AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

Original Research

OTO Open
2026, Vol. 10(2):e70224

DOI: 10.1002/oto2.70224
http://oto-open.org
WILEY

Histologic Origin and Survival in Salivary Duct Carcinoma: A Retrospective Cohort Study

Lily Gao, BA[1], Sindhura Sridhar, BS[2], Daniel R. S. Habib, BA[1], Marina Aweeda, MD[2], Michael C. Topf, MD, MSCI[2], and Alexander Langerman, MD[2]

Abstract

Objective. To evaluate the impact of histologic origin on survival in salivary duct carcinoma (SDC) and characterize its clinical and pathologic features.

Study Design. Retrospective cohort study.

Setting. Single, tertiary academic medical center.

Methods. This study included treatment-naïve patients diagnosed with SDC (2000-2024). Histologic origin (ex pleomorphic adenoma [PA] vs de novo) was determined pathologically or clinically. Kaplan-Meier analysis and log-rank tests assessed overall survival (OS) and disease-free survival (DFS). Cox regression estimated hazard ratios (HR) and 95% confidence intervals (CI) for 13 covariates.

Results. Out of N = 85 SDC patients, 68 were treated with curative intent, including 43 de novo and 25 ex PA cases. Median follow-up was 19.8 months. OS and DFS survival were not significantly different by histologic origin (OS $P = .28$; DFS $P = .19$), though 2-year OS and DFS were numerically higher in ex PA (OS: 87% vs 81%, DFS: 63% vs 57%). Histologic origin was not associated with OS (univariate $P = .29$) or DFS (univariate $P = .19$; multivariable $P = .23$). Distant recurrence was the most common failure pattern, occurring more frequently in de novo cases (37% vs 21%, $P = .23$).

Conclusion. Histologic origin was not independently associated with OS or DFS, although numerically higher 2-year survival in SDC ex PA may suggest potential biologic differences between ex PA and de novo origins that warrant further study. Distant metastasis was the primary mechanism of treatment failure for both subtypes of SDC, highlighting the need to explore novel treatments, such as neoadjuvant therapies.

Keywords

carcinoma ex pleomorphic adenoma, de novo carcinoma, head and neck cancer, prognosis, salivary duct carcinoma, salivary gland neoplasm, survival

Received September 22, 2025; accepted February 14, 2026.

Salivary duct carcinoma (SDC) is the most aggressive tumor of the 21 subtypes of primary salivary gland carcinoma classified by the WHO.[1] SDC predominantly arises in the parotid glands of older men and often presents with lymph node involvement and distant metastases, leading to poor prognosis.[2-5] However, no standardized treatment for SDC exists given the lack of evidence-based guidelines. Instead, treatment of SDC is largely guided by expert opinion and institutional practice patterns, with most patients undergoing a multimodal approach that includes surgical resection with or without neck dissection, followed by adjuvant therapy such as radiation, chemotherapy, or targeted hormone therapy against human epidermal growth factor receptor 2 (HER2) or androgen receptor (AR).[2,6,7] Even with these therapeutic advances, treatment of SDC remains challenging because the genetic and molecular underpinnings of tumor development are not fully understood.[8,9] As such, treatment decisions are largely guided by risk stratification of patients based on prognostic factors.[10]

Prior studies have identified certain histologic features such as nuclear pleomorphism, mitotic rate, vascular invasion, and extracapsular spread as prognostic indicators associated with poor outcomes in SDC.[11-14] However, tumor histologic origin has not been conclusively linked to prognosis.[3,11,15,16] SDC can arise de novo or from a preexisting pleomorphic adenoma (ex PA); SDC ex PA has traditionally been diagnosed clinically as a long-standing mass that suddenly increases in size, or pathologically by

[1]Department of Otolaryngology–Head & Neck Surgery, Vanderbilt University School of Medicine, Nashville, Tennessee, USA
[2]Department of Otolaryngology–Head & Neck Surgery, Vanderbilt University Medical Center, Nashville, Tennessee, USA

