[DOI]10.12016/j.issn.2096-1456.2024.07.004

·临床研究·

涎腺导管癌临床病理特征及预后分析

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【摘要】 目的 分析涎腺导管癌（salivary duct carcinoma，SDC）的临床病理特征及其预后相关因素。**方法** 本研究已通过单位伦理委员会审查批准，并获得患者知情同意。回顾性分析河北医科大学第四医院2014—2022年收治的30例SDC患者的临床资料，包括病历记录、病理诊断、免疫组化指标、治疗方式、随访资料等数据，采用SPSS 26.0软件处理数据并制作生存曲线，卡方检验分析免疫组化分类变量与SDC复发、转移的关系，单因素用于分析临床预后因子。**结果** 30例SDC患者中，男女比例5:1，中位年龄61.5岁，约60%发生于腮腺，其余发生于下颌下腺、舌下腺、腭部小涎腺等。其中，19例雄激素受体阳性，23例人表皮生长因子受体-2阳性，26例Ki-67阳性。术后随访18～94个月，中位随访37个月，复发13例，远端转移14例，5年总生存率31.2%。术后放疗及术后放化疗患者的总生存率高于单纯手术患者，其组间差异具有统计学意义（$P=0.027$）。肿瘤T分期、淋巴结转移与预后生存率相关（$P<0.05$），Ki-67阳性细胞数≥40%与术后复发或转移有一定相关性（$P=0.025$）。**结论** 根治性手术联合术后放疗、放化疗对提高SDC患者远期总生存率有益，肿瘤T分期、淋巴结转移情况可能是影响SDC患者预后的主要因素，Ki-67阳性细胞数≥40%的患者，易出现术后复发或转移。

【关键词】 涎腺导管癌；Ki-67；人表皮生长因子受体-2；雄激素受体；T分期；淋巴结转移；生存率；预后

【中图分类号】 R78 **【文献标志码】** A **【文章编号】** 2096-1456（2024）07-0509-08

微信公众号

【引用著录格式】 陈永强，柴国超，李天客，等. 涎腺导管癌临床病理特征及预后分析[J]. 口腔疾病防治，2024, 32(7): 509-516. doi:10.12016/j.issn.2096-1456.2024.07.004.

Clinicopathological features and prognosis analysis of salivary duct carcinoma

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【Abstract】 Objective To summarize the clinicopathological characteristics and prognostic factors of salivary duct carcinoma (SDC) patients. **Methods** This study was reviewed and approved by the Ethics Committee, and informed consent was obtained from the patients. The clinical data of 30 SDC patients who were admitted to the Fourth Hospital of Hebei Medical University from 2014 to 2022, including case records, pathological diagnoses, immunohistochemical indicators, treatment methods, follow-up data, and other data, were retrospectively analyzed. SPSS 26.0 software was used to process the data and construct relevant curves. The chi-square test was used to analyze the correlation between different immunohistochemical indices and the recurrence and metastasis of SDC, and a single factor was used to analyze clinical prognostic factors. **Results** Among the 30 SDC patients, the male-to-female ratio was 5∶1, with a median age of 61.5 years. Approximately 60% of cases occurred in the parotid gland, whereas the remainder occurred in the submaxillary gland, sublingual gland, or minor salivary gland. Among them, 19 patients were androgen receptor-positive, 23 patients were human epidermal growth factor receptor-2 positive, and 26 patients were Ki-67 positive. Postoperative follow-up was 18-94 months, with a median follow-up of 37 months. There were 13 cases of recurrence and 14 cases of

【收稿日期】 2024-01-15；**【修回日期】** 2024-04-09
【基金项目】 河北省财政厅老年病防治项目（13000022P00860410186E）；河北省卫生健康委员会重点科技研究计划（20240888）
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distant metastasis. The 5-year overall survival rate was only 31.2%. The long-term survival of patients who underwent postoperative radiotherapy and chemoradiotherapy was better than that of patients who underwent surgery alone (P= 0.027). T stage and lymph node invasion were associated with prognosis and survival (P < 0.05). There was a correlation between a Ki-67-positive cell count ≥ 40% and postoperative recurrence or metastasis (P = 0.025). **Conclusion** Radical surgery combined with postoperative radiotherapy and chemoradiotherapy is helpful for improving long-term overall survival, and tumor T stage and lymph node metastasis may be the main factors affecting the prognosis of patients with SDC. Patients with Ki-67-positive cell counts ≥ 40% are prone to postoperative recurrence or metastasis.

