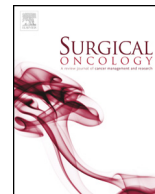


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Review

Consideration of tumor size improves the accuracy of TNM predictions in patients with gastric cancer after curative gastrectomy

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ABSTRACT

Objective: To investigate whether addition of tumor size improves the prognostic accuracy of the UICC 7th TNM staging system in gastric cancer patients who underwent radical surgery (R0 resection).

Methods: The clinical and pathological data and postoperative 5-year survival rate of 507 patients with gastric cancer who underwent radical surgery (R0 resection) in our department from January 2004 to June 2006 were evaluated retrospectively. The prognostic accuracy of conventional UICC 7th TNM staging was compared with that of UICC 7th TNM staging plus tumor size. The ability of tumor size to improve the 95% confidence interval (CI) of postoperative 5-year survival rate in gastric cancer patients was assessed.

Results: Of the 507 patients, 470 (92.7%) were followed up. The five-year survival rate of these patients was 50.4%. The survival rates of patients with pT1, pT2, pT3, and pT4 stage tumors were 89.3%, 72.4%, 36.9%, and 23.7%, respectively ($P < 0.05$), and the survival rates of patients with pN0, pN1, pN2, and pN3 stage tumors were 75.2%, 68.8%, 46.7%, and 21.3% ($P < 0.05$). Depth of invasion, lymph node metastasis stage, metastatic lymph node ratio (MLR), lymphatic invasion and tumor size were independent predictors of patient prognosis. The accuracy of UICC 7th TNM staging in predicting 5-year survival was 75.4% and the accuracy of tumor size plus the UICC 7th TNM staging was 77.9% ($P < 0.05$). This combination improved the 95% CI of postoperative 5-year survival rate in gastric cancer patients.

Conclusion: Tumor size can improve the accuracy of UICC 7th TNM staging in predicting survival in gastric cancer patients following radical surgery (R0 resection). Tumor size is likely to be another important indicator in future UICC-TNM staging systems for gastric cancer patients.

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Introduction

Gastric cancer is one of the most common malignancies of the digestive tract throughout the world, with the second highest number of cancer deaths annually [1,2]. Factors associated with patient prognosis include depth of tumor invasion and lymph node metastasis [3–6]. Unfortunately, these prognostic factors are obtained postoperatively only. Tumor size, on the contrary, can be measured easily before or during operation with no special tools. The tumor size is a well-known prognostic factor in patients with breast cancer and lung cancer. However, its clinical value in patients with gastric cancer remains elusive [7]. Although tumor size was recently suggested to affect prognosis [8–10], the impact of tumor size on the TNM staging system has not been assessed. We therefore retrospectively analyzed the clinical and pathological data of 507 gastric cancer patients who underwent radical surgery (R0 resection) in our center, to determine whether that addition of tumor size improves the prognostic accuracy of the UICC 7th TNM staging system.

Materials and methods

Patients

A total of 507 patients with gastric cancer who underwent radical surgery (R0 resection) at Fujian Medical University Union Hospital, a cancer center located in Fuzhou, China between January 2004 and June 2006 were included in this study. Patients were included if (1) they had a clear preoperative diagnosis of primary gastric cancer; (2) they had no distant metastases to the liver, lung and abdominal cavity, as shown by preoperative chest X-ray, abdominal ultrasound and CT scan of the upper abdomen; (3) they were postoperatively shown to have undergone R0 resection on pathology examination; and (4) their tumor sizes were clearly recorded in the surgical records. Patients were excluded if they had (1) underwent any neoadjuvant (2) pathologically diagnosed T4b tumors, (3) multiple stomach tumors, (4) intraoperative peritoneal dissemination of the tumor, (5) another malignancy or another life-threatening disease during the previous five years, (6) an insufficient pathological diagnosis, or (7) patients who died in the postoperative period.

