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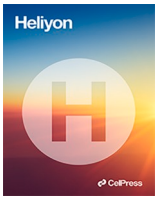

Research article

Association between tumor size and prognosis in patients with small bowel adenocarcinoma-a SEER-based study

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ABSTRACT

Background: The association between small-bowel adenocarcinoma (SBA) tumor size and prognosis is unclear, and we used the Surveillance, Epidemiology, and End Results (SEER) database to assess the prognostic value of SBA tumor size.

Methods: Patients with postoperative SBA were selected from the SEER database, and overall survival (OS) and cancer-specific survival (CSS) were used as outcome variables. Tumor size was used as a categorical and continuous variable, respectively, to adjust for confounders and analyze the association between SBA tumor size and prognosis using Cox proportional hazard regression, and the results were visualized using restricted cubic splines (RCS). Spearman correlation coefficient was used to evaluate the statistical correlation between tumor size and tumor invasion depth (T-stage). Kaplan-Meier survival curves were used to estimate OS at different T stages.

Results: When the tumor size was analyzed as a quantitative variable, the adjusted covariate model showed that the HR was 1.008 ($P = 0.04$) for OS and 1.021 ($P = 0.03$) for CSS. And regardless of OS or CSS, when the tumor size < 3–4 cm, there was a close linear relationship between tumor size and HR. What's more, in the SEER database, the 5-year survival rates of T1, T2, T3 and T4 patients were 81.8 %, 81.1 %, 66.0 % and 50.9 % ($P < 0.001$) according to AJCC T-stage. However, in the modified T-stage (mT), these rates were 82.8 %, 70.6 %, 60.7 % and 39.8 % ($P < 0.001$). When patients within each of the AJCC T stages were stratified by mT stages, significant survival heterogeneity was observed within each of the AJCC T1 to T4 stages($P < 0.001$).

Conclusion: When tumor size is used in a quantitative way, tumor size is an independent predictor of poor outcome in patients with SBA. Furthermore, we established a modified T-stage based on tumor size and depth of invasion.

1. Introduction

The small bowel is the longest digestive organ, but the incidence of small bowel tumors is extremely low, accounting for only 5 % of digestive tract tumors [1]. Small bowel adenocarcinoma (SBA) is the most common type of small bowel tumor, accounting for approximately 30%–40 % of small bowel tumors [2]. Due to the limitations of diagnostic methods, SBA is often diagnosed at a later stage, leading to a poor prognosis with a 5-year overall survival (OS) rate of less than 30 % [3]. However, according to recent

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epidemiological analyses, the incidence of small-bowel cancer is increasing every year [4]. Further research on this issue is urgently required to increase awareness.

In the newly published 8th edition of the American Joint Committee on Cancer Staging Manual, the size of tumors for various types of cancer has been incorporated into the T stage of the tumor node metastasis (TNM) staging system, including breast, lung, kidney, and thyroid cancer [5–8]. However, the tumor size has not been incorporated into the TNM staging system for SBA. The reason for this may be that the relationship between tumor size and SBA prognosis remains unclear. Currently, there is limited research on the relationship between SBA and tumor size, and SBA diagnosis and treatment mainly refers to colorectal cancer. In research on colorectal cancer tumor size and prognosis, some studies have suggested that smaller tumors have a poorer prognosis [9–11]. However, some studies have indicated a negative correlation between tumor size and prognosis [12]. However, the conclusions drawn from these studies are controversial. As for research on SBA and tumor size, only a few prior studies have categorized tumor size [13,14]. This makes the conclusions drawn from these studies partial and does not reflect the relationship between tumor size and prognosis in a comprehensive and intuitive way.

This study aimed to examine the relationship between tumor size and prognosis in SBA using data extracted from the Surveillance, Epidemiology, and End Results (SEER) database. Tumor size was treated as a continuous variable, and confounding factors were adjusted for. Restricted cubic splines (RCS) were used to plot the relationship between tumor size and prognosis in a more intuitive manner. To facilitate clinical analysis, the tumor size was divided into 11 groups at 1 cm intervals. The results of this study will provide a better understanding of the relationship between tumor size and prognosis in SBA and establish an improved T-stage classification based on tumor size and tumor invasion, that can help inform clinical decision making.

2. Method

2.1. Population

Data of 25,695 SBA patients from 2004 to 2019 were collected from the SEER database using the SEER*Stat software (version 8.4.0.1). Patients with primary tumor site of C17.0-duodenum/C17.1-jejunum/C17.2-ileum were included in this study, excluding patients with primary tumor site of C24.1-Vater ampulla. The last follow-up time of this study was November 2019. Data were submitted in November 2021 and released in April 2022. The SEER database is a cancer registry system established by the National Cancer Institute in the United States that regularly collects follow-up data on patients' demographic data, primary tumor characteristics (including location and spread), main treatment processes, and life status. The cases included in this study met the following criteria: (1) pathology confirmed as SBA, (2) surgery and complete postoperative follow-up data, that is, whether the patient survived and the month of survival, and whether lymph node metastasis and distant metastasis occurred during the follow-up period and (3) histological type code 8140–8380. Patients with unknown tumor location, size, TNM staging, race, and degree of differentiation were excluded.