【Key words】 salivary duct carcinoma; Ki-67; human epidermal growth factor receptor 2; androgen receptor; T stage; lymph node invasion; survival rate; prognosis

J Prev Treat Stomatol Dis, 2024, 32(7): 509-516.

【Competing interests】 The authors declare no competing interests.

This study was supported by the grants from Hebei Province Department of Finance Geriatric Disease Prevention Project (No. 13000022P00860410186E); Key Scientific and Technological Research Plan of Hebei Provincial Health Commission (No. 20240888).

涎腺导管癌(salivary duct carcinoma,SDC)较罕见,其发生率约占所有涎腺肿瘤的0.9%,因与乳腺浸润性导管癌组织学特征类似而使用了“涎腺导管癌”一词,目前已被归为高级别涎腺恶性肿瘤[1-3]。SDC受累部位以腮腺居多,其次为下颌下腺,偶见于泪腺、腭部小唾液腺等[4]。SDC临床多为腮腺区和颌下腺区的结节状硬性肿块,早期便易侵犯周围组织,出现神经麻痹症状。SDC与其他恶性肿瘤不易鉴别,而且早期复发、局部及远处转移倾向性极强,预后较差[5]。目前关于SDC患者病理特征及生存分析的研究较少,本研究收集30例SDC患者的生存状态,结合患者的临床病理特征和治疗方式,分析SDC复发/转移的影响因素和有益生存的治疗方式,同时为靶向治疗SDC提供依据。

1　资料与方法

1.1　临床资料

本研究已通过单位伦理委员会审查批准(2021KS024),并获得患者知情同意。收集2014—2022年于河北医科大学第四医院口腔科经病理证实为SDC并完成以手术为主的相关治疗及随访的患者的临床资料,包括临床病理特征、治疗情况及随访结果等。

1.2　治疗方法

30例手术患者中,单纯手术治疗8例,手术+放疗9例,手术+放疗+化疗11例,手术+化疗2例。18例腮腺导管癌的手术患者,3例行部分腮腺及肿物切除术,4例行全腮腺及肿物切除术,11例行全腮腺及肿物扩大切除+颈淋巴清扫术,其中9例术中切除面神经;8例颌下腺导管癌患者,均行颌下腺及肿物扩大切除术+颈淋巴清扫术,3例术中舌神经损伤;1例舌下腺及1例腭部小涎腺导管癌的治疗方式为原发灶扩大切除+颌骨部分切除+颈淋巴清扫术;发生于颞下窝咽旁间隙和左侧翼腭窝的SDC患者各1例均行原发灶根治性切除+根治性颈淋巴清扫术。部分处于早期的SDC病变累及范围小或行细针穿刺细胞学检查只找到瘤细胞,而行部分腺体或全腺体及肿物切除术。一般经临床查体及影像学表现怀疑为恶性原发灶转移肿大淋巴结者、术前粗针穿刺或术中冰冻活检证实为SDC者考虑行同侧颈淋巴清扫术。经术后病理证实为SDC者建议术后局部追加放射治疗,视情况行术后辅助化疗。常规术后放疗靶区为术区及颈部,每部位放射量50~70 Gy,化疗类药物无统一方案,以紫杉醇+顺铂+氟尿嘧啶(TPF)和紫杉醇+顺铂(TP)为主。