Tumor size was measured by opening the stomach specimens along the greater curvature, except if the tumor was located in the greater curvature, in which case the specimens were opened along the lesser curvature of the stomach. The specimens were placed onto the plate with the mucosal side up, and the boundaries of the tumor were determined by measuring the tumor diameter along all degrees of curvature. The maximum diameter was defined as the tumor size [5]. All patients underwent D2 lymph node dissection according to the rules of the Japanese Classification of Gastric Carcinomas (JCGC) [11]. Surgeons routinely removed lymph nodes from the excised specimens as much as possible after the operation based on the JCGC and postoperative histological typing were also performed as described in the JCGC. According to Lauren's classification, the cancers were classified to the intestinal type and the diffuse-mixed type [12]. Metastatic lymph node ratio (rN) intervals were determined using the best cutoff approach and the survival

rate of patients (log-rank statistic) was considered a dependent variable. The best-fit cutoff values of rN intervals were rN0:0, rN1:1%–20%, rN2:21%–50%, rN3:>50%. The TNM stage of each tumor was assessed according to the 7th edition of the UICC (Union Internationale Contre le Cancer) TNM staging criteria. All patients with advanced gastric cancer were received 5-fluorouracil (5FU)-related adjuvant chemotherapy.

Follow-up

All patients were periodically contacted through exchanging written letters (using the postal service) or telephone interviews with patients and their relatives. The follow-up was every 3 mo during the first year, every 6 mo beyond the second year, all surviving patients were followed for more than 5 years. The survival time was the time from date of surgery until the last contact (January 2013), or the date of death. The non follow-up patients failed to get follow-up through the all above ways.

Statistical analyses

All statistical analyses were performed using the SPSS17.0 statistical package. Qualitative data were compared using the chi-squared test. Survival rate was calculated by the Kaplan–Meier method and compared using the log-rank test. A Cox proportional hazards model was used to evaluate factors prognostic of survival. Finally, Cox regression models addressed cancer-specific survival, where T stages, N groups and M stages were complemented with tumor size. Each model was subjected to bootstrap resamples for internal validation and to reduce overfit bias. Predictive accuracy estimates were then compared between those models that either included or did not include tumor size. The confidence interval (CI) method was used to compare the difference in means between predictive accuracy estimates for models that either included or did not include tumor size. $P < 0.05$ was considered statistically significant.

Results

Tumor size distribution

In the 507 patients, tumor size ranged from 10 to 120 mm, with a median of 50 mm and a mean of 48.4 ± 18.8 mm. Using the median value of 50 mm as the cutoff point, we divided the patients into two groups, those with small (<50 mm) and large (≥ 50 mm) tumors.

Postoperative follow-up results

The median follow-up time was 72 mo (range 6–108 mo). Of the 507 patients, 470 (92.7%) were followed up and the five-year survival rate was 50.4%. The median survival of all patients was 57 mo (range 6–108 mo), and the median survival of all patients' survivors and non-survivors was 71 mo (range 12–108 mo) and 47 mo (range 6–68 mo), respectively. Patients with pT1, pT2, pT3, and pT4a stage tumors had 5-year survival rates of 89.3%, 72.4%, 36.9%, and 23.7%, respectively ($P < 0.05$; Fig. 1). Patients with pN0, pN1, pN2, and pN3

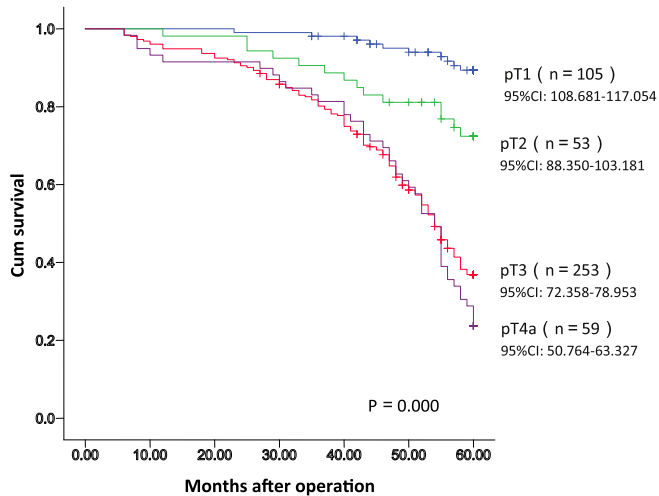


Figure 1. Survival curves of gastric carcinoma patients based on T stage.

stage tumors had 5-year survival rates of 75.2%, 68.8%, 46.7%, and 21.3%, respectively ($P < 0.05$; Fig. 2).

Univariate and multivariate analyses of factors associated with patient prognosis

Univariate analysis showed that gender, tumor size, Borrmann type, depth of invasion, Lauren's histotype, lymphatic invasion, lymph node metastasis and metastatic lymph node ratio (MLR) were significantly associated with patient prognosis ($P < 0.05$ each; Table 1).