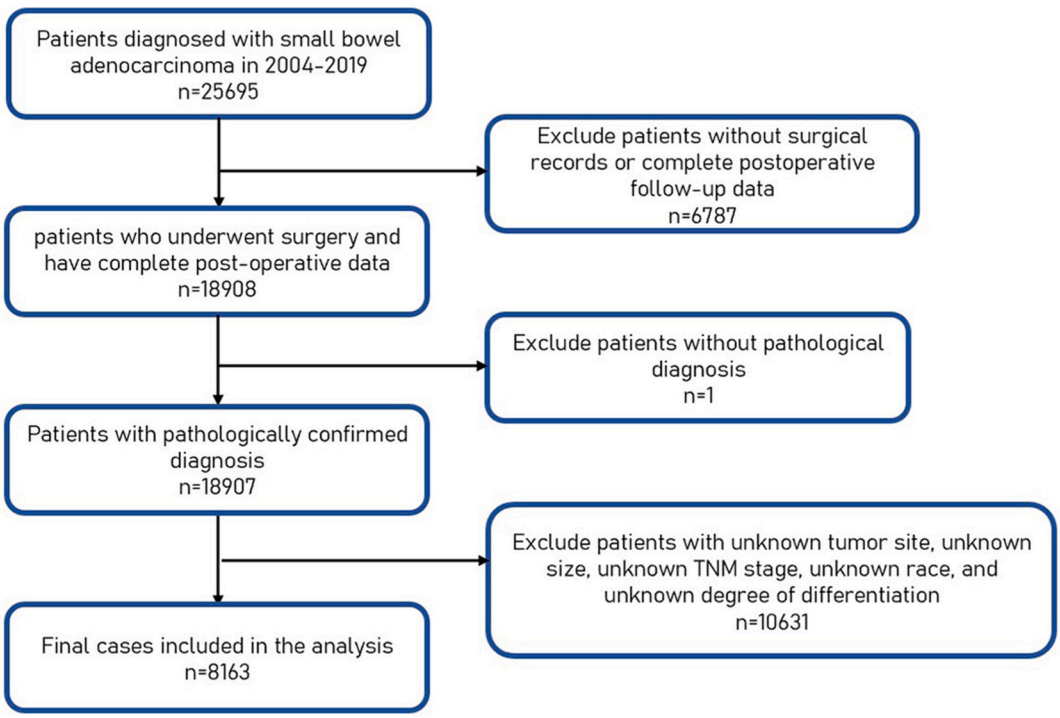

Fig. 1. Selection process of final cases included in the analysis.

Ultimately, 8163 eligible patients were included in the analysis (Fig. 1). The SEER database is a public database; therefore, no institutional ethics approval or informed consent was required.

The variables extracted from the SEER database included age, sex, race, tumor location, grade, TNM stage, total number of in situ/malignant tumors, harvested lymph nodes, survival time, cause of death, and survival status. Tumor size was grouped in intervals of 1 cm, with tumors >10 cm being merged into one group due to limited cases (11 subgroups:1 [0–1 cm], 2 [1.1–2 cm], 3 [2.1–3 cm], 4 [3.1–4 cm], 5 [4.1–5 cm], 6 [5.1–6 cm], 7 [6.1–7 cm], 8 [7.1–8 cm], 9 [8.1–9 cm], 10 [9.1–10 cm], and 11 [>10 cm]). The tumor size was also treated as a continuous variable. The study outcomes were the OS and cancer-specific survival (CSS). OS was defined as the time from diagnosis to death due to any cause. CSS was defined as the time from diagnosis to death owing to SBA.

2.2. Statistical analysis

In this study, Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95 % confidence intervals (95%CIs) and to adjust for confounding factors, such as age, sex, race, tumor location, grade, TNM stage, number of in situ/malignant tumors, and number of harvested lymph nodes. The relationship between tumor size and OS or CSS was analyzed with tumor size as both a categorical and continuous variable to facilitate clinical decision-making and to have a general understanding of the relationship between tumor size and prognosis. Subgroup analysis was also performed for patients with lymph node metastasis and distant metastasis to determine if there were differences in the relationship between tumor size and prognosis in these patients. And then, RCS was used to visually display the relationship between tumor size and prognosis. In addition, according to the classification of AJCC T-stages of SBA, (T1 stage: tumor invasion of lamina propria and submucosa; T2 stage: the tumor invaded the proper muscle layer; T3: Cross the muscular layer to invade the subserous membrane or the tissue without peritoneal coverage; T4: Penetration of the peritoneum or direct invasion of other organs or structures classifies the depth of invasion), Spearman correlation coefficient was used to evaluate the statistical correlation between tumor size (mm) and tumor invasion depth (T-stage). Finally, an modified T-staging classification was generated based on tumor size and tumor invasion. Kaplan-Meier survival curves were used to estimate OS at different T stages. To evaluate the performance of the current AJCC T staging system, each AJCC T staging is stratified by mT (modified T-stage) staging. The log-rank test was used to evaluate the OS between each AJCC T stage subgroup. Statistical significance was set at $p < 0.05$, and all statistical analyses were performed using R version 4.2.1, with the completion of RCS using the "rms" package.

3. Results

In this study, 8163 patients were screened, and their characteristics are shown in Table 1. The median tumor diameter was 2.1 cm. Among these patients, 4036 (49.4 %) had tumors that were less than or equal to 2 cm in size, and 4127 (50.6 %) had tumors larger than 2 cm. Lymph node or distant metastasis was observed in 60.1 % of the patients, while 39.9 % did not.

As shown in Table 2, when using OS or CSS as the outcome variable in the unadjusted Cox proportional hazard regression, when tumor size was a categorical variable, the HR value showed a turning point in the 4th group (3.1–4 cm), where HR was positively correlated with tumor size below the turning point and showed a fluctuating trend with tumor size above the turning point. When tumor size was a continuous variable, the HR were 1.032 (95 % CI 1.027–1.037; $P < 0.001$) for OS and 1.039 (95 % CI 1.034–1.044; $P < 0.001$) for CSS. After adjusting for confounders, the results were similar to those of the unadjusted analysis, with a turning point compared to the 3rd and 5th groups in the 4th group. When tumor size was a continuous variable, the HR was 1.008 (95 % CI 0.997–1.019; $P = 0.04$) for OS and 1.021 (95 % CI 1.009–1.032; $P < 0.001$) for CSS.

The adjusted Cox model was plotted as RCS (Fig. 2) to visualize the relationship between tumor size and prognosis. A median value of 2.1 cm was chosen as a reference. When the tumor size was 3 cm, the steep curve flattened.

To further observe the difference in the relationship between tumor size and prognosis in patients with or without metastasis, a subgroup analysis was performed on patients with or without lymph node metastasis or distant metastasis. We analyzed the relationship between tumor size and OS and CSS after adjustment using the Cox model. In the non-metastasis group, HR showed an upward trend with tumor size in groups 1–4 (0–4 cm), whereas in groups 5–11 (≥4.1 cm), HR showed an up-and-down fluctuation. A similar distribution was observed in the metastatic group (Table 3). We plotted the relationship between tumor size and SBA with or without lymph node metastasis or distant metastasis adjusted for the Cox model as RCS curves. In the RCS graph for the non-metastasis group (Fig. 3) with OS as the endpoint, HR increased with tumor size when the tumor size was less than 3 cm and decreased with tumor size when the tumor size was greater than 3 cm. A similar trend was observed when CSS was the endpoint, with a turning point of 4 cm. In the metastasis group (Fig. 3), the HR was positively correlated with tumor size regardless of the endpoint (OS or CSS), and the curve became flat when the tumor size exceeded 3 cm.