This article was presented at the AAO-HNSF 2025 Annual Meeting & OTO EXPO, October 11-14, Indianapolis, Indiana

Corresponding Author:
Lily Gao, BA, Vanderbilt University School of Medicine, 2209 Garland Ave, Unit 226, Nashville, TN 37240, USA.
Email: lily.gao@vanderbilt.edu

identifying SDC cells arising within or adjacent to residual PA tissue.[2,8,17] Recent molecular studies suggest that mutations in genes such as PLAG1 and HMGA2 are implicated in the development of PA and SDC ex PA, but are typically absent in de novo SDC.[8,9,11,17-20] These biological differences between histologic origins may affect survival outcomes.[11] Although some studies suggest a trend toward worse survival in SDC de novo, there is no consensus on the prognostic significance of histologic origin, with prior work by Gilbert et al showing a trend towards improved prognosis in SDC ex PA.[3,11,15,16]

This study aims to evaluate the impact of histologic origin on overall survival (OS) and disease-free survival (DFS) in salivary duct cancer in a large, single-institution cohort. Based on prior literature, we hypothesized that patients with SDC de novo will have poorer OS and DFS compared to patients with SDC ex PA. By stratifying patients according to treatment intent and applying consistent histologic classification, this study seeks to complement prior studies and provide additional data on recurrence patterns and clinical outcomes of SDC. Clarifying the prognostic significance of histologic origin may enhance clinical decision-making and improve patient counseling for this rare and aggressive salivary malignancy.

Methods

Study Design and Population

This retrospective cohort study was conducted at Vanderbilt University Medical Center (VUMC) with Institutional Review Board approval (IRB #240685). Potential SDC cases were identified from the VUMC Research Derivative database using a keyword search for "salivary duct carcinoma" in pathology reports or clinic notes between January 2000 and December 2024 (**Figure 1**). Upon chart review, patients were excluded if they had a different final diagnosis per VUMC pathology, less than 3 months of follow-up, incomplete treatment history, or indeterminate histologic origin. Data collection was performed using REDCap.

Patients were classified as SDC ex PA if their pathology report confirmed origin from PA or, if pathologically indeterminate, based on clinical features consistent with PA (eg, previous slow-growing mass present for at least 1 year