1.3　术后随访

患者术后随访方式包括定期门诊复诊、再次入院及回顾性电话询问等,随访时长为18~94个月,中位随访期37个月,随访终止日期为2022年12月。随访过程中诊断原发灶复发或远处转移须至少有影像学表现及组织病理学其中一项指标证实。纳入患者均完成随访。

1.4　统计学分析

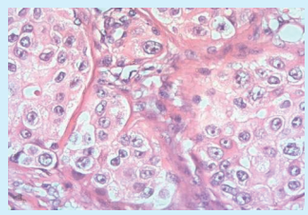
所得数据均采用SPSS 26.0进行统计学分析,用Kaplan-Meier法进行生存分析并制作相关曲线,Log-Rank检验对生存曲线差异进行比较,单因素用于分析临床预后因子,卡方检验用于检验免疫组化表型与复发、转移组间的关系,P < 0.05为差

异有统计意义。

2　结　果

2.1　涎腺导管癌病理特点及免疫组化表型

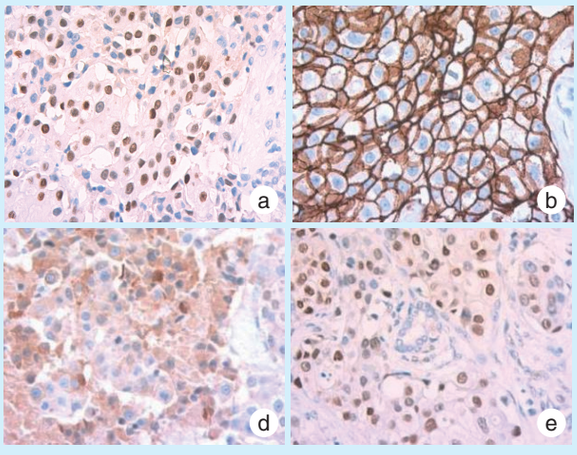
SDC镜下HE染色观察，其肿瘤细胞多浸润周围组织并突向导管上皮，排列形成类似巢状、乳头状的结构，部分导管扩展，内可见粉刺样坏死区，部分标本可见血管及神经受侵（本组约14个标本可见神经受侵）（图1）。在30例SDC患者中，免疫组化检测19例雄激素受体（androgen receptor，AR）阳性，23例人表皮生长因子受体-2（human epidermal growth factor receptor 2，HER-2）阳性，26例Ki-67阳性，6例转录因子GATA结合蛋白3（GATA binding protein 3，GATA3）阳性，12例特异性囊肿病液体蛋白15（gross cystic disease fluid protein 15，GCDFP-15）阳性（图2）。



Microscopically, the tumors were nested and some of the ducts were dilated

Figure 1　HE staining image of salivary duct carcinoma (×400)

图1　涎腺导管癌的HE染色图像（×400）



a: AR(+); b: HER-2(+); c: Ki-67(+); d: GCDFP-15(+); e: GATA3(+). AR: androgen receptor; HER-2: human epidermal growth factor receptor 2; GATA3: GATA binding protein 3; GCDFP-15: gross cystic disease fluid protein 15

Figure 2　Staining images of different immunohistochemically positive indicators in salivary duct carcinoma(×400)