There was a positive correlation between tumor size and tumor invasion depth (T stage), and the Spearman correlation coefficient was 0.583 ($P < 0.001$), which was statistically significant. The included SBA patients were classified according to the eighth edition of AJCC T stage, with T1 stage accounting for 18.2 %, T2 stage 17.2 %, T3 stage 37.0 %, and T4 stage 27.7 %. Groups with overlapping survival curves were progressively combined based on tumor size and depth of invasion until a statistically significant difference was determined by log-rank test. Final grouping based on tumor size and depth of invasion resulted in an improved T-stage classification (Table 4). As shown in Table 4. The proportion of patients with mT1 to mT4 was 32.4 %, 25.2 %, 29.1 % and 13.2 %, respectively. According to AJCC T staging, the 5-year survival rates of T1, T2, T3 and T4 patients were 81.8 %, 81.1 %, 66.0 % and 50.9 % ($P < 0.001$) (Fig. 4A). Using the modified T staging classification, the 5-year survival rates of mT1, mT2, mT3 and mT4 patients were 82.8 %, 70.6 %, 60.7 % and 39.8 % ($P < 0.001$) (Fig. 4B). It can be seen that it is better to stratify patients according to mT stage than AJCC T stage. The 5-year survival rate difference between the neighboring groups of mT1 to mT4 disease is 12.2 %, 9.9 %, 20.9 %, respectively,

Table 1
Baseline clinical characteristics of SBA patients according to tumor size.

Variables	Overall	Ts group									
		0–1	1.1–2	2.1–3	3.1–4	4.1–5	5.1–6	6.1–7	7.1–8	8.1–9	9.1–10	>10
Age												
<45	668(8.2)	178(9.7)	157(7.1)	126(7.8)	83(8.9)	42(7.5)	29(7.2)	22(8.7)	9(6.3)	5(6.3)	8(13.6)	9(11.1)
45–59	2436(29.8)	548(30.0)	675(30.6)	506(31.4)	247(26.5)	160(28.5)	126(31.3)	64(25.3)	47(32.6)	25(31.3)	13(22.0)	25(30.9)
60–74	3384(41.5)	780(42.6)	938(42.5)	687(42.6)	375(40.2)	218(38.8)	158(39.2)	102(40.3)	48(33.3)	29(36.3)	21(35.6)	28(34.6)
≥75	1675(20.5)	323(17.7)	437(19.8)	294(18.6)	227(24.4)	142(25.3)	90(22.3)	65(25.7)	40(27.8)	21(26.3)	17(28.8)	19(23.5)
Sex												
Female	3872(47.4)	937(51.2)	1037(47.0)	751(46.6)	426(45.7)	284(50.5)	181(44.9)	102(40.3)	53(36.8)	41(51.3)	32(54.2)	28(34.6)
Male	4291(52.6)	892(48.8)	1170(53.0)	862(53.4)	506(54.3)	278(49.5)	222(55.1)	151(59.7)	91(63.2)	39(48.8)	27(45.8)	53(65.4)
Race												
Black	1260(15.4)	322(17.6)	298(13.5)	236(14.6)	135(14.5)	90(16.0)	68(16.9)	51(20.2)	22(15.3)	15(18.8)	11(18.6)	12(14.8)
White	6522(79.9)	1419(77.6)	1827(82.8)	1308(81.1)	749(80.4)	440(78.3)	313(77.7)	188(74.3)	108(75.0)	61(76.3)	43(72.9)	66(81.5)
Other	381(4.7)	88(4.8)	82(3.7)	69(4.3)	48(5.2)	32(5.7)	22(5.5)	14(5.5)	14(9.7)	4(5.0)	5(8.5)	3(3.7)
Location												
Duodenum	2933(35.9)	964(52.7)	482(21.8)	375(23.2)	380(40.8)	264(47.0)	193(48.0)	140(55.3)	50(34.7)	37(46.3)	17(28.8)	31(38.3)
Jejunum	1175(14.4)	86(4.7)	261(11.8)	243(15.1)	165(17.7)	142(25.3)	104(25.8)	54(21.3)	52(36.1)	24(30.0)	20(33.9)	24(29.6)
Ileum	4055(48.8)	779(40.1)	1464(65.6)	995(61.4)	387(41.5)	156(27.6)	106(26.0)	59(23.3)	42(28.5)	19(23.8)	22(37.3)	26(32.1)
Grade												
1	4442(54.4)	1523(83.3)	1509(68.4)	830(51.5)	298(32.0)	121(21.5)	72(17.9)	36(14.2)	21(14.6)	14(17.5)	4(6.8)	14(17.3)
2	2565(31.4)	284(15.5)	556(25.2)	567(35.2)	396(42.5)	280(49.8)	212(52.6)	117(46.2)	63(43.8)	34(42.5)	25(42.4)	31(38.3)
3	1094(13.4)	20(1.1)	129(5.8)	201(12.5)	230(24.7)	156(27.8)	111(27.5)	97(38.3)	54(37.5)	32(40.0)	29(49.2)	35(43.2)
4	62(0.8)	2(0.1)	13(0.6)	15(0.9)	8(0.9)	5(0.9)	8(2.0)	3(1.2)	6(4.2)	0(0.0)	1(1.7)	1(1.2)
T												
T1	1486(18.2)	1320(72.2)	69(3.1)	36(2.2)	16(1.7)	11(2.0)	17(4.2)	5(2.0)	7(4.9)	0(0.0)	1(1.7)	4(4.9)
T2	1400(17.2)	266(14.5)	745(33.8)	211(13.1)	66(7.1)	37(6.6)	31(7.7)	18(7.1)	12(8.3)	4(5.0)	6(10.2)	4(4.9)
T3	3018(37.0)	179(9.8)	880(39.9)	764(47.4)	456(48.9)	259(46.1)	199(49.4)	122(48.2)	68(47.2)	41(51.3)	23(39.0)	27(33.3)
T4	2259(27.7)	64(3.5)	513(23.2)	602(37.3)	394(42.3)	255(45.4)	156(38.7)	108(42.7)	57(39.6)	35(43.8)	29(49.2)	46(56.8)
N												
N0	3542(43.4)	1377(75.3)	749(33.9)	441(27.3)	300(32.2)	231(41.1)	176(43.7)	99(39.1)	66(45.8)	36(45.0)	23(39.0)	44(54.3)
N1	4158(50.9)	446(24.4)	1402(63.5)	1077(66.8)	537(57.6)	263(46.8)	173(42.9)	117(46.2)	60(41.7)	35(43.8)	27(45.8)	21(25.9)
N2	461(5.6)	6(0.3)	56(2.5)	95(5.9)	95(10.2)	68(12.1)	54(13.4)	37(14.6)	18(12.5)	9(11.3)	9(15.3)	16(19.8)
M												
M0	6736(82.5)	1750(95.7)	1768(80.1)	1181(73.2)	724(77.7)	471(83.8)	323(80.0)	228(90.1)	115(79.9)	67(83.7)	47(79.7)	62(76.5)
M1	1427(17.5)	79(4.3)	439(19.9)	432(26.8)	208(22.3)	91(16.2)	80(20.0)	25(9.9)	29(20.1)	13(16.3)	12(20.3)	19(23.5)
Total number of in situ/malignant tumors												
1	5615(68.8)	1245(68.1)	1551(70.3)	1136(70.4)	647(69.4)	381(67.8)	262(65.0)	169(66.8)	87(60.4)	49(61.3)	37(62.7)	50(61.7)
>1	2549(31.2)	584(31.9)	656(29.7)	477(29.6)	285(30.6)	181(32.2)	141(35.0)	84(33.2)	57(39.6)	31(38.8)	22(37.3)	31(38.3)
Lymph node metastases or distant metastases												
no	3254(39.9)	1347(73.6)	669(30.3)	352(21.8)	260(27.9)	218(38.8)	159(39.5)	94(37.2)	61(42.4)	33(41.3)	21(35.6)	40(49.4)
yes	4909(60.1)	482(26.4)	1538(69.7)	1261(79.2)	672(72.1)	344(61.2)	244(60.5)	159(62.8)	83(57.6)	47(58.7)	38(64.4)	41(50.6)
Harvested lymph nodes(median [IQR])												
	11.00 (2.00,14.00)	10.00 (2.00,17.00)	10.00 (6.00,18.00)	12.00 (6.00,19.00)	12.00 (6.00,19.00)	12.00 (6.00,19.00)	13.00 (6.00,19.00)	14.00 (7.00,19.00)	12.00 (6.00,17.00)	13.00 (9.00,18.25)	14.00 (8.50,21.50)	14.00 (7.00,21.00)

