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可切除膀胱肉瘤样癌患者临床病理特征及预后影响因素分析*

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【摘要】 **目的** 探究可切除膀胱肉瘤样癌（sarcomatoid carcinoma of the bladder, SCB）患者的临床病理特征及其预后影响因素。**方法** 回顾性分析2008年9月–2023年12月天津医科大学第二医院收治的可切除SCB患者的临床病理资料。根据手术方式分为保留膀胱手术（bladder-preserving surgery, BPS）组和根治性膀胱切除术（radical cystectomy, RC）组。采用Kaplan-Meier曲线评估两组患者总生存期，并采用Cox回归模型分析影响生存的危险因素。**结果** 共纳入77例可切除SCB患者，其中35例（45.5%）BPS组，42例（54.5%）RC组。Ki-67表达≥30%占91.7%，细胞角蛋白（cytokeratin, CK）阳性92.2%，波形蛋白（vimentin）阳性98.1%，人表皮生长因子受体2（human epidermal growth factor receptor 2, Her-2）评分为“0”和“1+”的比例分别为62.5%（5/8）和37.5%（3/8）。中位随访时间23.2个月(范围：0.4～164.7个月)，BPS组和RC组的1年、3年和5年生存率分别为76.2% vs. 84.9%、46.7% vs. 61.1%、35.6% vs.43.2%。多因素Cox回归分析显示，RC组中年龄≥75岁〔风险比（hazard ratio, HR）=3.836, 95%置信区间（confidence interval, CI）: 1.168～12.595, *P*=0.027〕、肿瘤多发（HR=3.439, 95%CI: 1.235～9.574, *P*=0.018）以及未接受术后辅助治疗（HR=3.164, 95%CI: 1.015～9.862, *P*=0.047）是影响生存的独立危险因素。BPS组中，女性性别是影响生存的独立危险因素（HR=3.601, 95%CI: 1.200～10.804, *P*=0.022）。**结论** Ki-67、CK和vimentin在可切除SCB患者中显著高表达，Her-2则呈零表达或低表达。在RC患者中，肿瘤多发、年龄≥75岁及未接受术后辅助治疗是影响总生存期的独立危险因素，女性性别是影响BPS患者预后的独立危险因素。

【关键词】 膀胱 肉瘤样癌 预后 回顾性研究 危险因素

Analysis of Clinicopathological Characteristics and Factors Affecting the Prognosis of Patients With Resectable Sarcomatoid Carcinoma of the Bladder

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【Abstract】 **Objective** To investigate the clinicopathological characteristics and the factors affecting the prognosis of patients with resectable sarcomatoid carcinoma of the bladder (SCB). **Methods** A retrospective analysis was conducted with the clinical data of patients with resectable SCB treated at the Second Hospital of Tianjin Medical University between September 2008 and December 2023. The patients were divided into two groups, a bladder-preserving surgery (BPS) group and a radical cystectomy (RC) group, according to the specific surgical approach used for each patient. Kaplan-Meier survival curves were used to evaluate overall survival (OS) in both groups, and Cox regression models were employed to identify risk factors affecting survival. **Results** A total of 77 patients with resectable SCB were included. Among them, 35 patients (45.5%) underwent BPS, while 42 patients (54.5%) underwent RC. Ki-67 expression≥30% was observed in 91.7% of the patients. A total of 92.2% of the patients was tested positive for cytokeratin (CK) and 98.1% for vimentin. In addition, 62.5% and 37.5% of patients had the human epidermal growth factor receptor 2 (Her-2) scores of 0 and 1+, respectively. The median follow-up time was 23.2 months (ranging from 0.4 to 164.7 months). The 1-year, 3-year, and 5-year survival rates for the BPS group and the RC group were as follows, 76.2% vs. 84.9%, 46.7% vs. 61.1%, and 35.6% vs. 43.2%, respectively. Multivariate Cox regression analysis revealed that in the RC group, age≥75 years old (hazard ratio [HR]=3.836, 95% confidence interval [CI]: 1.168-12.595, *P*=0.027), tumor multiplicity (HR=3.439, 95% CI: 1.235-9.574, *P*=0.018), and lack of adjuvant therapy (HR=3.164, 95% CI: 1.015-9.862, *P*=0.047) were independent risk factors affecting survival. In the BPS group, female sex was identified as an independent risk factor for survival (HR=3.601, 95% CI: 1.200-10.804, *P*=0.022). **Conclusion** Ki-67, CK, and vimentin are significantly overexpressed in SCB patients, while Her-2 is either unexpressed or expressed at low levels. In the RC group, tumor multiplicity, age ≥75

