



Total Tumor Volume Should be Considered as an Important Prognostic Factor for Synchronous Multiple Gastric Cancer Patients with Curative Gastrectomy

Xiaolong Tang¹ · Qingsi He¹ · Guorui Sun¹ · Hui Qu¹ · Jia Liu² · Lei Gao³ · Jingbo Shi³ · Jianhong Ye³ · Yahang Liang³

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Abstract

Synchronous multiple gastric cancer (SMGC) was a special type of gastric cancer with relatively low incidence. This article was designed to demonstrate that the total tumor volume (TTV) should be treated as an important prognostic factor in SMGC patients with curative gastrectomy. This study retrospective analyzed 140 SMGC patients who received curative gastrectomy between December 2004 and December 2014 in our hospital. Clinicopathological features, preoperative evaluation, surgical treatment, and outcome parameters were reviewed and analyzed. This study applied univariate and multivariate analyses to identify the most significant prognostic factors. In the univariate analysis, the TTV, pT_{TV}NM, pN stage, pT of main tumor were all significant prognostic factors in SMGC patients (all $P < 0.05$). In the multivariate analysis, pN stage, TTV and pT_{TV}NM were confirmed to be independent prognostic factors (all $P < 0.05$). In the comparison of survival analysis, the pT_{TV}NM stage system ($P < 0.05$) was superior to the pTNM stage system ($P > 0.05$) in SMGC patients. In conclusion, the TTV should be considered as an independent prognostic factor in overall survival in SMGC patients who received curative gastrectomy. The pT_{TV}NM stage should be recommended as a suitable staging system for SMGC patients.

Keywords Gastric cancer · Tumor volume · Gastrectomy · Prognosis

Abbreviations

SMGC	Synchronous multiple gastric cancer
TTV	Total tumor volume
GC	Gastric cancer
AJCC	American Joint Committee on Cancer
UICC	Union of International Cancer Control
TNM	Tumor-node-metastasis
TV	Tumor volume

Introduction

Gastric cancer (GC) is the second leading cancer in the world, and the prognosis of advanced GC remains poor [1]. Synchronous multiple gastric cancer (SMGC) was a special type of gastric cancer. In previous studies, the incidence of SMGCs was reported to be 5–10% [2]. The criteria for SMGCs were defined as follows: (1) each tumor must be histopathologic confirmed by pathology reports; (2) tumors are separated from each other in the stomach; (3) no tumor is result from extension or metastasis of another tumor [3].

In recent years, the American Joint Committee on Cancer (AJCC)/ Union of International Cancer Control (UICC) tumor-node-metastasis (TNM) staging system was widely used in gastric cancer. However, in patients with SMGCs, some studies suggested that the traditional TNM classification for GC may not suitable [4]. In several types of malignant tumors, such as hepatocellular carcinoma, tumor volume (TV) was proved to be an important prognostic factor [5]. However, the relationship between TV and overall survival in SMGC patients was still unknown. This study was designed

✉ Guorui Sun
doctorsungr@163.com

¹ Department of General Surgery, Qilu Hospital of Shandong University, No.107, West of Wenhua Street, Lixia District, 250012 Jinan, China

² Department of Health Management Center, Qilu Hospital of Shandong University, 250012 Jinan, China

³ Qilu Medical College of Shandong University, 250011 Jinan, Shandong, China

to elucidate the prognostic significance of TV in SMGC patients after curative surgery.

Materials and Methods

Patients

A total of 2360 patients with gastric cancer who underwent gastrectomy at Shandong University Qilu Hospital during December 2004 and December 2014 were enrolled into this study. The inclusion criteria were as follows: (1) patients who had more than one primary gastric tumor, with each tumor been identified as gastric adenocarcinoma by histopathological examination; (2) complete clinicopathological records including follow-up data; (3) received curative resection with D2 lymphadenectomy. The exclusion criteria were: (1) patients with distant metastasis before or during surgery; (2) patients with incomplete clinicopathological information; (3) patients with Borrmann type IV GC (diffuse infiltration type).

In a resected specimen, tumor with the most advanced depth of invasion was defined as the main tumor, while the other was defined as accessory tumor [6]. The tumor volume (TV) equaled to $\pi \times (\text{tumor diameter}/2)^2 \times \text{tumor invasion depth}$. The tumor diameter was the maximum diameter of the tumor. The tumor invasion depth was the maximum invasion depth of tumor. The tumor diameter and invasion depth were recorded in pathology reports after surgery. The total tumor volume (TTV) equaled to the sum of each TV in SMGC patients.