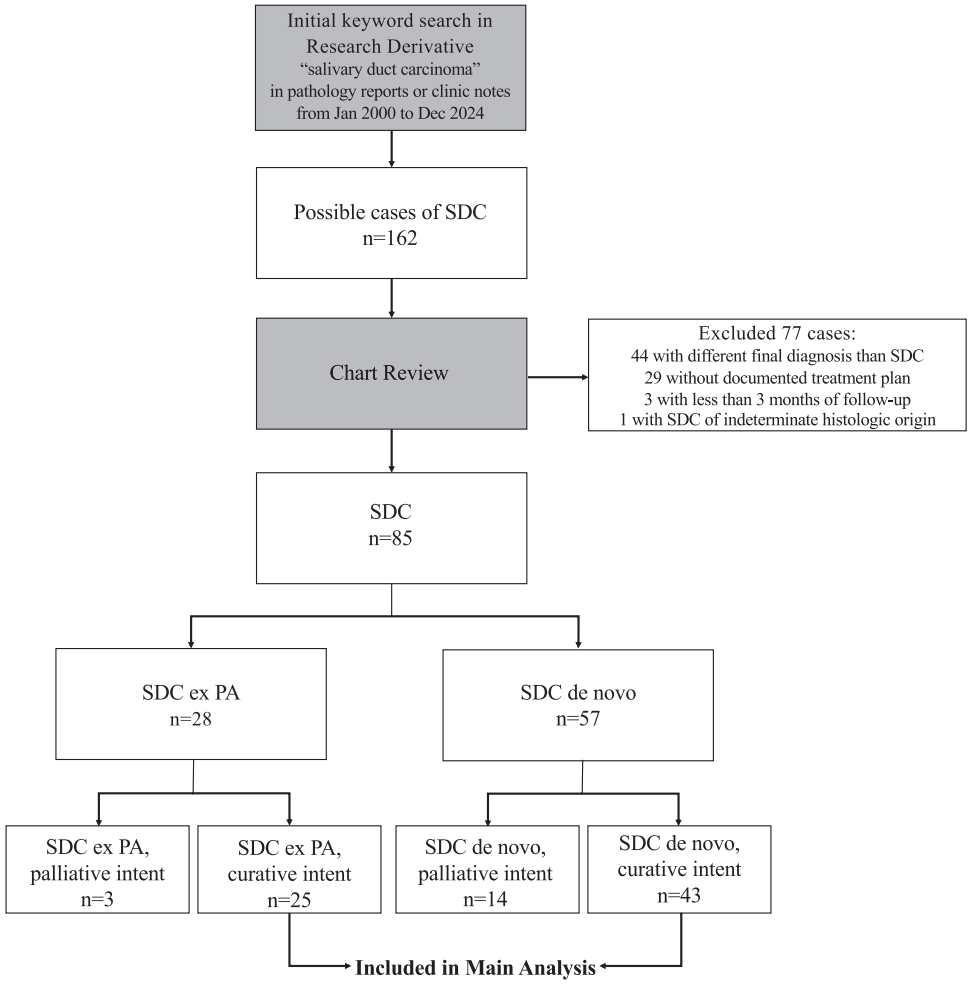

Figure 1. Methods flowchart. Of 162 possible cases of SDC, 85 were confirmed upon chart review and categorized by histologic origin and treatment intent. Sixty-eight cases treated with curative intent were included in the main analysis.

without neural involvement).[2,8,17] Patients who did not meet these criteria were classified as SDC de novo. Patients with distant metastases at time of diagnosis or with unresectable tumors were assigned to the palliative intent subgroup and excluded from the main analysis to focus on curatively treated cases. Otherwise, patients were assigned to the curative intent subgroup.

Outcomes

OS was defined as time from diagnosis to death. Disease-free survival (DFS) was defined as time from diagnosis to recurrence or death, whichever occurred first.

Statistical Analysis

Analyses were performed using R. Categorical variables were compared using chi-square or Fisher's exact tests, and continuous variables using the Mann-Whitney *U* test. Kaplan-Meier curves estimated OS and DFS, with log-rank tests evaluating differences by histologic origin. Survival analysis only included patients treated with curative intent. Patients were censored at the time of an event or date of last contact. Cox proportional hazards regression estimated hazard ratios (HR) and 95% confidence intervals (CI) for 13 covariates: age, sex, histologic origin, tumor location, pathologic T- and N-stage, postoperative radiation, neck dissection, number of positive lymph nodes, tumor size, perineural and lymphovascular invasion, and margin status. Cases with missing data were excluded. Covariates were selected for multivariable analysis based on univariate associations ($P < .05$) and clinical relevance. Due to limited events, multivariable analysis was not performed for OS.

Results

Baseline Characteristics

Eighty-five patients with a confirmed pathologic diagnosis of SDC were identified, including 28 ex PA and 57 de novo cases (**Figure 1**). Demographic and treatment characteristics were largely similar between ex PA and de novo cases (**Tables 1** and **2**). Most patients were male (68%, n = 57) and Caucasian (85%, n = 72), with a median age at diagnosis of 66 years (range 23-88 years). The most common primary tumor subsite was the parotid gland (80%, n = 68). Baseline tumor differences between ex PA and de novo included presenting symptoms ($P = .035$), overall stage ($P = .011$), and pathologic T stage ($P = .040$). De novo cases more frequently presented with pain and neural involvement (65% vs 32%), Stage IV disease (61% vs 32%), and T4 or unknown T stage (53% vs 28%) compared to ex PA.