Multivariate analysis showed that depth of invasion, lymph node metastasis, MLR, lymphatic invasion and tumor size were the independent factors predicting patient prognosis ($P < 0.05$ each; Table 2).

Impact of tumor size on 5-year postoperative survival rate with the TNM staging system

Calculations using the 7th edition of the UICC-TNM staging system showed that the accuracies of depth of invasion and lymph node metastasis in predicting 5-year survival rate were 70.1% and 72.3%, respectively (Table 3). The accuracy of the UICC 7th TNM

Table 1
Univariate analysis of patients by Kaplan–Meier method.

Variables	Cases (n)	5-Year survival (%)	P value
Sex			0.032
Male	323	53.3	
Female	147	43.4	
Age (year)			0.994
< 60	206	51.0	
≥ 60	264	49.5	
Tumor size (mm)			0.000
< 50	227	68.3	
≥ 50	243	33.7	
Borrmann type			0.000
I/II	165	71.9	
III/IV	305	38.6	
Depth of invasion			0.000
pT1	105	89.3	
pT2	53	72.4	
pT3	253	36.9	
pT4a	59	23.7	
Histologic grade			0.170
Differentiated	130	55.3	
Undifferentiated	340	48.3	
Lauren's histotype			0.034
Intestinal	315	54.1	
Diffuse or mixed	155	42.5	
Lymphatic invasion			0.000
Yes	361	25.8	
No	109	57.1	
Lymph node metastasis			0.000
pN0	113	75.2	
pN1	102	68.8	
pN2	105	46.7	
pN3	150	21.3	
Total Lymph node count			0.189
≤ 14	44	45.4	
15–19	94	44.0	
20–24	111	50.0	
25–29	100	54.7	
≥ 30	121	53.1	
MLR			0.000
0(rN0)	114	75.2	
1–20%(rN1)	119	61.8	
21–50%(rN2)	109	40.7	
> 50%(rN3)	128	25.8	
Total gastrectomy			0.531
Yes	134	56.2	
No	336	47.3	

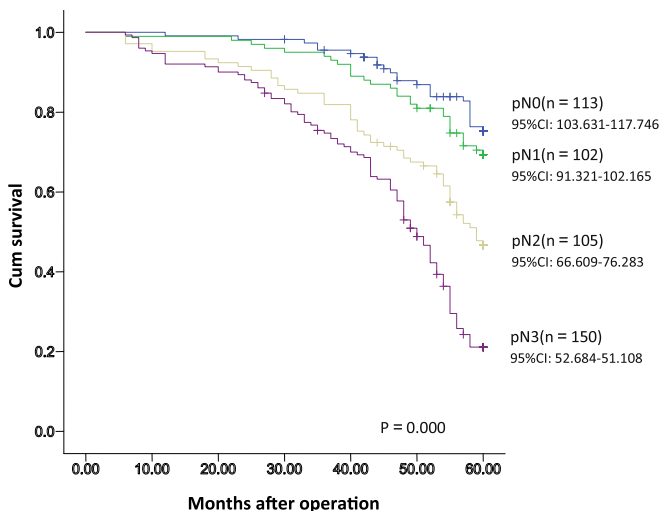


Figure 2. Survival curves of gastric carcinoma patients based on N stage.

Table 2
Prognostic factors retained at multivariate analysis by Cox model.

Variables	P	RR	95.0% CI
Sex	0.235	1.189	0.893–1.582
Depth of invasion	0.000		
pT2 vs pT1	0.006	1.115	1.056–1.233
pT3 vs pT1	0.003	2.018	1.223–2.782
pT4a vs pT1	0.000	2.582	1.408–2.829
Lymph node metastasis	0.000		
pN1 vs pN0	0.002	1.274	1.161–1.464
pN2 vs pN0	0.000	2.140	1.308–3.499
pN3 vs pN0	0.000	2.772	1.405–3.754
MLR	0.000		
rN1 vs rN0	0.018	1.655	1.127–2.241
rN2 vs rN0	0.000	2.461	1.381–2.793
rN3 vs rN0	0.000	3.429	2.392–3.536
Lymphatic invasion	0.036	1.341	1.022–1.781
Tumor size	0.027	1.216	1.041–1.903
Borrmann type	0.061	1.129	0.984–1.788
Lauren's histotype	0.145	0.732	0.486–1.107

staging system in predicting 5-year survival rate was 75.4%, whereas the addition of tumor size to the UICC 7th TNM increased the accuracy of predicting 5-year survival rate to 77.9% ($P < 0.05$).