Table 2
Cox proportional hazards models with OS and OSS as outcome variables.

	Model1		Model2		Model3		Model4	
Tumor size	HR (95 % CI)	P value	HR (95 % CI)	P value	HR (95 % CI)	P value	HR (95 % CI)	P value
0–1 cm	1		1		1	Ref	1	Ref
1–2 cm	1.493(1.303–1.711)	**<0.001**	2.752(2.197–3.447)	**<0.001**	1.025(0.856–1.23)	0.79	1.094(0.830–1.443)	0.52
2–3 cm	2.133(1.862–2.444)	**<0.001**	4.683(3.755–5.840)	**<0.001**	1.129(0.939–1.358)	0.20	1.251(0.948–1.652)	0.11
3–4 cm	3.288(2.852–3.792)	**<0.001**	8.501(6.804–10.621)	**<0.001**	1.304(1.073–1.583)	**0.007**	1.650(1.242–2.191)	**<0.001**
4–5 cm	3.175(2.706–3.725)	**<0.001**	8.338(6.578–10.569)	**<0.001**	1.140(0.925–1.405)	0.22	1.461(1.086–1.966)	**0.01**
5–6 cm	2.715(2.263–3.256)	**<0.001**	6.894(5.324–8.926)	**<0.001**	1.008(0.8053–1.263)	0.94	1.262(0.923–1.726)	0.14
6–7 cm	3.077(2.503–3.783)	**<0.001**	7.751(5.849–10.272)	**<0.001**	0.989(0.771–1.27)	0.93	1.221(0.873–1.7082)	0.24
7–8 cm	3.069(2.379–3.959)	**<0.001**	7.929(5.709–11.012)	**<0.001**	1.204(0.904–1.605)	0.20	1.519(1.045–2.207)	**0.03**
8–9 cm	3.892(2.848–5.318)	**<0.001**	8.826(5.893–13.220)	**<0.001**	1.389(0.987–1.955)	0.06	1.598(1.025–2.489)	**0.04**
9–10 cm	3.161(2.174–4.597)	**<0.001**	6.316(3.821–10.441)	**<0.001**	0.913(0.612–1.363)	0.66	0.881(0.515–1.504)	0.64
>10 cm	3.807(2.786–5.203)	**<0.001**	9.852(6.697–14.494)	**<0.001**	1.406(1.000–1.977)	**0.04**	1.733(1.129–2.659)	**0.01**
Tumor size*	1.032(1.027–1.037)	**<0.001**	1.039(1.034–1.044)	**<0.001**	1.008(0.997–1.019)	**0.04**	1.021(1.009–1.032)	**0.03**

Model1: Unadjusted Cox proportional hazards model with OS as the outcome variable.
Model2: Unadjusted Cox proportional hazards model with CSS as the outcome variable.
Model3: Cox proportional hazards model adjusted for age, sex, race, tumor location, grade, T stage, N stage, M stage, total number of in situ/malignant tumors and harvested lymph nodes with OS as the outcome variable.
Model4: Cox proportional hazards model adjusted for age, sex, race, tumor location, grade, T stage, N stage, M stage, total number of in situ/malignant tumors and harvested lymph nodes with CSS as the outcome variable.
Tumor size*: Tumor size as continuous variable is included in model.

and the 5-year survival rate difference between the neighboring groups of AJCC T1 to T4 stage is 0.7 %, 15.1 %, and 15.1 %, respectively. Subsequently, cross-stratification was used to stratify the T stages of AJCC by modified T stages, showing that patients with significant heterogeneity were misclassified into AJCC T1, T2, T3, and T4 groups (Fig. 5). In the AJCC T1 group, significant survival differences were observed when patients were classified according to a mT stage classification. The 5-year survival rates of mT1 and mT2 patients were 82.4 % and 66.8 % (Fig. 5A, $P < 0.001$). In the AJCC T2 group, significant survival differences were also observed when patients were classified based on modified T staging. 5-year survival rates for mT1 and mT2 patients were 83.2 % and 67.2 % (Fig. 5B, $P < 0.001$). In the AJCC T3 group, significant survival differences were also observed when patients were classified based on modified T staging; The 5-year survival rates for mT2 and mT3 patients were 70.2 % and 58.9 % (Fig. 5C, $P < 0.001$). In the AJCC T4 group, classified by modified T stage, 5-year survival rates were 61.1 % and 39.8 % in mT3 and mT4 patients (Fig. 5D, $P < 0.001$).

As shown in Table S1, we conducted a study on the impact of basic characteristics and clinicopathological features of 8163 patients included in the research on survival time. Cox univariate proportional hazards analysis indicated that age, sex, tumor size, tumor grade, TNM staging, number of primary malignant tumors, and tumor location had a significant impact on overall survival ($P < 0.001$). Univariate proportional hazards analysis suggested that race had no statistically significant impact on overall survival ($P = 0.059$). After adjusting for other influencing factors, those with univariate proportional hazards $P < 0.1$ were included in the Cox multivariate proportional hazards model for further analysis. This study found that advanced age, male sex, tumor size $\geq$3 cm, histological moderate-to-poor differentiation, TNM stages II, III, and IV, and the presence of more than one primary malignant tumor were independent prognostic factors for poor outcomes in SBA. Individuals of other races had a better prognosis than Black and White individuals. The prognosis was better for ileal adenocarcinoma and jejunal adenocarcinoma than for duodenal adenocarcinoma.