Treatment Characteristics

Of 85 SDC cases, 20% (n = 17) received palliative treatment due to distant metastasis at diagnosis (n = 15) or unresectable tumor (n = 2). Among these 17 palliative cases were 3 ex PA and 14 de novo cases. The 68 patients treated with curative intent included 25 ex PA and 43 de novo cases. Fisher's exact test showed no significant association between histologic origin and treatment intent ($P = .16$). In the curative intent subgroup, treatment was similar for SDC ex PA and de novo. Nearly all patients (94%, n = 64) had surgery, mostly primary resection with neck dissection (66%, n = 42). Postoperatively, 81% (n = 52) received adjuvant therapy, split evenly between concurrent chemoradiation (53%, n = 27) and radiation only (47%, n = 24). Only 3 patients (4%) received adjuvant hormone therapy targeting HER2. No patients received neoadjuvant therapy.

Follow-Up and Recurrence Patterns

Sixty-eight patients treated with curative intent were included in the main analysis (median follow-up: 19.8 months, range 3.1-131). Median follow-up was not significantly different between ex PA (21.5 months, range: 3-62.7) and de novo (18.3 months, range: 4.1-131; $P = .96$). Among 25 SDC ex PA cases, there were 3 deaths and 7 recurrences: 5 distant, 1 regional, and 1 local. Among 43 SDC de novo cases, there were 10 deaths and 19 recurrences: 16 distant, 2 regional, and 1 local. The overall rate of distant recurrence was 35%. The rate of distant recurrence was not different between SDC de novo and ex PA (37% vs 20%; $\chi^2 = 1.46$, $P = .23$) despite a numerically higher rate of metastases in SDC de novo. The most common sites of recurrence overall were bone (14%), lung (11%), liver (8%), and local (8%) (**Figure 2**).

Survival Analyses

Overall median DFS and OS were 3.1 and 7.1 years, respectively. For SDC de novo, median DFS and OS were 2.9 years (95% CI 1.6-NA) and 7.1 years (95% CI 3.7-NA), respectively. Median DFS and OS for SDC ex PA were not reached, which indicates that less than half of the patients had an event during their follow-up. Log-rank tests showed no significant difference in OS ($P = .28$) or DFS ($P = .19$) between SDC ex PA and de novo (**Figure 3**). Although not statistically significant, SDC ex PA showed numerically higher estimates for OS (87% vs 81%) and DFS (63% vs 57%) compared to SDC de novo.

Predictors of Survival

Univariate and multivariable analyses found that histologic origin was not associated with OS (univariate $P = .29$) or DFS (univariate $P = .19$; multivariable $P = .23$). In univariate analysis, covariates associated with poorer OS included pathologic nodal metastasis ($P = .02$) and increased tumor size ($P = .003$). Covariates associated with poorer DFS included pathologic nodal metastasis ($P = .003$), performing neck dissection ($P = .01$), increasing number of positive lymph nodes ($P = .008$), increased tumor size ($P = .038$),

Table 1. Baseline Characteristics of SDC ex PA and SDC De Novo (All Treatment Intents)