Follow-up

All the patients were followed-up once per year or until death by telephone, e-mail or outpatient examination. The CT or MRI scan, endoscopy examination and laboratory tests were performed at every outpatient visit. The median follow-up time was 76 (range: 50–112) months. The last follow-up date was November 25, 2019. The overall survival (OS) was calculated from the date of surgery until the final date of follow-up or death.

Statistical Analysis

The Life Tables method analyzed OS rates according to the new subgroup of TTV. The univariate and multivariate analyses were applied to identify the most significant classification correlated with prognosis. To determine the appropriate cut-offs for the TTV, the cut-point survival analysis was adopted. The Kaplan-Meier method was used to calculate overall survival curves based on the length of time between primary surgical treatment and final follow-up or death. The log-rank test was used to assess statistical differences between curves. Cox proportional hazards regression model was used to

identify independent prognostic factors. $P < 0.05$ was considered statistically significant. To decide the most appropriate cut-offs of TTV based on these SMGCs patients, we recomputed the likelihood associated with all possible pairs of TTV cut-offs ranging from 1 to 50 (cm^3) at intervals of 1. The statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Kerry, USA).

Results

Clinicopathological Outcomes

One hundred and forty SMGCs patients were included in this study based on these criteria. Among these patients, 86 (61.4%) patients were male and 54 (38.6%) were female. The median age of these patients was 61.2 years (range, 41–91 years). All 140 SMGC patients had more than one primary tumor in the stomach, with a total of 287 tumors. Among these tumors, 86 (30.0%), 71 (24.7%), and 130 (45.3%) were located in the lower, middle, and upper thirds of the stomach, respectively. Poor differentiation and signet ring cell histology (182 tumors, 63.4%) was more than high and middle differentiation histology (105 tumors, 36.6%). The average total tumor volume (TTV) of each patient was 7.1 (range, 0.4–25.5) cm^3 .

All patients received curative gastrectomy with D2 lymphadenectomy. A total of 58 (41.4%) patients underwent subtotal gastrectomy, while 82 (58.6%) patients underwent total gastrectomy. The median number of lymph nodes resected per patient was 21 (range, 11–54) by histopathological examination after surgery. A total of 101 patients with tumor stage of II/ III received adjuvant chemotherapy after surgery. In these patients, 53 patients received XELOX (capecitabine plus oxaliplatin), 38 patients received SOX (S-1 plus oxaliplatin) and 10 patients received other regimens (S-1/ mFOLFOX/ DCF/ ECF). The patient characteristics were summarized in Table 1.

Univariate and Multivariate Analyses of Prognostic Factors

The results of cut-point survival analysis demonstrated that the appropriate cut-offs of TTV between resulting subgroups were 1.0, 7.0 and 12.0 cm^3 . According to this stratified standard, the 140 patients were classified into 4 groups: 57 (40.7%) patients were TTV1, 37 (26.4%) patients were TTV2, 30 (21.4%) patients were TTV3, 16 (11.5%) patients were TTV4. In the univariate analysis, these 4 groups which classified according to the TTV classification were significantly correlated with prognosis ($P < 0.001$). To further study the prognostic factors of SMGC, we introduced the TTV to

