor stage in this group. Liu et al. [14] found that the independent prognostic factor in the SST group was lymph node status, while in the LST group it was only the resection type. The authors concluded that the poor survival of LST patients who underwent total resection was related to a more advanced tumor stage, irrespective of the presence of lymph node metastasis.

We found that tumor size significantly affected survival in patients with stages IIIA, IIIB, and IV. Two-year OS rates for these stages in patients with SST were significantly better than those of patients with LST. Our results were compatible with the results of Liu et al. [14], except for stage IIIA patients. Either median survival time or OS rate were very poor for patients with LST compared with the SST group after curative D2 gastrectomy. Therefore, it is essential to detect effective and optimal therapeutic options for LST patients to improve the prognosis. The effect of neoadjuvant chemotherapy has been previously investigated in gastric cancer. Cunningham et al. [5] indicated that perioperative chemotherapy with epirubicin, cisplatin, and fluorouracil decreased the disease stage and improved progression-free survival and OS in the MAGIC trial. Therefore, neoadjuvant chemotherapy may be an acceptable and effective therapeutic option for patients with LST. On the other hand, our patients did not receive neoadjuvant chemotherapy, but these results may guide our treatment options in the future.

The retrospective nature of our study could be considered as a significant limitation and might have influenced the results. The other limitations of this study were small sample size and short follow-up time. Although our results should be confirmed by prospective studies, we believe that they contribute to the literature because of the detection of a cutoff point for tumor size by ROC analysis unlike in previous studies, and because the study only included patients with pT3 gastric cancer which is responsible for more than 40% of gastric cancer cases.

In conclusion, our study shows that the frequency of LST is high in patients with pT3 gastric cancer without distant metastasis, who underwent R0 curative gastrectomy. In addition, tumor size is an independent prognostic factor in pT3 gastric cancer patients, and the ratio of LST increases with aggressiveness and advanced stage of disease. Tumor size provides important additional information as an independent prognostic indicator for survival compared to classical prognostic features. It may be a new and useful prognostic factor in the detection and staging of patients who have a poor prognosis after curative resection of gastric cancer, and it may also help as a guide for more appropriate therapies for pT3 tumors.

Conflict of Interest

There have been no financial or other relationships that might lead to a conflict of interest.

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