4. Discussion

The value of tumor size in predicting prognosis has been established in many solid organs, but it remains controversial in small-bowel cancer. In this retrospective study, the relationship between tumor size and prognosis of SBA was analyzed using a large dataset. Our study found that tumor size had a statistically significant relationship with prognosis in patients with SBA who underwent surgery and had a history of metastasis (including lymph node and distant metastases). There was a negative correlation between tumor size and prognosis. however, when the tumor was less than 3 cm, the relationship between tumor size and prognosis was closer than that when the tumor was larger than 3 cm.

Regarding the relationship between the size of SBA and prognosis, there is currently no study that considers tumor size as a continuous variable. Lee et al. [14] included 42 patients with SBA who underwent surgery at the West China Hospital of Sichuan University between 2001 and 2013. Tumor size was divided into two groups, <5 cm and $\geq$5 cm, and a univariate Cox proportional hazards model proved that tumor size was an independent factor for poor prognosis of SBA. Another study of 30 patients with SBA treated by surgery from 1990 to 2009 divided tumor size into two subgroups, <7 cm and $\geq$7 cm, and through univariate and multivariate Cox proportional hazards models, it was proven that tumor size was an independent factor for the prognosis of SBA [13]. The above two studies, although different in grouping, both proved the correlation between tumor size and prognosis in SBA, which is in line with our conclusion. However, due to the limited sample size and analysis of tumor size as a categorical variable, the conclusions have some limitations. Our study utilized a large sample size and analyzed tumor size as a continuous variable, which can result in a more reliable conclusion.

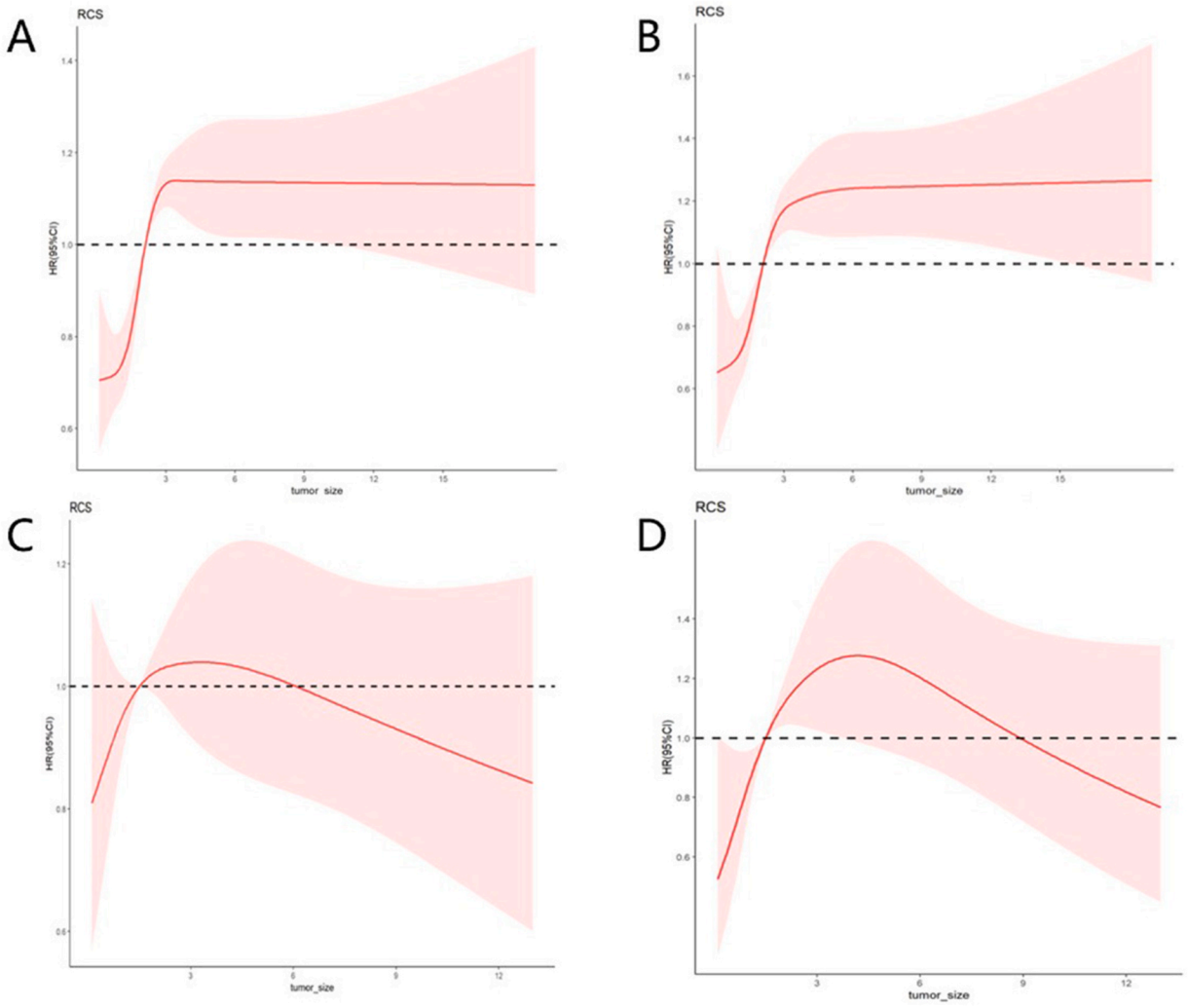

Fig. 2. RCS curves of the association between tumor size and prognosis of SBA after adjustment by Cox model. Red lines = estimated HR of tumor size (2.1 cm reference); shadow area = 95 % CI. (A) RCS curves for OS as study outcome variable. (B) RCS curves for CSS as study outcome variable.