Impact of tumor size plus the TNM staging system on postoperative 5-year survival rate

The median 5-year survival rate predicted by the UICC 7th TNM staging system was 70.3% (95% CI 66.2%–74.8%), whereas the median 5-year survival rate predicted by a combination of tumor size and the UICC 7th TNM staging system was 72.8% (95% CI 69.8%–77.5%), resulting in a median increase of 2.5% (95% CI 1.5%–4.1%) (Fig. 3).

Discussion

Gastric tumor size is closely related to histological grade, lymph node metastasis, depth of invasion, vascular invasion and neural and peritoneal metastases [13–15]. However, studies to date have yielded conflicting data on whether tumor size is an independent factor predicting the prognosis of patients with gastric cancer.

A retrospective analysis showed that, although tumor size was significantly associated with patient prognosis on univariate analysis, it was not an independent predictor on multivariate analysis [16]. Other authors [15], however, have found that tumor size is an independent predictor of patient prognosis. According to their research, when patients were divided into three groups based on tumor size ≤ 4 cm, >4 but ≤ 10 cm, and >10 cm, tumor size was an independent factor affecting patient prognosis. Bilici et al. [17] defined a threshold of 8 cm in diameter for dividing patients into two groups and their results found that tumor size was an independent predictor of patient prognosis. We observed a median gastric tumor size of 5 cm. Analysis confirmed that, in addition to depth of invasion and lymph node metastasis staging, tumor size

was an independent factor predicting patient prognosis. Among several clinicopathologic factors, tumor size can be measured easily before or during operation using no special tools. Tumor size provides important information on tumor aggressiveness and patient outcomes. Larger tumors are usually associated with a greater degree of malignancy and a worse biological behavior. Interestingly, this study also revealed that men appear to have a better prognosis than women. Bando et al. [18] concluded that age and sex both have a valuable role as prognostic indicators in patients with early gastric cancer. Nakamura et al. [19] reported that young patients (40 years of age or younger [19,20]) with gastric cancer, in comparison to older patients, showed a more aggressive clinical course and have a poorer prognosis. We believe that the difference of survival rate in our study was due to the high proportion of young people among the female patients.

The UICC-TNM staging system is important for estimating the prognosis of patients with gastric cancer [21–23]. In 2009, the guidelines of the Japanese Gastric Cancer Association substituted the original staging method using lymph node stations with a staging system based on depth of invasion and lymph node and distant metastases, similar to the 7th edition UICC staging system [6,7]. Tumor size, however, was not included in this gastric cancer classification system, and its prognostic value remains unresolved. Although tumor size was not included in the new UICC gastric cancer staging system, the addition of tumor size is likely to improve the accuracy of TNM staging. A retrospective analysis of 513 gastric cancer cases showed that tumor size not only was an independent predictor of patient prognosis, but reflected lymph node status and the depth of tumor invasion [24]. An assessment of 1473 gastric cancer patients, using a size cutoff of 8 cm, showed that the survival of patients with smaller tumors and stage IIIa-, IIIb-, and IV disease was similar to that of patients with larger tumors and stage II-, IIIa-, and IIIb disease, indicating that tumor size was a simple predictor of survival in patients with gastric cancer [25].

Table 3
Univariate and multivariate Cox regression models predicting depth of invasion, lymph node metastasis, tumor size and 5-year survival, according to 7th UICC-TNM classification.

Variables	5-Year survival			
	Univariate		Multivariate (T + N + M0)	Multivariate (T + N + M0 + S)
	OR P value (95% CI)	Predictive accuracy of univariate	OR P value (95% CI)	OR P value (95% CI)
T stage	—	0.701	—	—
T2vsT1	5.713 0.000 (2.381–11.871)		4.768 0.003 (2.763–11.235)	2.834 0.041 (1.056–4.569)
T3vsT1	18.657 0.000 (13.581–28.779)		12.159 0.000 (6.806–20.862)	6.025 0.000 (3.946–14.473)
T4avsT1	29.789 0.000 (16.890–41.301)		22.630 0.000 (16.671–41.731)	15.156 0.000 (8.594–30.739)
N stage	—	0.723	—	—
N1vsN0	2.344 0.022 (1.983–5.953)		2.305 0.025 (1.336–5.539)	2.301 0.044 (1.823–8.474)
N2vsN0	5.737 0.000 (2.092–9.954)		4.737 0.000 (2.469–10.835)	4.238 0.000 (2.932–11.969)
N3vsN0	15.986 0.000 (11.698–26.049)		11.367 0.000 (5.917–25.924)	9.906 0.000 (5.571–20.528)
Tumor size (S)	1.069 0.000 (1.043–5.685)	0.668	—	1.092 0.000 (1.019–4.752)
Predictive accuracy of the model	—		0.754 (0.658–0.783)	0.779 (0.711–0.804) + 2.5%