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years, and lack of postoperative adjuvant therapy are independent risk factors for overall survival. Female sex is an independent risk factor affecting prognosis in the BPS group.

【Key words】 Urinary bladder Sarcomatoid carcinoma Prognosis Retrospective studies Risk factors

膀胱肉瘤样癌(sarcomatoidcarcinoma of the bladder, SCB)和膀胱癌肉瘤曾被视为两种不同的膀胱癌病理亚型。然而，2016版世界卫生组织恶性尿路上皮癌病理分级体系将二者统称为SCB，定义为由上皮细胞和间充质细胞组成的恶性双相型肿瘤[1-2]。SCB是一种罕见的尿路上皮癌组织学变异，占尿路上皮癌的0.1%～0.3%[3-4]。目前，与SCB预后相关的文献主要为小样本研究或个案报道[2, 5-6]。由于其病理类型的罕见性及对其认识相对不足，目前还没有相关的治疗指南或推荐[6]。本研究旨在收集可切除SCB患者的临床资料，总结、分析其临床病理特征，探究影响患者预后的危险因素。

1 资料与方法

1.1 研究对象

将2008年9月–2023年12月在天津医科大学第二医院接受手术治疗，且术后病理证实为SCB的患者纳入本研究。本研究经天津医科大学第二医院医学伦理委员会审查并批准(批准号：KY2024K213)。

纳入标准：①临床分期T1-T4aN0M0；②接受保膀胱手术(bladder preservation surgery, BPS)或根治性膀胱切除术(radical cystectomy, RC)治疗；③术后组织病理学证实为SCB。

排除标准：①术后接受了放射治疗；②同时伴有其他肿瘤。

1.2 数据收集

收集患者的临床资料，包括年龄、性别和吸烟史，以及与肿瘤相关的变量，例如肿瘤大小、数量、肿瘤T分期(按照美国癌症联合委员会第八版肿瘤分期系统)[7]、淋巴管血管侵犯情况。同时，记录患者接受的手术方式(BPS或RC)以及是否接受了术后辅助治疗(化疗和/或免疫治疗)。此外，收集患者的病理结果，包括镜下肉瘤样分化区域表现，以及肿瘤细胞核染色(Ki-67)、细胞角蛋白(cytokeratin, CK)、波形蛋白(vimentin)以及人表皮生长因子受体2(human epidermal growth factor receptor 2, Her-2)的表达情况。

1.3 随访及终点指标

术后至少每3～4个月复查一次，为期2年；此后每6个月复查一次，为期3年；此后每年复查一次。复查项目可包括膀胱镜检查、泌尿系彩超、尿脱落细胞检查以及胸和腹部CT等。在必要时，可以行全身骨显像检查。所有患者均通过电话或者门诊随访。

研究终点为总生存期(overall survival, OS)，定义为从手术日至任何原因死亡的时间。

1.4 统计学方法

采用R语言4.2.2版本统计软件分析数据，计数资料以例数(百分率)的形式呈现。分类资料的组间差异使用χ^2检验或Fisher确切概率法进行比较。生存曲线采用Kaplan-Meier法进行绘制，并使用log-rank检验进行比较。采用Cox回归模型计算相关因素的风险比(hazard ratio, HR)值及其95%置信区间(confidence interval, CI)，进行单因素和多因素分析以筛选影响SCB患者预后的危险因素。$P<0.05$为差异有统计学意义。