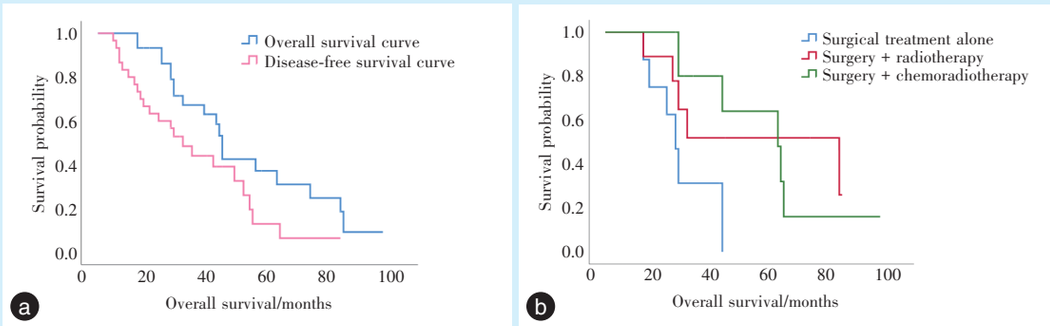
图2　涎腺导管癌不同免疫组化阳性指标的染色图像（×400）

2.2　涎腺导管癌患者术后随访及生存分析

随访过程中共有21例局部复发或出现远端转移情况，原术区复发13例，复发率达43.33%；远端转移14例，转移率达46.67%，其中9例转至肺，4例转至骨，2例转至脑，1例转至全身多脏器。18例因肿瘤死亡，死亡率高达60%。Kaplan-Meier方法分析显示，SDC患者3年和5年的总生存率（overall survival，OS）分别为60.8%和31.2%，3、5年的无疾病生存率（disease-free survival，DFS）分别为43.4%和6.5%。在随访时间内，手术+放疗组、手术+放化疗组均比单纯手术组总体生存率高（$P = 0.027$）（图3）。

2.3　涎腺导管癌患者临床病理特征的单因素总生存率比较

30例SDC患者中，男性比例为83%。患者最大年龄80岁，最小年龄35岁，中位年龄61.5岁。其中发生于腮腺18例，下颌下腺8例，舌下腺1例，腭部小涎腺1例，另可见发生于左侧翼腭窝和右侧颞下窝咽旁间隙SDC各1例。SDC临床多表现局部硬性肿块并伴早期神经麻痹症状，其中伴面瘫、麻木的患者约占46.7%，根据AJCC第八版TNM分期，T1、T2期12例（40.0%），T3、T4期18例（60.0%），淋巴结转移16例（53.3%），淋巴结未转移14例（46.7%）。将性别、年龄、肿瘤部位、肿瘤T分期、淋巴结转移、AR表达、HER-2表达、AR、HER-2双表达、Ki-67表达等10个参数进行单因素分析，结果提示肿瘤T分期、淋巴结转移对SDC患者的总生存率具有统计学意义（$P < 0.05$）（表1）。T分期、淋巴结转移对SDC患者总生存期影响的生存曲线显示，T3、T4期患者的5年OS（20.9%）较T1、T2期患



a: overall survival curve of salivary duct carcinoma patients and disease-free survival curve of salivary duct carcinoma patients; b: comparison of overall survival rates among the operation group, operation + radiotherapy group and operation + chemoradiotherapy group

Figure 3　Disease-free survival and overall survival curves of patients with salivary duct carcinoma and analysis of overall survival after different treatments

图3　涎腺导管癌患者的无疾病生存率、总生存率生存曲线以及不同治疗方式的总体生存率分析

表1　涎腺导管癌患者临床病理特征的单因素总生存率比较

Table 1　Univariate overall survival comparison of clinicopathological features of salivary duct carcinoma

Variable	*n*	χ^2	*P*	Variable	*n*	χ^2	*P*
Gender				Neck lymph metastasis			
Male	25	0.013	0.909	Yes	16	5.220	0.022
Female	5			No	14		
Age/year				AR (+)			
≤ 50	4	1.687	0.640	Yes	19	3.260	0.071
50-60	9			No	11		
60-70	11			HER-2 (+)			
≥ 70	6			Yes	23	0.153	0.695
Tumor site				No	7		
Parotid gland	18	1.941	0.379	AR (+) and HER-2 (+)			
Submaxillary gland	8			Yes	16	0.259	0.611
Other site	4			No	14		
Neck lymph dissection				Ki-67 (+)			
Yes	23	1.584	0.621	Yes	26	2.611	0.106
No	7			No	4		
T stage							
T1、T2	12	5.404	0.020				
T3、T4	18						