Table 1 Univariate Survival Analysis

	No. of patients (n = 140)	Median survival (months)	χ^2	P^*	Hazard ratio (95% CI)	χ^2	$P^{\#}$
Sex			0.48	0.490			
Male	86	49 (31–87)			1.00		
Female	54	62 (33–103)			0.81 (0.45–1.47)	0.47	0.494
Age (years)			0.11	0.741			
≤ 60	62	53 (33–110)			1.00		
> 60	78	51 (31–97)			1.08 (0.67–1.75)	0.11	0.742
Location of main tumor			3.25	0.197			
Lower	49	46 (28–94)			1.00		
Middle	40	59 (33–103)			0.66 (0.37–1.17)	2.02	0.159
Upper	51	51 (30–89)			0.65 (0.37–1.13)	2.33	0.127
Differentiation of main tumor			2.31	0.510			
High	8	53 (53–NA)			1.00		
Middle	36	49 (27–62)			1.51 (0.35–6.45)	0.31	0.577
Poor	72	53 (33–76)			1.03 (0.25–4.25)	0.00	0.972
Signet ring cell	24	70 (22–103)			1.28 (0.21–7.71)	0.07	0.789
pT of main tumor			12.54	0.006			
T1	24	69 (33–103)			1.00		
T2	31	53 (43–89)			1.61 (0.55–4.42)	0.75	0.386
T3	35	51 (32–103)			3.11 (1.19–8.11)	5.39	0.020
T4	50	37 (21–94)			3.77 (1.46–9.72)	7.52	0.006
Location of accessory tumor			1.51	0.680			
Lower	32	63 (36–103)			1.00		
Middle	29	34 (13–98)			1.48 (0.66–3.31)	0.93	0.336
Upper	79	51 (33–97)			1.14 (0.57–2.27)	0.13	0.719
Differentiation of accessory tumor			0.78	0.851			
High>	29	63 (36–89)			1.00		
Middle	28	51 (27–97)			1.30 (0.59–2.86)	0.42	0.519
Poor	58	48 (31–79)			1.34 (0.69–2.60)	0.75	0.386
Signet ring cell	25	103 (19–103)			1.21 (0.34–4.34)	0.08	0.771
pT of accessory tumor			5.00	0.288			
T1	61	54 (34–89)			1.00		
T2	25	51 (31–109)			1.01 (0.52–1.97)	0.00	0.985
T3	24	41 (15–89)			1.69 (0.88–3.24)	2.48	0.116
T4	30	39 (30–102)			1.45 (0.79–2.67)	1.43	0.231
Surgical type			0.39	0.530			
Subtotal	82	48 (31–103)			1.00		
Total	58	59 (31–112)			0.86 (0.53–1.38)	0.39	0.533
Total tumor volume (TTV)			81.81	<0.001			
TTV1	57	79 (39–103)			1.00		
TTV2	37	62 (53–102)			4.92 (2.49–8.74)	14.28	0.015
TTV3	30	33 (30–40)			3.13 (1.64–5.99)	11.97	0.021
TTV4	16	10 (5–19)			15.36 (7.01–33.65)	46.62	<0.001
pN stage			47.47	<0.001			
N0	27	103 (54–121)			1.00		
N1	21	89 (51–102)			0.53 (0.14–2.04)	0.87	0.351
N2	39	51 (33–98)			2.78 (1.19–6.51)	5.57	0.018
N3	53	32 (16–41)			7.55 (3.25–17.57)	22.04	<0.001
pTNM			7.58	0.091			

Table 1 (continued)

	No. of patients (n = 140)	Median survival (months)	χ^2	P^*	Hazard ratio (95% CI)	χ^2	P^{\ddagger}
I	27	90 (57–120)			1.00		
II	49	76 (58–101)			1.44 (0.71–2.95)	12.53	0.322
III	64	66 (56–91)			1.83 (0.98–3.43)	18.76	0.060
pT _{TV} NM			48.95	< 0.001			
I	22	81 (47–112)			1.00		
II	48	59 (41–102)			7.14 (2.07–24.57)	9.70	0.002
III	70	32 (16–51)			23.99 (6.84–84.23)	24.60	< 0.001
Resected vein invasion			1.70	0.193			
Yes	40	38 (21–89)			1.41 (0.84–2.37)	1.66	0.198
No	100	53 (33–102)			1.00		
Adjuvant chemotherapy			5.72	0.017			
XELOX	53	63 (36–103)			0.66 (0.45–0.97)	4.95	0.026
SOX	38	46 (34–71)			0.88 (0.65–1.14)	3.15	0.076
Other regiments	10	42 (32–56)			0.99 (0.68–1.45)	2.29	0.131
No chemotherapy	39	40 (27–89)			1.00		

*Log rank test

‡Cox regression analysis

the 8th AJCC/UICC pTNM staging system by replace the pT stage of main tumor with TTV. Other variables, including the pT stage of main tumor ($P = 0.006$), pN stage ($P < 0.010$) and pT_{TV}NM ($P < 0.001$) were all significant predictors of survival. We did observe the improvement of median survival in patients who received adjuvant chemotherapy (54 months vs. 40 months). Patients who received chemotherapy of XELOX regiment showed better survival than patients who did not receive adjuvant chemotherapy ($P < 0.05$). However, there was no statistical significance between patients who received SOX or other regiments (S-1/ mFOLFOX/ DCF/ ECF) and patients who did not receive adjuvant chemotherapy ($P > 0.05$). Survival curves of SMGC patients according to TTV, pT, pN and pT_{TV}NM were shown in Figs. 1a, b and c and 2a.