2 结果

2.1 基本情况

见表1。本研究共纳入77例可切除的SCB患者，其中35例(45.5%)接受了BPS，包括33例经尿道膀胱肿瘤电切术和2例膀胱部分切除术；其余42例(54.5%)接受了RC。37例(48.1%)接受了术后辅助治疗，其中15例(19.5%)接受了免疫检查点抑制剂(合并化疗或未化疗)，22例(28.6%)接受了单独化疗。在随访期间，共有14例患者失访，占18.2%。整体中位随访时间为23.2个月(范围：0.4～164.7个月)。与接受BPS的患者相比，接受RC的患者年龄较低，基线肿瘤T分期较高，差异有统计学意义($P<0.05$)；其余基线资料(包括性别、肿瘤大小、数目、有无术后辅助治疗等)的差异均无统计学意义。

2.2 病理学特征

镜下观察显示，肉瘤样分化区域存在大量梭形细胞，呈不规则束状或散在排列，具有一定的异形性(图1A、图1B)。免疫组化染色结果显示，Ki-67的表达水平在91.7%(44/48)的患者中≥30%，CK阳性表达率为92.2%(59/64)，而vimentin阳性表达率则高达98.1%(52/53)(图1C、图1D)。此外，在Her-2免疫组化评分中，评分为“0”的患者占62.5%(5/8)，评分为“1+”的患者占37.5%(3/8)(图1E、图1F)。

2.3 生存分析

Kaplan-Meier生存曲线显示，接受BPS和RC治疗的SCB患者在1年、3年和5年的生存率分别为：76.2% vs.

表 1　研究对象的基线资料

Table 1　The baseline data of the subjects

Variable	Total (n=77)	Bladder preservation surgery (n=35)	Radical cystectomy (n=42)	P
Age/case (%)				0.029
<75 yr.	38 (49.4)	12 (34.3)	26 (61.9)	
⩾75 yr.	39 (50.6)	23 (65.7)	16 (38.1)	
Sex/case (%)				>0.999
Male	60 (77.9)	27 (77.1)	33 (78.6)	
Female	17 (22.1)	8 (22.9)	9 (21.4)	
Smoking history/case (%)				0.755
Current	37 (48.1)	18 (51.4)	19 (45.2)	
Non-smoker	40 (51.9)	17 (48.6)	23 (54.8)	
Tumor size/case (%)				0.770
<5 cm	43 (68.8)	23 (65.7)	30 (71.4)	
⩾5 cm	24 (31.2)	12 (34.3)	12 (28.6)	
Number of tumor(s)/case (%)				0.673
Single	52 (67.5)	25 (71.4)	27 (64.3)	
Multifocal	25 (32.5)	10 (28.6)	15 (35.7)	
T stage/case (%)				<0.001
T1	23 (29.9)	19 (54.3)	4 (9.5)	
T2-T4a	54 (70.1)	16 (45.7)	38 (90.5)	
Lymphovascular invasion/case (%)				0.055
Present	65 (84.4)	33 (94.3)	32 (76.2)	
Absent	12 (15.6)	2 (5.7)	10 (23.8)	
Adjuvant therapy/case (%)				0.546
No	40 (51.9)	20 (57.1)	20 (47.6)	
Yes	37 (48.1)	15 (42.9)	22 (52.4)	