Characteristics	SDC ex PA (N = 28)	SDC de novo (N = 57)	Total (N = 85)	*P*
Age at diagnosis, median (IQR), years	65.5 (52.3-72)	67 (61-76)	66 (59-75)	.14
Male, n (%)	19 (68)	39 (68)	58 (68)	1
Race, n (%)				.80
White	24 (86)	48 (84)	72 (85)	
Black or African American	1 (4)	3 (5)	4 (5)	
Hispanic or Latino	2 (7)	1 (2)	3 (4)	
Asian	0	1 (2)	1 (1)	
Other or Unknown	1 (4)	4 (7)	5 (6)	
Smoking history, n (%)	14 (50)	27 (47)	41 (48)	1
Primary tumor subsite, n (%)				.61
Parotid gland	23 (82)	45 (79)	68 (80)	
Submandibular gland	1 (4)	4 (7)	5 (6)	
Minor salivary gland	1 (4)	2 (4)	3 (4)	
Lacrimal gland	2 (7)	1 (2)	3 (4)	
Other/unknown	1 (4)	5 (8.8)	6 (7)	
Presenting symptoms, n (%)				**.035**
Painless mass	17 (61)	29 (51)	46 (54)	
Painful mass	4 (14)	17 (30)	21 (25)	
Facial weakness or paralysis	3 (11)	14 (25)	17 (20)	
Facial numbness	2 (7)	6 (11)	8 (9)	
Incidental finding on imaging	6 (21)	1 (2)	7 (8)	
Otalgia	2 (7)	6 (11)	8 (9)	
Hearing loss	0	3 (5)	3 (4)	
Visual changes	0	2 (4)	2 (2)	
Follow-up, median (range), months	21.5 (3.1-62.7)	18.3 (4.1-131)	19.8 (3.1-131)	.960
Overall stage, n (%)				**.011**
0	1 (4)	1 (2)	2 (2)	
I	3 (11)	5 (8.8)	8 (9)	
II	5 (18)	6 (11)	11 (13)	
III	9 (32)	4 (7)	13 (15)	
IV	9 (32)	35 (61)	44 (52)	
Unknown	1 (4)	6 (11)	7 (8)	
Pathologic T stage, n (%)				**.040**
Tis	1 (4)	0 (0)	1 (1)	
T1	4 (14)	9 (16)	13 (15)	
T2	10 (36)	13 (23)	23 (27)	
T3	8 (29)	5 (9)	13 (15)	
T4	3 (11)	16 (28)	19 (22)	
Unknown	2 (7)	14 (25)	16 (19)	
Pathologic N stage, n (%)				.27
N0	9 (32)	12 (21)	21 (25)	
N1	4 (14)	4 (7)	8 (9)	
N2	4 (14)	19 (33)	23 (27)	
N3	4 (14)	7 (12)	11 (13)	
Nx	4 (14)	12 (21)	16 (19)	
Unknown	3 (11)	3 (5)	6 (7)	
M stage, n (%)				.43
M0	24 (86)	43 (75)	67 (79)	
M1[a]	3 (11)	12 (21)	15 (18)	
Mx	1 (4)	1 (2)	2 (2)	
Unknown	0 (0)	1 (2)	1 (1)	

Bolded values indicate significance at $P < .05$.

Abbreviations: PA, pleomorphic adenoma; SDC, salivary duct carcinoma.

[a]The percentages listed only reflect patients treated with curative intent. So the percentages were calculated by dividing the count listed by 25 ex PA instead of 28, by 43 de novo instead of 57.

Table 2. Treatment, Surgical, and Pathologic Features Between SDC ex PA and SDC De Novo