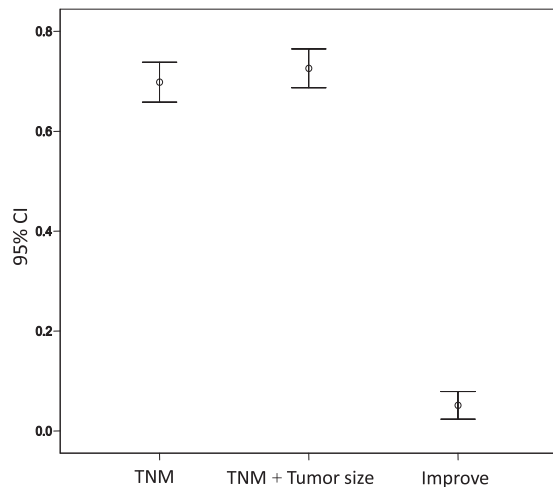


Figure 3. Tumor size plus the UICC 7th TNM classification significantly improved the 95% CI of predicting 5-year survival rate.

These research indicate that tumor size provides important information about the malignant potential of tumors.

So far, whether tumor size independently correlates with the ability to improve the accuracy of TNM predictions is still unclear. To the best of our knowledge, the present study is the first to compare the accuracy of a combination of tumor size and UICC 7th TNM staging with that of UICC 7th TNM staging alone to predict 5-year survival rate in gastric cancer patients in China. In the present study, the addition of tumor size to UICC 7th TNM stages increased predictive accuracy by 2.5%, in a statistically significant fashion ($P < 0.05$). Our study also clarified that the addition of tumor size to the UICC 7th TNM staging system significantly improved the 95% CI of predicting 5-year survival rate. These findings indicate that combined evaluation can improve the accuracy of the UICC 7th TNM staging system in predicting the postoperative 5-year survival rate among gastric cancer patients who underwent radical surgery (R0 resection). Moreover, tumor size may become another important indicator of future UICC-TNM staging systems. Despite the above considerations, we should also realize that the improvement of accuracy with TNM plus size is only 2–3%. We believe that tumor size is closely linked to the parameters of tumor progression, such as depth of invasion, degree of lymph node metastasis, lymphatic invasion, and so on. Therefore, we must bear in mind that the impact of tumor size on the clinical practice can not be estimated solitarily. Prospective, large scale, multicenter studies are needed to assess whether measurement of tumor size can enhance the ability of the UICC 7th TNM staging system to predict 5-year overall survival rate.

Authorship statement

Guarantor of the integrity of the study: Jun Lu, Chang-ming Huang.

Study concepts: Jun Lu, Chang-ming Huang, Chao-hui Zheng.

Study design: Jun Lu.

Definition of intellectual content: Jun Lu, Chang-ming Huang, Chao-hui Zheng.

Literature research: Jun Lu, Ping Li, Jian-wei Xie.

Clinical studies: Jun Lu, Jia-bin Wang, Jian-xian Lin.

Data acquisition: Jia-bin Wang, Jian-xian Lin.

Data analysis: Jun Lu, Jia-bin Wang, Jian-xian Lin.

Statistical analysis: Jun Lu, Jia-bin Wang, Jian-xian Lin.

Manuscript preparation: Jun Lu.

Manuscript editing: Jun Lu, Chang-ming Huan.

Manuscript review: Jun Lu, Chang-ming Huang, Chao-hui Zheng.

Conflict of interest statement

I certify that all financial and material support for this study is identified in this manuscript. All of my affiliations and financial involvement over the past five years and for the foreseeable future with any organization or entity with financial interest in or financial conflict with the subject matter or materials mentioned in the manuscript are completely disclosed below or in an attachment.

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