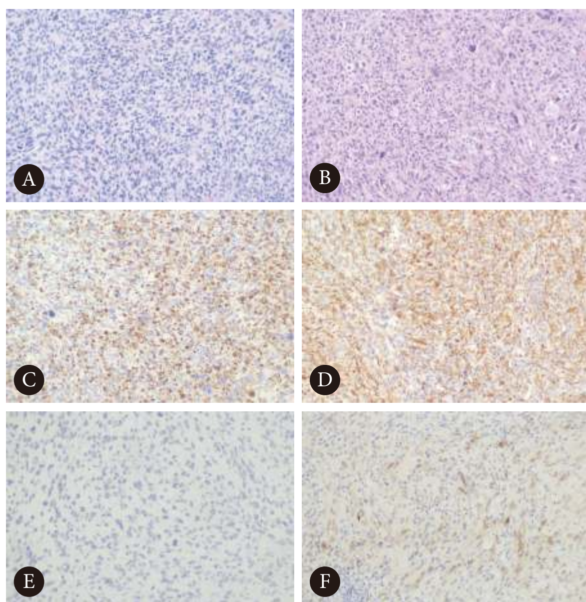

图 1 膀胱肉瘤样癌组织中肉瘤样分化区域的病理图片（×200）

Fig 1 Pathological images of sarcomatoid differentiation in sarcomatoid carcinoma of the bladder (original magnification ×200)

A and B, HE staining; C-F, CK (C) and vimentin (D) positive expression, Her-2 scores of "0" (E) and "1+" (F), immunohistochemistry staining.

84.9%、46.7% vs. 61.1%、35.6% vs. 43.2%。尽管差异无统计学意义，但接受RC治疗的SCB患者在生存期上表现出一定优势（中位OS: 53.4个月 vs. 34.0个月）。在接受RC治疗的SCB患者中，发病年龄小于75岁、肿瘤为单发或接受了术后辅助治疗的患者生存期较长（P< 0.05），见图2A～图2C。对于接受BPS治疗的SCB患者中，女性的预后较差（中位OS: 20.2个月vs. 47.4个月），差异有统计学意义（P= 0.014），见图2D。

在接受RC治疗的SCB患者中，单因素Cox回归分析结果显示，年龄⩾75岁、肿瘤多发以及未接受术后辅助治疗均与死亡风险显著相关（P< 0.05），见表2。使用双向逐步回归进行的多因素Cox回归分析结果显示，年龄⩾75岁（HR= 3.836, 95%CI: 1.168～12.595, P= 0.027）、肿瘤多发（HR= 3.439, 95%CI: 1.235～9.574, P= 0.018）以及未接受术后辅助治疗（HR= 3.164, 95%CI:1.015～9.862, P= 0.047）是独立的死亡危险因素，见表2。

对于接受BPS治疗的SCB患者，单因素Cox回归分析显示性别是生存的显著危险因素（HR= 3.601, 95%CI: 1.200～10.804, P= 0.022），见表3。进一步的双向逐步回归