In the multivariate survival analysis, the TTV classification, pN stage and pT_{TV}NM stage were confirmed to be independent prognostic factors (All $P < 0.05$). However, the pT stage was not independent prognostic factor ($P > 0.05$). The detailed data of univariate and multivariate analyses were shown in Table 2.

Comparison of Survival Analysis Between the TNM Stage System and T_{TV}NM Stage System

Moreover, we directly compared the differences in prognostic prediction between the 8th edition pTNM classification and

the pT_{TV}NM classification. Detailed survival differences between the traditional pTNM staging system and our suggested pT_{TV}NM staging system were showed in Table 3. The results indicated that the pT_{TV}NM categorization system significantly predicted survival in patients with SMGCs ($P < 0.05$) (Fig. 2a). However, the 8th pTNM staging system could not ($P > 0.05$) (Fig. 2b).

Discussion

Synchronous multiple gastric carcinomas (SMGCs) were defined as two or more cancerous tumors in one stomach [7]. So far, the etiology of SMGC is still not clear. The SMGC can occur in any part of the stomach, but most occur in the antrum or cardia of gastric wall. With the improvement of endoscopic and imaging diagnostic techniques, the detection rate of SMGC is increasing. The incidence of SMGC reported in the literature is about 0.4%–2.4%, accounting for about 1.2%–10.7% of all gastric cancer [8]. This study shows that SMGC accounts for about 5.9% (140/ 2360) of all gastric cancer patients. Some studies suggested that SMGC were more common in early gastric cancer. They compared multiple primary early gastric cancer with single early gastric cancer, found that there was no significant difference in prognosis [9]. However, with the increasing application of endoscopic submucosal dissection (ESD) in early gastric cancer in recent years, surgically resected SMGC gradually transformed into