Because SBA is a rare disease, there is currently a lack of research on this subject, and conclusions are usually drawn from studies related to colorectal cancer. Although it has not been included in the T stage of the TNM classification, many studies have already confirmed that the size of the tumor in colorectal cancer independently predicts prognosis [10,15–18]. However, some studies suggest that smaller tumors are associated with a poorer prognosis [9,11,19,20], On the other hand, another group of studies believes that a larger tumor size is associated with poor prognosis of the cancer [16,21]. The study by Li et al. [10] included 3971 patients with stage I-III colon cancer and divided the tumor size into two subgroups of $\leq$4 cm and >4 cm. Through a multivariable Cox proportional hazards model in a propensity score-matched cohort, it was found that tumor size $\leq$4 cm was an independent risk factor for colon cancer. DAI et al.' s research also yielded interesting results. They [18] confirmed that tumor size is the key clinical factor of T1 colon cancer, which has considerable prognostic and predictive value. At the same time, the study found that as T stage increased, the HR of tumor size decreased, meaning that the higher the degree of tumor invasion, the larger the volume of the tumor and the smaller the impact on the prognosis. A retrospective study based on SEER showed a significant negative correlation between colon cancer tumor size and prognosis, and the relationship between tumor size and prognosis was closer when the tumor diameter was less than 4 cm than when it was greater than 4 cm [12].

Several studies have investigated the adverse prognostic factors of SBA. Relevant research has shown that advanced age, elevated levels of tumor markers (CEA and CA19-9), primary site in the duodenum, poorly differentiated cancer, tumor stage T4, positive surgical margins, lymphatic/blood vessel invasion, number of lymph node metastases, incomplete resection of the primary tumor, low albumin, high lactate dehydrogenase, symptomatic presentation at diagnosis, stage III and IV SBA, residual cancer at surgical margins, extramural venous spread, and a history of Crohn's disease are all negative prognostic factors affecting the prognosis of SBA patients [22–24]. These findings were consistent with our conclusions. Compared to previous findings, our study additionally identified male sex and the presence of more than one primary malignant tumor as negative prognostic factors.

Table 3
Cox proportional hazards models with OS and OSS as outcome variables with or without lymph node metastases or distant metastases.

Tumor size	patients without metastases				patients with metastases			
	Model1		Model2		Model1		Model2	
	HR (95 % CI)	P value	HR (95 % CI)	P value	HR (95 % CI)	P value	HR (95 % CI)	P value
0–1 cm	1	Ref	1	Ref	1	Ref	1	Ref
1–2 cm	1.406(1.101–1.794)	**0.006**	1.599(1.056–2.422)	**0.03**	0.903(0.691–1.180)	0.45	0.995(0.686–1.442)	0.98
2–3 cm	1.658(1.263–2.178)	**<0.001**	1.790(1.150–2.787)	**0.009**	1.066(0.815–1.394)	0.64	1.236(0.853–1.790)	0.26
3–4 cm	1.581(1.180–2.118)	**0.002**	2.385(1.520–3.744)	**<0.001**	1.291(0.975–1.709)	0.07	1.618(1.107–2.366)	**0.01**
4–5 cm	1.323(0.961–1.822)	0.09	1.832(1.135–2.955)	**0.01**	1.139(0.846–1.533)	0.39	1.453(0.979–2.155)	0.06
5–6 cm	0.994(0.698–1.416)	0.97	1.273(0.748–2.166)	0.37	1.146(0.838–1.568)	0.39	1.450(0.964–2.184)	0.07
6–7 cm	1.334(0.897–1.986)	0.16	1.513(0.850–2.695)	0.16	0.870(0.620–1.221)	0.42	1.114(0.723–1.718)	0.62
7–8 cm	1.490(0.951–2.335)	0.08	1.716(0.906–3.247)	0.10	1.117(0.757–1.649)	0.58	1.495(0.926–2.413)	0.10
8–9 cm	1.846(1.092–3.120)	**0.02**	2.287(1.111–4.704)	**0.03**	1.256(0.791–1.994)	0.33	1.393(0.787–2.468)	0.26
9–10 cm	1.135(0.562–2.290)	0.72	0.674(0.201–2.254)	0.52	0.793(0.480–1.315)	0.37	0.874(0.467–1.635)	0.67
>10 cm	1.262(0.731–2.180)	0.40	1.431(0.680–3.011)	0.34	2.339(1.491–3.671)	**<0.001**	3.148(1.838–5.393)	**<0.001**
Tumor size*	0.991(0.969–1.014)	0.44	0.992(0.962–1.023)	0.61	1.025(1.007–1.043)	**0.006**	1.036(1.018–1.055)	**<0.001**

Model1: Cox proportional hazards model adjusted for age, sex, race, tumor location, grade, T stage, total number of in situ/malignant tumors and harvested lymph nodes with OS as the outcome variable.
Model2: Cox proportional hazards model adjusted for age, sex, race, tumor location, grade, T stage, total number of in situ/malignant tumors and harvested lymph nodes with CSS as the outcome variable.
Tumor size*: Tumor size as continuous variable is included in model.

Tumor size can serve as a simple indicator that is easily standardized across different hospital systems and has already been widely measured as part of routine pathology exams Although there may be differences between the evaluation of tumor size by imaging examination and the actual size of the tumor due to bowel movement and artifacts, imaging examination still has great significance in evaluating tumor size. In addition, the emergence of techniques such as multidetector CT enterography and spectral CT imaging have greatly improved the detection and characterization of the small bowel [25,26]. Therefore, if doctors and patients can judge the tumor prognosis based on the size of the tumor before surgery, it will have great significance for patients to more accurately determine prognosis and potentially influence decisions on postoperative treatment and monitoring. Currently, TNM staging is the most widely accepted system for risk stratification of SBA. However, the prognosis of patients with the same TNM stage varies greatly. Therefore, more readily available prognostic factors should be identified from daily medical records to improve prognostic prediction and develop personalized treatment strategies for SBA patients. According to our research results, we suggest that we can refer to the staging methods of, lung cancer, cervical tumor, small intestinal neuroendocrine tumor and so on [6,27–31], and adopt a combination of invasion depth and tumor size. In particular, neuroendocrine tumors of the small bowel, which are the same small bowel tumors as SBA, are staged by tumor invasion of lamina propria or muscularis mucosa with a tumor size of $\leq$1 cm, and T2 stage by tumor invasion of muscle propria, or tumor size >1 cm [30,31]. Based on Spearman's analysis, we found that there was a highly correlated relationship between tumor size and depth of invasion. This suggests that tumor size can also be included in the TNM staging of SBA to make a more accurate judgment of the disease process. Therefore, we adopted a modified T-stage classification. In this study, we combined tumor size with tumor invasion to create an improved T-stage classification. In the AJCC T stage, the 5-year survival rates for T1 and T2 were 81.8 % and 81.1 % respectively. In the revised T-stage, this ratio was 82.8 % and 70.6 % respectively. The revised T staging solves the shortcoming of the existing AJCC classification of T1 and T2 in terms of small difference in prognosis, and improves the discriminability of prognosis among various T stage groups of SBA patients.

which is of great help to the treatment decision-making, to determine the scope of resection and the choice of postoperative adjuvant treatment, so as to improve the prognosis of patients.