Characteristics	SDC ex PA (N = 28)	SDC de novo (N = 57)	Total (N = 85)	*P*
Patients treated with curative intent, n (%)	25 (89)	43 (75)	68 (80)	.16
Treatment regimen, n (%)[a]				.23
Surgery only	7 (28)	5 (12)	12 (18)	
Surgery with adjuvant therapy	17 (68)	35 (81)	52 (76)	
Nonsurgical primary treatment	1 (4)	3 (7)	4 (6)	
Surgery, n (%)[b]				.17
Primary resection with neck dissection	13 (54)	29 (73)	42 (66)	
Primary resection only	11 (46)	10 (25)	21 (33)	
Neck dissection only	0 (0)	1 (3)	1 (2)	
Neoadjuvant therapy, n (%)	0 (0)	0 (0)	0 (0)	
Adjuvant therapy, n (%)[c]				.928
Concurrent chemotherapy radiation therapy	10 (59)	17 (49)	27 (52)	
Radiation therapy only	7 (41)	17 (49)	24 (46)	
Chemotherapy only	0 (0)	1 (3)	1 (2)	
HER2-targeted hormone therapy	1 (6)	2 (6)	3 (6)	
Non-surgical primary treatment, n (%)[a]				.50
Close surveillance	1 (4)	0 (0)	1 (1)	
Definitive chemoradiation therapy	0 (0)	2 (5)	2 (3)	
Definitive chemotherapy	0 (0)	1 (2)	1 (1)	
Neck dissection				
Median number of resected lymph nodes, range	31 (10-52)	24.5 (4-63)	26 (4-63)	.48
Median number of positive lymph nodes, range	1 (0-40)	4 (0-34)	3 (0-40)	.65
Facial nerve sacrifice, n (%)[d]				.45
Yes	2 (11)	7 (21)	9 (17)	
No	14 (74)	20 (61)	34 (65)	
Unknown	3 (16)	6 (18)	9 (17)	
Perineural invasion, n (%)[b]				.16
Yes	8 (33)	22 (55)	30 (47)	
No	13 (54)	14 (35)	27 (42)	
Unknown	3 (13)	4 (10)	7 (11)	
Lymphovascular invasion, n (%)[b]				.79
Yes	6 (25)	13 (33)	19 (30)	
No	13 (54)	20 (50)	33 (52)	
Unknown	5 (21)	7 (18)	12 (19)	
Tumor greatest dimension, median (range), cm[b]	2.65 (1.5-5.2)	2.45 (0.8-6.5)	2.55 (0.8-6.5)	.45
Margin status, n (%)[b]				.90
Yes	7 (29)	11 (28)	18 (28)	
No	17 (71)	21 (53)	38 (59)	
Unknown	0 (0)	8 (20)	8 (13)	
Androgen receptor (AR), n (%)[b]				.49
Yes	18 (75)	18 (45)	36 (56)	
No	0 (0)	2 (5)	2 (3)	
Unknown	6 (25)	20 (50)	26 (41)	
HER2 receptor, n (%)[b]				.67
Yes	5 (21)	8 (20)	13 (20)	
No	4 (17)	4 (10)	8 (13)	
Unknown	15 (63)	28 (70)	43 (67)	

Bolded values indicate significance at $P < .05$.

Abbreviations: PA, pleomorphic adenoma; SDC, salivary duct carcinoma.

[a]Percentages shown are of 68 patients treated with curative intent (25 ex PA and 43 de novo).

[b]Percentages shown are of 64 patients who underwent surgery (24 ex PA and 40 de novo).

[c]Percentages shown are of 52 patients who received adjuvant therapy (17 ex PA and 35 de novo)

[d]Percentages shown are of 52 patients who underwent parotidectomy (19 ex PA and 33 de novo).