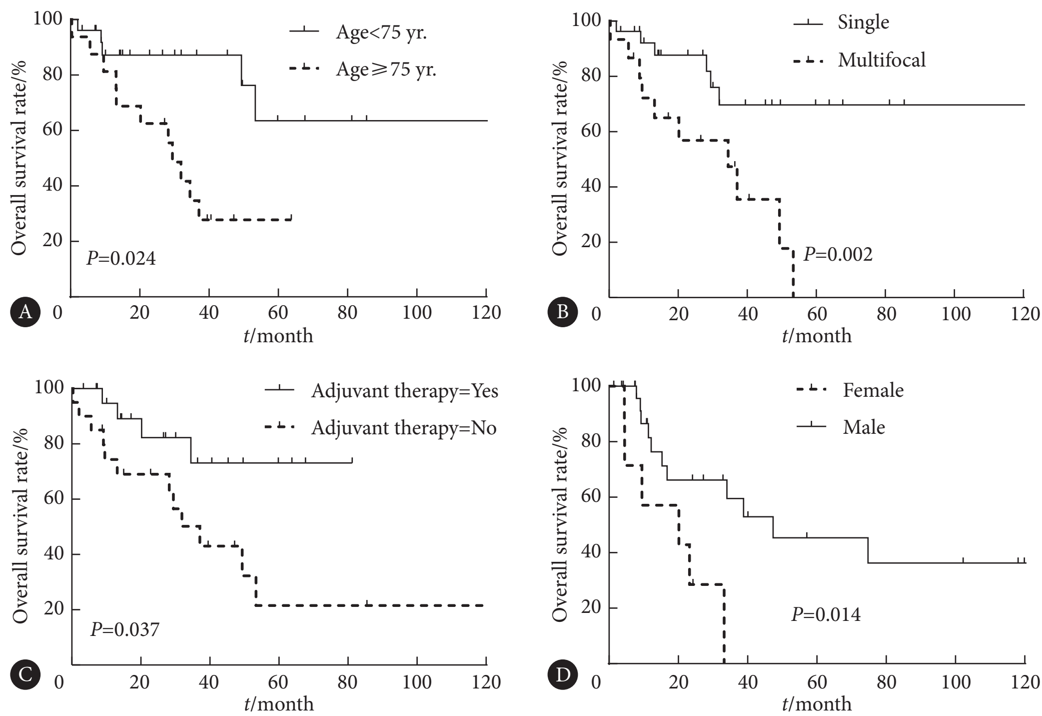

图 2 总生存曲线:按年龄、肿瘤数目、术后辅助治疗和性别分组

Fig 2 Overall survival curves stratified by age, number of tumors, receiving adjuvant therapy or not, and sex

A-C: RC group; D: BPS group.

表 2 SCB根治性切除术患者总生存期的单因素和多因素Cox回归分析

Table 2 Univariate and multivariate Cox regression analysis of overall survival in patients who underwent radical cystectomy for sarcomatoid carcinoma of the bladder

Variable	Univariate		Multivariate*	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age				
<75 yr. (reference)				
≥75 yr.	4.155 (1.391-12.410)	0.011	3.836 (1.168-12.595)	0.027
Sex				
Male (reference)				
Female	1.770 (0.562-5.556)	0.329		
Smoking history				
Non-smoker (reference)				
Current	0.589 (0.204-1.697)	0.327		
Tumor size				
<5 cm (reference)				
≥5 cm	0.446 (0.127-1.569)	0.208		
Number of tumor(s)				
Single (reference)				
Multifocal	3.834 (1.378-10.670)	0.010	3.439 (1.235-9.574)	0.018
T stage				
T1 (reference)				
T2-T4a	2.208 (0.291-16.750)	0.444		
Lymphovascular invasion				
Absent (reference)				
Present	2.174 (0.788-5.997)	0.134		
Adjuvant therapy				
Yes (reference)				
No	3.413 (1.099-10.593)	0.034	3.164 (1.015-9.862)	0.047

CI: confidence interval. * Variable selection was conducted using bidirectional stepwise regression.

表 3　SCB保留膀胱手术患者总生存期的单因素Cox回归分析

Table 3　Univariate Cox regression analysis of overall survival in patients who underwent bladder-preserving surgery for sarcomatoid carcinoma of the bladder

Variable	Univariate		Multivariate*	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age				
<75 yr. (reference)				
⩾75 yr.	2.014 (0.690-5.881)	0.200		
Sex				
Male (reference)				
Female	3.601 (1.200-10.804)	0.022	3.601 (1.200-10.804)	0.022
Smoking history				
Non-smoker (reference)				
Current	1.127 (0.433-2.934)	0.807		
Tumor size				
<5 cm (reference)				
⩾5 cm	2.140 (0.783-5.852)	0.138		
Number of tumor(s)				
Single (reference)				
Multifocal	1.152 (0.404-3.286)	0.791		
T stage				
T1 (reference)				
T2-T4a	0.832 (0.315-2.198)	0.710		
Lymphovascular invasion				
Absent (reference)				
Present	2.167 (0.274-17.170)	0.464		
Adjuvant therapy				
Yes (reference)				
No	2.382 (0.809-7.013)	0.115		

CI: confidence interval. * The univariate and multivariate analysis results are identical because the bidirectional stepwise regression retained only the gender variable.