Although the relationship between tumor size and prognosis has been established, the mechanism of tumor formation remains unclear. The reasons for us to reach this conclusion may include the following: First, it is speculated that this is because larger tumors are often accompanied by more obvious biological features and clinical presentations, such as anemia, which leads to a poorer prognosis [2]. Moreover, when the size of a growing tumor within a cavity exceeds the diameter of the small bowel (3–4 cm), it can cause symptoms of intestinal obstruction and help patients detect and treat SBA at an earlier stage for better prognosis [32,33]. Second, a larger tumor size means that more intestinal segments will be removed and cleared [34], which may reduce the likelihood of cancer recurrence, thereby decreasing the possibility of long-term adverse prognosis. Third, for patients with SBA without metastasis, these types of tumors, even if larger, do not have distant metastasis and are often accompanied by better grading and lower invasiveness, which may be the reason why prognosis is negatively correlated with tumor size when the tumor is $\geq$ 4.1 cm. For patients with metastatic SBA, larger tumors are often associated with a higher likelihood of metastasis and worse stage [35]. Therefore, when the tumor size was $\geq$3 cm, the prognosis remained positively correlated with tumor size.

This study is the first to examine the relationship between tumor size and prognosis as a continuous variable, which helps improve the accuracy of predictions. We used RCS curves to better reveal the nonlinear relationship between tumor size and prognosis. Our study also has some limitations, the main limitation of our study is the retrospective nature using the administrative registry database with limited variables. Moreover, being a retrospective analysis, excluding patients without surgical resection, pathological non-confirmation, or insufficient data, with over 60 % of the patients not included in our study, leading to selection bias. Additionally,

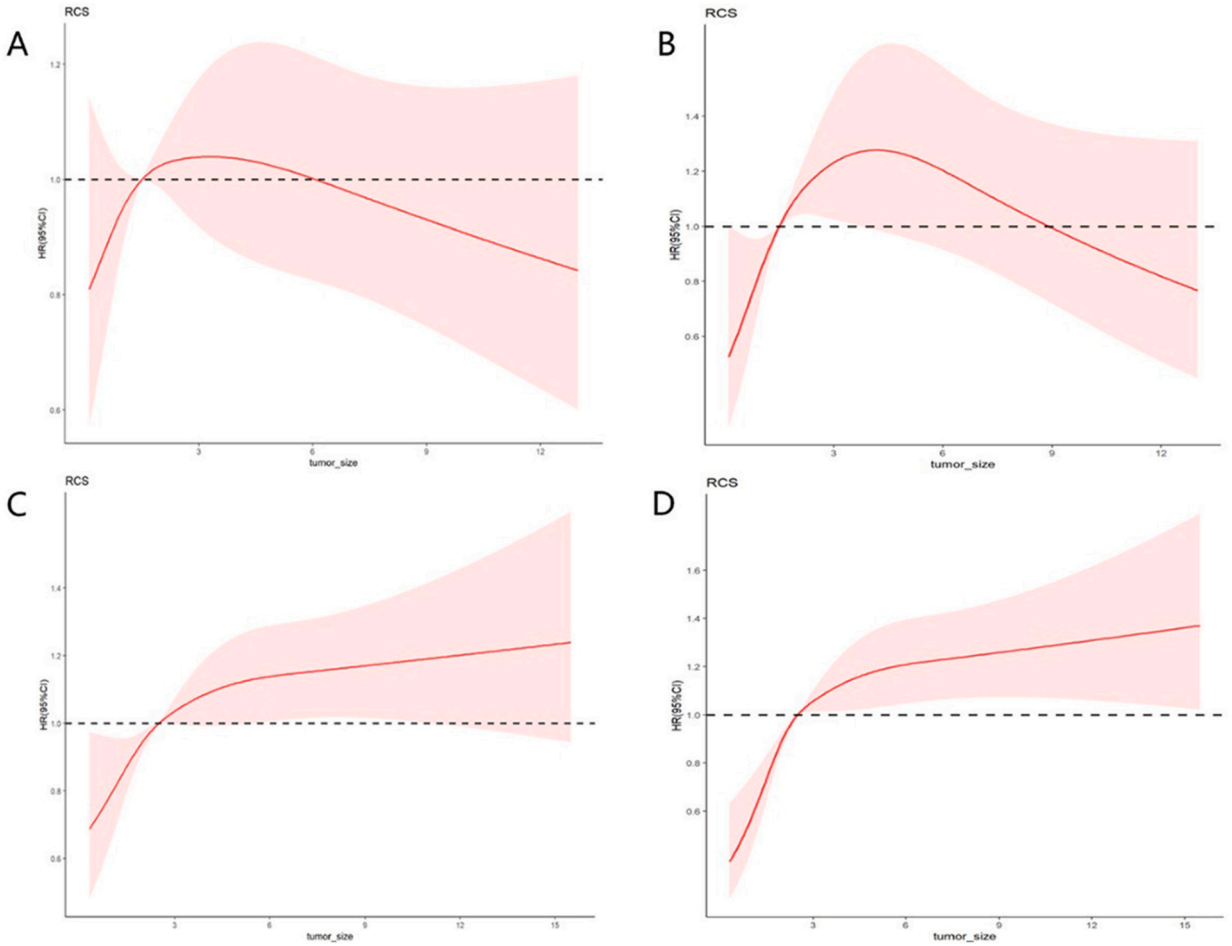

Fig. 3. RCS curves of the association between tumor size and prognosis of SBA with patients with or without lymph node metastases and distant metastases after adjustment by Cox model. Red lines = estimated HR of tumor size (1.5 cm reference); shadow area = 95 % CI. (A), (B) are non-metastatic subgroups. (A) RCS curves for OS as outcome variable. (B) RCS curves for CSS as outcome variable. (C), (D) are metastatic subgroups. (C) RCS curves for OS as outcome variable. (D) RCS curves for CSS as outcome variable.

Table 4
Modified T-stage classification based on nearest-neighborhood grouping analysis of patients with SBA in the SEER database.