AR: androgen receptor; HER-2: human epidermal growth factor receptor 2

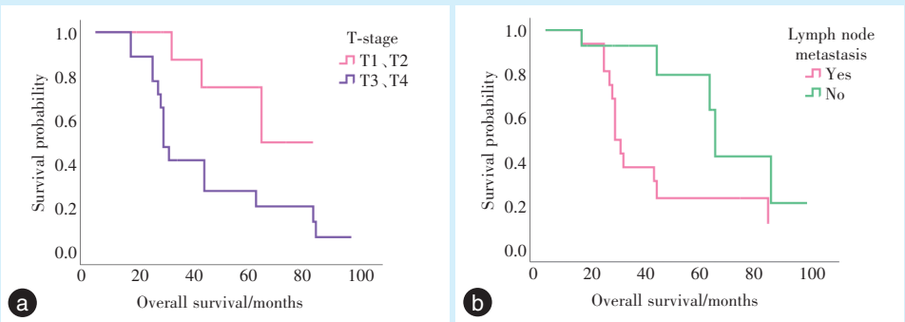
者的5年OS(75.0%)显著降低($P<0.05$),而有淋巴结转移的患者5年OS(23.4%)也显著低于无淋巴结转移的患者(63.7%)($P<0.05$),见图4。

2.4　免疫组化表型与涎腺导管癌复发及转移的关系

AR、HER-2阳性检测结果与肿瘤是否复发或转移间无统计学差异($P>0.05$),而当Ki-67阳性细胞数≥40%时,其与肿瘤复发或转移间具有明显相关性($P=0.025$)(表2),易出现术后复发或转移。

3　讨　论

SDC临床罕见,其发病原因尚不明确,部分研究表明SDC多为原发性,少数也可在长期存在的多形性腺瘤癌变的基础上发生,也有报道可以在慢性阻塞性涎腺炎基础上继发而来[6-7]。SDC高发于中老年男性患者,文献报道男女比例约为7∶3[8-9],中位年龄68岁,多为60岁以上的老年男性患者。本研究中,SDC的发病部位主要是腮腺,其次为颌



a: survival curve of the effect of T stage on overall survival; b: survival curve of the effect of lymph node metastasis on overall survival. There were significant differences in the overall survival rate of patients with different T stages and lymph node metastasis

Figure 4　Survival curve of T stage and lymph node metastasis on overall survival of salivary duct carcinoma patients

图4　T分期、淋巴结转移对涎腺导管癌患者总生存期影响的生存曲线

表2　不同免疫组化表型与涎腺导管癌复发、转移的相关性

Table 2　Correlation between different immunohistochemical phenotypes and salivary duct carcinoma recurrence or metastasis

	AR			HER-2			Ki-67 positive cells		
Recurrence or metastasis	(−)	(+)		(−)	(+)		< 40%	≥ 40%	
No (n = 9)	3	6	P = 0.804	2	7	P = 0.925	7	2	P = 0.025
Yes (n = 21)	8	13		5	16		7	14	

AR: androgen receptor; HER-2: human epidermal growth factor receptor 2

下腺，此与文献报道[8-9]基本一致。本研究中发生于颞下窝咽旁间隙和翼腭窝处的SDC各1例，为罕见部位，文献回顾表明，SDC亦可见发生于鼻窦、鼻腔等部位，甚至眼部泪腺也可见受累[10-11]。SDC临床表现多为腮腺区和颌下腺区的结节状硬性肿块，生长较快，病程短，早期便易侵犯周围组织，出现神经麻痹症状，同时多伴区域淋巴结及远处转移。据报道，SDC患者面神经麻痹的发生率为30%～40%，而在诊断SDC时已出现阳性淋巴结转移率可达50%[8, 12-13]。在Ran等[8]报道的266例SDC患者中，经影像学检查及临床查体发现约有78.46%的可疑转移淋巴结，最终病理确诊的阳性淋巴转移率达62.41%。Kusafuka等[14]发现有约30%的SDC患者可出现远处转移。本研究的30例SDC患者中，有14例出现神经受侵症状，术前面瘫发生率44.44%，入院初诊时经专科查体及影像学检查发现66.67%淋巴结转移率(20/30)，经术后病理证实为阳性转移淋巴结者16例，转移率约达53%，随访期间14例出现远端转移，远端转移率达46.67%，以肺、骨多见，表明SDC具有易侵犯神经、淋巴浸润、远处转移等特点。