多因素Cox回归分析确认了这一结果，性别仍为唯一保留的独立危险因素（HR= 3.601, 95%CI: 1.200 ~ 10.804, *P*= 0.022）。

2.4　术后复发和转移情况

在接受BPS手术治疗的35例SCB患者中，6例发生术后肿瘤复发，2例发生转移，4例出现术后复发并转移。对于接受RC治疗的42例SCB患者，术后肿瘤复发2例，转移2例，复发并转移3例。整体术后复发及转移率为24.7%(19/77)。

3　讨论

SCB是一种罕见且高度恶性的尿路上皮癌病理亚型，有关其临床病理特征的文献较少。LOPEZ-BELTRAN等[8]分析了26例SCB病例资料，其中25例(96.2%)为≥pT3期，仅1例(3.9%)为T2期，平均癌症特异性死亡时间9.8个月。WANG等[9]研究了14例SCB病例，发现其中12例(85.7%)在初次诊断时即为肌层浸润性膀胱癌，2年总生存率为53.5%。另一项研究分析了SEER数据库中221例患者的病历资料，发现中位总生存期为16.0个月，1年和5年总生存率分别为53.9%和28.4%[10]。这些研究表明，SCB具有高度侵袭性，通常在确诊时已处于较高分期，预后较差。本研究纳入的77例可切除SCB患者中，23例(29.9%)为T1期，54例(70.1%)为T2-T4a期。BPS组和RC组的1年、3年和5年生存率分别为76.2% vs. 84.9%、46.7% vs. 61.1%、35.6% vs. 43.2%。与其他研究相比，本研究中T1期患者的比例及生存率略高，这可能与本研究仅纳入了T1-T4aN0M0患者有关。既往研究表明，肿瘤T分期与淋巴结转移呈正相关，而淋巴结转移是膀胱癌的重要预后危险因素[11]。由于本研究未纳入伴有淋巴结转移的患者，因此T2-T4a期伴有淋巴结转移的患者被排除在外，可能导致了T1期患者比例及总生存率稍高的结果。

目前，关于影响SCB预后的因素存在一些争议。WANG等[10]经分析后发现，肿瘤的远处转移与疾病特异性生存期显著相关，但治疗方案、年龄和性别等因素与之无显著相关性。然而，LOPEZ-BELTRAN等[8]认为，肿瘤T分期和治疗方案是影响总生存期的最佳预测因素。另

外，SUI等[12]发现，年龄、肿瘤T分期和治疗方案是总生存期的独立危险因素。本研究多因素Cox回归分析显示，RC组中年龄≥75岁、肿瘤多发以及未接受术后辅助治疗是影响生存的独立危险因素。BPS组中，女性性别是唯一显著的生存影响因素。

经根治性切除术后，SCB具有较高的复发和转移倾向。研究表明，在术前未发生远处转移的患者中，术后复发及转移的概率高达60%[13]。在本研究中，截至末次随访，共有33例患者（占42.9%）死亡，19例患者（占24.7%）出现了复发及转移。复发及转移率低于其他研究结果，可能由以下原因导致：首先，本研究未包括存在淋巴结侵犯的患者，因此复发及转移的概率较低。其次，近一半的患者在随访期间死亡，这意味着部分患者在复发及转移之前就已经死亡。最后，研究人群的不同也可能是影响复发和转移率的因素。