	Tumor size	
Extent of tumor invasion	<3cm	≥3cm
Invasion of lamina propria, submucosa, muscularis propria	mT1	mT2
Invasion of subserous or non-peritoneal covered tissues through the muscular layer	mT2	mT3
Penetrates the peritoneum or directly invades other organs or structures	mT3	mT4

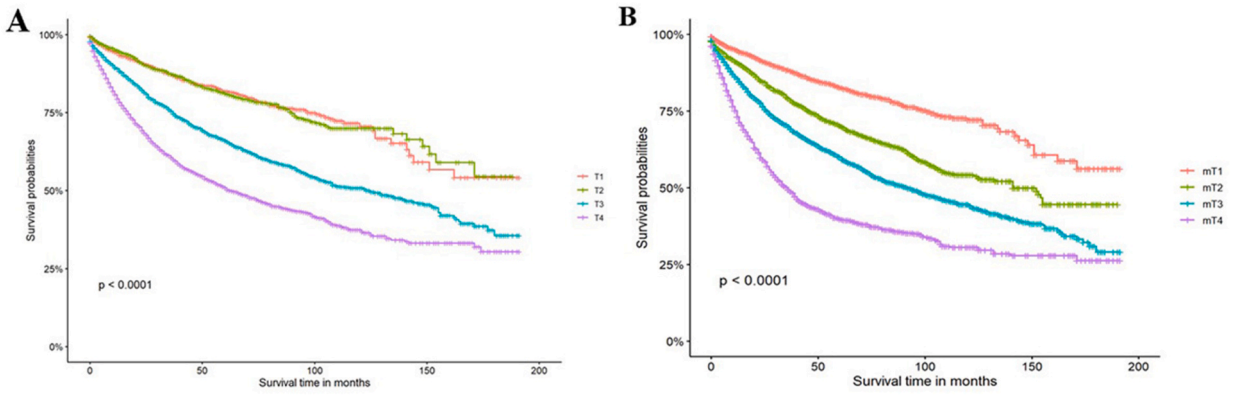

Fig. 4. (A) Overall survival analysis of AJCC T-stage and (B) Overall survival analysis of modified T-stage.

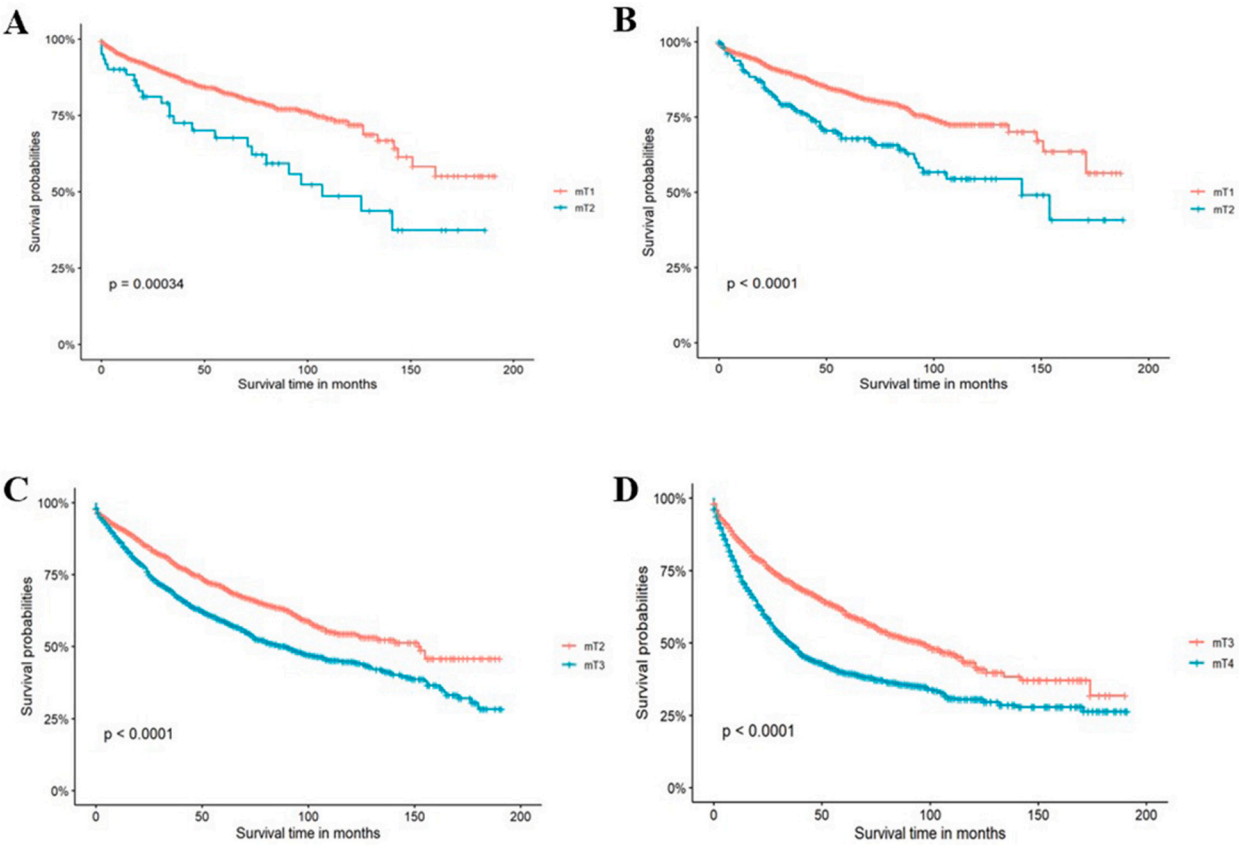

Fig. 5. Overall survival analysis of each AJCC T-stage stratified by the modified T-stage classification in the training dataset. (A) T1-stage (B) T2-stage (C) T3-stage (D) T4-stage.

we were unable to know the patient's past medical history, such as whether patients had any previous SBA-related diseases. Nor the form of occurrence of the disease, for example whether the presentation of the tumor was urgently with obstruction or perforation. we were unable to collect more detailed information on treatment, such as cancer antigens, vascular invasion, chemotherapy drugs, and number of treatment cycles. Our analysis did not consider adjuvant chemotherapy. Despite these limitations, our study is the largest to date on SBA tumor size and prognosis, and tumor size was found to have prognostic significance.

In conclusion, this study has revealed the relationship between SBA size and prognosis. When tumor size is used in a quantitative way, tumor size is an independent predictor of poor outcome in patients with SBA. Furthermore, we established a modified T-stage based on tumor size and depth of invasion.

Declaration section

i) Ethics approval and consent to participate: Not Applicable.
ii) Consent for publication: Yes
iii) Competing interests: There are no relevant financial or non-financial competing interests to report
iv) Funding: Dalian Science and Technology Innovation Fund (2023JJ13SN050)

Data availability statement

Availability of Data and Material (ADM): The datasets used and/or analyzed during the current study have been stored in a publicly accessible repository.

CRediT authorship contribution statement

Jialin Zhou: Writing – original draft, Data curation. **Cong Wang:** Writing – original draft, Formal analysis. **Tingcong Lv:** Writing – original draft, Conceptualization. **Zhe Fan:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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No.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e36881.

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