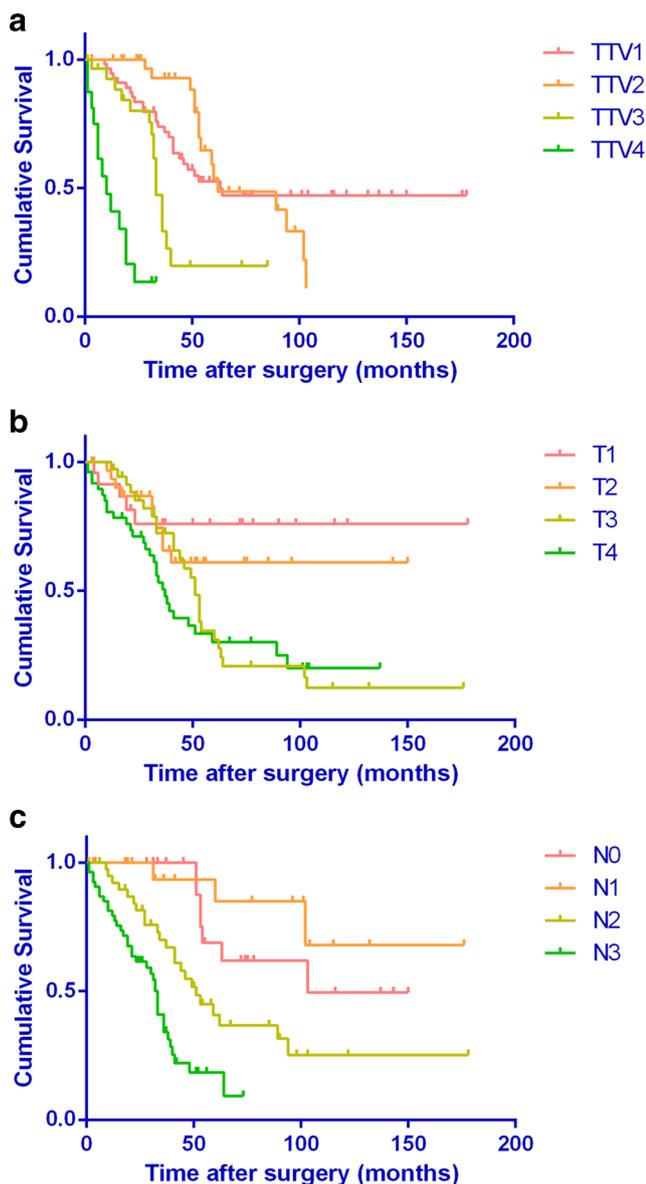


Fig. 1 Survival curve according to TTV classification, pT stage and pN stage after surgery. **a.** There were statistically significant differences between patients with TTV2, TTV3 and TTV4 ($P=0.015$, $P=0.021$, $P<0.001$, respectively) **b.** There were statistically significant differences between patients with pT2, pT3 and pT4 ($P=0.386$, $P=0.020$, $P=0.006$, respectively). **c.** Patients with pN1, pN2 and pN3 were significantly associated with different survival outcomes ($P=0.351$, $P=0.018$, $P<0.001$, respectively)

advanced gastric cancer [10]. In our study, we included 80.7% (113/140) cases of advanced gastric cancer (T stage: 2–4 stages of primary tumor) in surgical cases.

The main treatment for SMGC is surgical resection. The extent of resection depends on the location of each primary lesion and the number of primary tumors [11]. Some early studies recommended total gastrectomy for SMGC to avoid residual lesions, however, with the improvement of

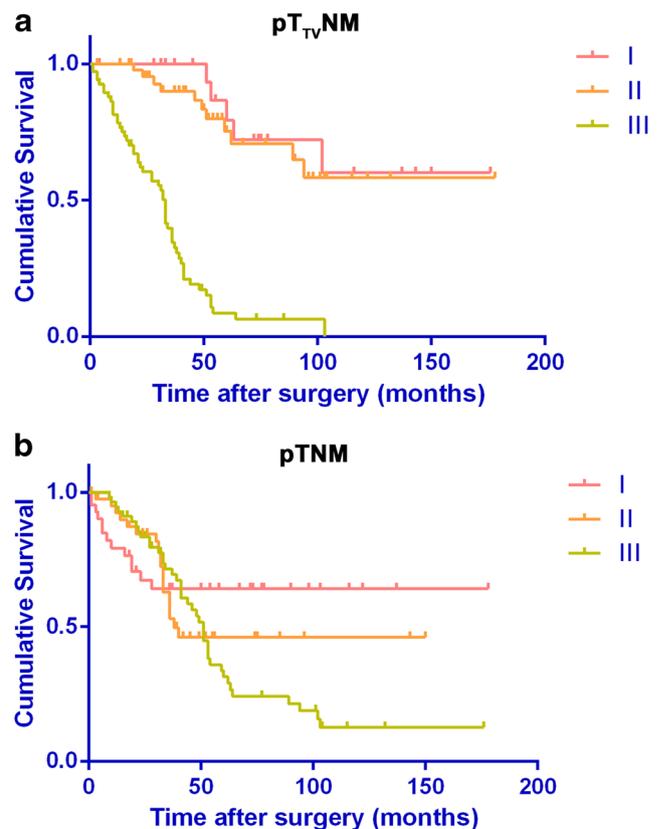


Fig. 2 Comparison of survival analysis between the 8th AJCC/ UICC pTNM classification and our suggested pT_{TV}NM classification in SMGC patients. **a.** Patients classified according to the pT_{TV}NM classification were significantly correlated with prognosis ($P=0.002$, $P<0.001$, respectively). **b.** Patients classified according to the 8th AJCC/UICC pTNM classification were not correlated with prognosis ($P>0.05$, $P=0.060$, respectively)

preoperative examination, prophylactic total gastrectomy is unnecessary [12]. However, patients with gastric cancer should still be aware of possible missed lesions. Detailed preoperative gastroscopy is an effective mean to detect SMGC. Other imaging examinations, such as nuclear magnetic resonance (MRI), contrast-enhanced computed tomography (CT) and upper gastrointestinal angiography can also help to detect missed lesions [13]. The combination of multiple examinations can effectively improve the diagnostic rate of SMGC. Due to the non-specific distribution of SMGC in the stomach, the whole stomach should be carefully checked during surgery to avoid missed lesions. Postoperative regular endoscopic fiberoptic is an effective mean to detect tumor recurrence.