SCB的治疗方案尚未达成共识[6]。WANG等[10]的研究报道，相较于经尿道膀胱肿瘤电切术，根治性膀胱切除术并未显著提高患者的生存率。KILTIE等[14]则建议，对于具有较高转移和扩散风险的肿瘤，保膀胱策略可能更为适宜。KRASNOW等[15]的研究表明，SCB患者与单纯尿路上皮癌患者在接受保膀胱三联治疗后，两组间的疾病特异性生存期差异无统计学意义。然而，SUI等[12]的研究发现，根治性膀胱切除术可显著降低死亡风险。尽管根治性膀胱切除术对SCB患者的生存获益仍存在争议，但目前它仍是SCB患者的主要治疗手段[14, 16-17]。在本研究中，虽然BPS组与RC组之间的生存差异无统计学意义，但接受根治性膀胱切除术治疗的患者在生存期上表现出一定的优势。鉴于RC组患者的基线肿瘤分期高于BPS组，这一结果似乎进一步支持了根治性膀胱切除术在治疗SCB中的潜在优势。然而，根治性膀胱切除术对SCB的治疗效果仍需进一步研究以确定其确切的临床获益。

化疗在SCB中的作用存在争议。SCB被视为化疗抵抗肿瘤，化疗效果似乎有限[4, 16]。然而，一些学者则主张在手术后采用术后辅助化疗[9]。有报道显示，一些患者接受吉西他滨和顺铂方案治疗后，SCB得到了完全缓解[2, 10]。另有研究表明，术后化疗和/或放疗可以显著降低SCB患者的死亡风险[12]。本研究结果显示，接受术后辅助治疗的患者生存时间延长。然而，需要注意的是，本研究仅为单中心小样本的回顾性研究，存在一些潜在的偏倚和限制。未来，大规模随机对照研究将更有说服力地评估术后辅助治疗在SCB患者中的实际效果。

免疫检查点抑制剂已在膀胱癌中取得了显著的疗效[18-19]。研究发现肉瘤样癌PD-L1常呈高表达（阳性率高达70.8%[20]），呈现较强的免疫浸润细胞[21-23]。考虑到PD-L1高表达通常对免疫治疗有更好的疗效[24]，免疫检查点抑制剂已在多种肉瘤样癌中展现出良好的治疗效果[25-29]，因此，SCB患者有望从免疫检查点抑制剂治疗中获益。

本研究尚存局限性：本研究为回顾性研究，可能存在一定的偏移；样本量小，导致95%CI跨度较大，结果需谨慎对待；术后辅助治疗药物种类多样；在这项长达15年的临床资料中，由于早期对SCB的认识和了解有限，可能会导致报告不足和分类错误。

*　　*　　*

作者贡献声明　黄世旺负责论文构思、数据审编、正式分析、调查研究和初稿写作，贾凯鹏负责论文构思、数据审编、调查研究和研究方法，沈冲负责数据审编、调查研究、研究方法和监督指导，陈惠童负责调查研究、研究方法和监督指导，张哲负责正式分析、调查研究、研究方法和验证，吴周亮和郄云凯负责调查研究、研究方法和审读与编辑写作，郭嘉宁负责数据审编、正式分析、调查研究和提供资源，胡海龙负责论文构思、经费获取、研究项目管理和审读与编辑写作。所有作者已经同意将文章提交给本刊，且对将要发表的版本进行最终定稿，并同意对工作的所有方面负责。

Author Contribution　HUANG Shiwang is responsible for conceptualization, data curation, formal analysis, investigation, and writing--original draft. JIA Kaipeng is responsible for conceptualization, data curation, investigation, and methodology. SHEN Chong is responsible for data curation, investigation, methodology, and supervision. CHEN Huitong is responsible for investigation, methodology, and supervision. ZHANG Zhe is responsible for formal analysis, investigation, methodology, and validation. WU Zhouliang and QIE Yunkai are responsible for investigation, methodology, and writing--review and editing. GUO Jianing is responsible for data curation, formal analysis, investigation, and resources. HU Hailong is responsible for conceptualization, funding acquisition, project administration, and writing--review and editing. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

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