SDC患者预后较差，局部复发及远处转移率高，这也是SDC病死率高的主要原因之一，本文30例SDC患者在接受以手术为主的综合治疗后局部复发13例，复发率达43.33%；出现远端转移14例，转移率达46.67%。3年期DFS和OS分别为43.4%和60.8%，5年期DFS和OS分别为6.5%和31.2%，OS的数据与其他研究接近[15]，DFS偏低，可能与本研究样本量较少且大多数病人属于晚期有关。对于SDC，原发灶的彻底切除是治疗的关键因素之一，如腮腺肿物往往需行肿物及腮腺全叶切除来达到原发病灶的根治，术中若面神经与肿物粘连不能分离或术前患者已有面瘫症状，则术中需行面神经切除术；颌下腺肿物除摘除颌下腺外通常还需扩大切除邻近组织如二腹肌前后腹、部分下颌骨等。SDC具有高度恶性的淋巴结转移特征，往往超过半数的患者入院初诊时就伴发可疑肿大淋巴结，即使临床及影像学表现未见明显肿大淋巴结者，也可能存在隐匿性转移，因此，多数学者建议同期行选择性颈淋巴清扫术来预防局部淋巴结转移复发[4, 16]。本研究30例SDC患者行手术治疗，23例行颈淋巴清扫术，余7例未行颈淋巴清扫，未行颈清的局部淋巴结转移率在2年内达70%。

与大多数涎腺恶性肿瘤相似，SDC的肿瘤细胞具有腺上皮的特征而缺乏肌上皮成分，如s-100、SMA通常呈阴性表达，提示SDC来源于涎腺导管上皮。多数研究显示HER-2、AR及Ki-67等均在SDC中呈高表达状态，在SDC免疫组化数据的相关研究[8, 17-19]中发现HER-2的阳性表达率达46%～80%，AR的阳性表达率可达45%～90%。本研究30例SDC患者免疫组化结果显示，AR的阳性率为63.3%，HER-2的阳性率为76.7%，与以往相关研究报道相符合。但关于HER-2、AR的表达意义目前尚不清晰，有学者认为，HER-2、AR过表达往往提示阴性预后及晚期疾病的出现[20-21]。但也有研究认为二者的阳性表达与OS和DFS没有显著相关性，与SDC的预后无关[22-23]。本研究采用单因素分析及卡方检验对HER-2、AR的表达情况进行统计，未发现二者与SDC转移复发及预后的相关性，但本研究样本量较小，可能造成误差。Ki-67为一种核抗原，多于增殖期表达，其繁殖侵袭能力强，在一些恶性肿瘤（如SDC）中均有较高的阳性指数表达[24]。本研究中Ki-67表达率高达87%，50%SDC手术患者Ki-67阳性细胞数达40%，Ki-67阳性细胞数与肿瘤复发或转移间具有明显相关性，当Ki-67阳性细胞数≥40%时，SDC更具有复发及远处转移的倾向。因此，对于此类患者临床中要提高警惕并密切随访。由于HER-2和AR在SDC中的高表达，针对这两种受体的靶向药物治疗的研究也越来越多，对于大多数晚期转移性SDC而言，分子靶向或靶向联合化疗可能是一种新颖有效的治疗手段。曲妥珠单抗目前临床多用于靶向治疗转移性乳腺导管癌，近期研究显示，使用曲妥珠单抗靶向治疗HER-2表达阳性的晚期转移性SDC患者也有良好的临床反应，并可延长其生存期[25-26]。在一项多中心II期临床试验中，研究者对43例HER-2阳性的晚期患者使用多西他赛联合曲妥珠单抗治疗SDC获得了满意效果，其客观缓解率为69.8%[27]。也有研究者认为多西紫杉醇联合曲妥珠单抗具有较好的协同效应且副反应小，在晚期HER-2阳性患者中可作为一个不错的治疗选择[25, 28]。另外，对于AR阳性的转移性SDC患者来说，雄激素受体阻断剂（比卡鲁胺等）有一定效果，可以使患者提高临床获益率[29]，但关于靶向或靶向联合化疗产生的耐药机制及不良反应仍有待进一步探索。除HER-2及AR外，可能还有较多基因突变靶点的存在，如H-RAS、TP53、PIK3CA等，这些靶点可能成为SDC的潜在预后因素，并为后期诊治提供有前景的思路。