For decades, tumor invasion depth (pT) has been considered as one of the most important pathological factors. However, our study suggested that the pT stage may be not suitable in patients with SMGC ($P>0.05$). The tumor volume (TV) was found to be an important prognostic factor in several carcinomas, such as hepatic carcinoma [14], malignant

Table 2 Multivariate Survival Analysis

	B	SE	HR	Hazard ratio (95% CI)	<i>P</i> [¶]
Total tumor volume (TTV)					
TTV1	-			1.00	
TTV2	0.22	0.36	1.25	0.62–2.52	0.539
TTV3	1.83	0.46	6.25	2.55–15.36	< 0.001
TTV4	2.28	0.45	9.74	4.04–23.50	< 0.001
pT of main tumor					
T1	-			1.00	
T2	-0.05	0.61	0.95	0.29–3.15	0.934
T3	0.08	0.27	1.09	0.64–1.86	0.759
T4	0.60	0.58	1.83	0.58–5.75	0.301
pN stage					
N0	-			1.00	
N1	-0.19	0.54	0.83	0.29–2.36	0.720
N2	1.53	0.46	4.63	1.89–11.33	< 0.001
N3	2.08	0.48	7.99	3.12–20.43	< 0.001
pT _{TV} NM					
I	-			1.00	
II	1.95	0.69	7.03	1.82–27.12	0.005
III	2.13	0.74	8.42	1.96–36.11	0.004

¶Cox regression analysis

melanoma [15] and non-small-cell lung cancer [16]. Previous study found that tumor volume could predict survival in patients with renal cell carcinoma [17]. In a retrospective study, Jiang et al. reported that tumor volume was a prognostic factor in patients with GCs [18]. In our study, the calculate of tumor volume was based on tumor diameter and tumor invasion depth. It gives a new index to improve the prognostic assessment in SMGC patients. Patients with SMGC have two or more lesions in the stomach. Take this point into

Table 3 The five-year overall survival (OS) differences between the 8th AJCC/UICC TNM classification and our suggested T_{TV}NM classification

	5-year OS (%)	Univariate Analysis	
		Hazard ratio (95% CI)	<i>P</i> [¶]
pTNM			
I	64.11%	1.00	
II	46.13%	1.44 (0.71–2.95)	0.322
III	31.49%	1.83 (0.98–3.43)	0.060
pT _{TV} NM			
I	79.44%	1.00	
II	65.42%	7.14 (2.07–24.57)	0.002
III	28.65%	23.99 (6.84–84.23)	< 0.001

¶Cox regression analysis

consideration, we first introduce a new index: total tumor volume (TTV). The TTV equals the sum of TV of each gastric tumor in a SMGC patient. In the univariate analysis, the 4 groups classified according to the TTV classification were significantly correlated with prognosis ($P < 0.05$). In multivariate survival analysis, the TTV classification was an independent prognostic factor ($P < 0.05$), however, the pT stage was not ($P > 0.05$). These results showed that the TTV classification was superior to the pT classification in SMGC patients.

To further investigate the prognostic significant of TTV, we introduced a new classification system: the total tumor volume-node-metastasis (T_{TV}NM) system. To further confirm the superiority of the pT_{TV}NM classification to the pTNM stage system in SMGC patients, we directly compared these two classifications in this study. We found that the pT_{TV}NM classification ($P < 0.05$) was an appropriate prognostic classification for predicting the overall survival of SMGC patients, rather than the 8th edition pTNM classification ($P > 0.05$). We assumed the reason was that TV was a direct indicator of tumor burden [19]. Larger TV generally indicated quicker proliferation of tumor cells, more lymph nodes metastasis, and more possible distant metastasis [20]. These results suggested that the pT_{TV}NM staging was superior to the pTNM staging for prognostic assessment in SMGC patients.

Our study showed that the traditional pTNM staging system exhibits some limitations in SMGC patients. In our opinion, although TTV was not a direct pathological factor in the postoperative pathology report, but we could easily calculate it by tumor diameter and tumor invasion depth. This index could reflect tumor burden better than pT in SMGC patients. Furthermore, we invented a new classification system in SMGC patients, which could predict the prognosis more accurately.

Conclusions

For patients with SMGC who underwent curative gastrectomy, TTV was an independent prognostic factor. Moreover, TTV-based classification was superior to pT classification for predicting prognosis in patients with SMGC. Incorporation of TTV into the pT_{TV}NM staging system could compensate for the limitations of traditional pTNM stage system in SMGC patients [21]. The TTV should be recommended as an important clinicopathologic factor to improve the accuracy of prognostic prediction in patients with SMGC.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest in this study.

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