除相关分子过表达及突变外，SDC的预后主要与肿瘤T分期、淋巴结转移及术后放化疗之间存在相关性。就肿瘤T分期而言，相比T1、T2的肿瘤，T3及T4期的肿瘤具有更低的OS。T分期越高、直径越大的肿瘤，术中切除的肿瘤其边缘阳性概率越大，术后更容易复发及转移。研究表明，当肿瘤直径≥3 cm时其局部复发率及远处或淋巴结转移率将大幅提高，而且当肿瘤直径＞3 cm时其淋巴结转移率将会提高至原来的2倍[8]，这就要求对肿瘤行早期切除，同时对肿瘤切除的范围需更全面、规范。目前大多数国内外研究均支持颈部淋巴结转移对SDC不良预后的影响，但关于淋巴结转移的分类如淋巴结转移率（lymph node ratio LNR）等对SDC预后的效果无确切共识[30-31]。有研究表明颈部淋巴结阳性个数比N分期及LNR对预后的影响更大，建议按照颈部淋巴结阳性个数来评估SDC的预后[9]。但近期也有研究表明LNR比淋巴结状态更能预测SDC生存结果并可作为临床常用预后工具，同时指导治疗决策[32]。本研究结果提示颈部有淋巴结转移的SDC患者，其总生存率低于无淋巴结转移的患者。

相对于单纯手术而言，术后辅以放疗或放化疗是提高患者生存水平的重要因素。笔者发现，在随访时间内，术后放疗组和术后放化疗组较单纯手术组总体生存率高，表明术后辅以放疗或放化疗在一定程度上可以延长SDC患者总生存期。有研究者指出，无论SDC的T分期和边缘状态如何，术后放疗都是一种有效且合适的治疗选择[33]。然而，虽然术后放疗可以实现良好的局部控制，但辅助放疗的远期生存价值仍有待确定[34-35]。术后辅助化疗主要用于控制远端转移，有学者认为术后接受化疗和放疗的患者可能并没有比单独接受放疗的患者有更好的生存结果。反而对于一些中晚期的SDC病人，若接受同步放化疗可能有更多的不利风险因素，包括慢性病的加重、身体消瘦等[36]。本研究术后放化疗患者在短期内与术后放疗患者相比具有较好的生存率，但其远期效果仍有待观察。

综上，SDC生存率低、预后差，根治手术是必要的，建议术中同期行颈淋巴清扫，术后配合放疗或放化疗对提高远期生存有益。肿瘤T分期、淋巴结转移可能是影响SDC患者预后的主要因素，对于

Ki-67阳性细胞数≥40%的患者,临床中要提高警惕并密切随访。

【Author contributions】 Chen YQ analyzed the data of the study, conceived and wrote the article. Chai GC collected, processed and revised the data. Li TK collated the data and revised the article. Bao Y analyzed the data and revised the article. Chen S provided experimental methods and followed up. Zhang SX gave a comprehensive analysis and guidance to the thesis. All authors read and approved the final manuscript submitted.

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