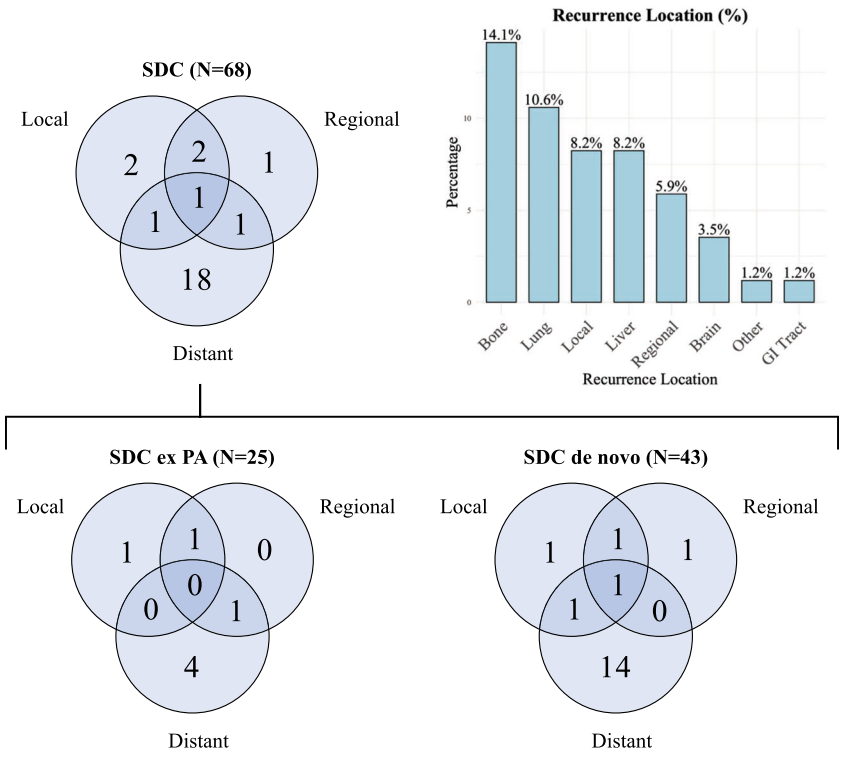

Figure 2. Patterns of recurrence. Local, regional, and distant recurrences are shown in aggregate and for both histologic origins. Distant metastasis was the predominant mechanism of failure. Bone was the most common recurrence site.

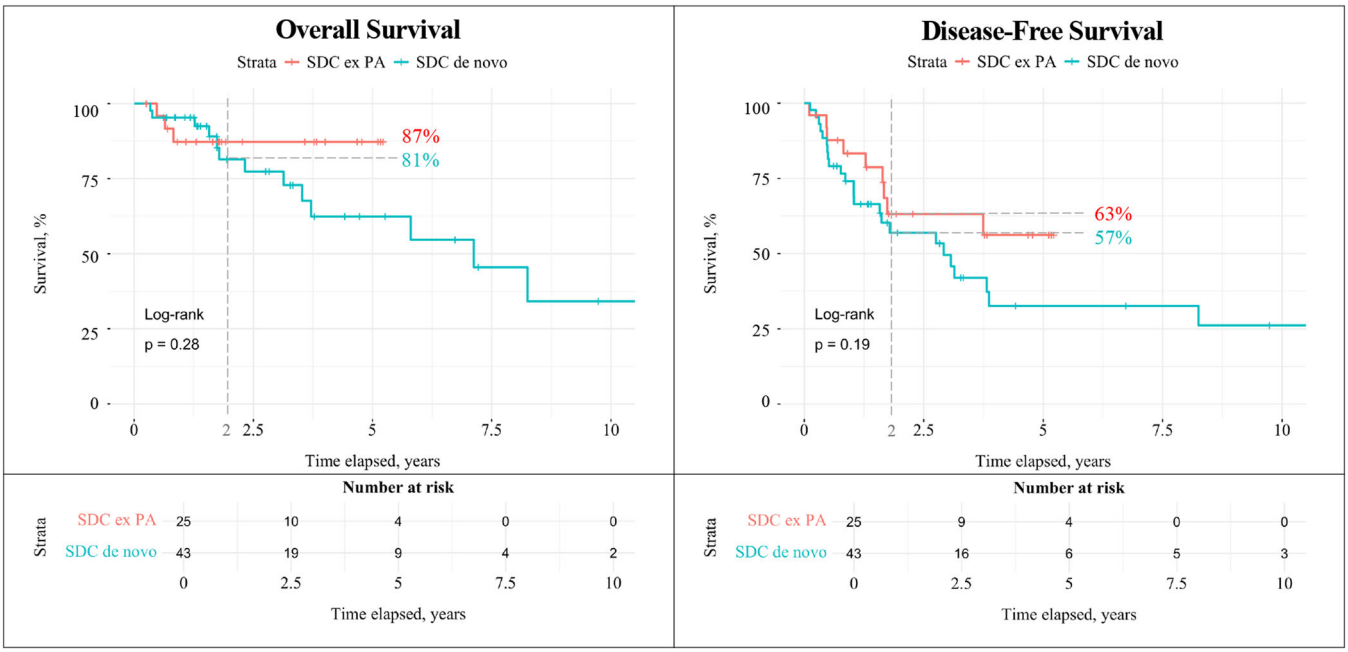

Figure 3. Overall and disease-free survival. OS and DFS did not differ significantly by histologic origin (log-rank: OS $P = .29$, DFS $P = .19$), although 2-year OS and DFS was numerically higher for SDC ex pleomorphic adenoma.

perineural invasion ($P = .025$), and lymphovascular invasion ($P = .022$) (**Table 3**). In multivariable analysis, pathologic nodal metastasis (HR 2.98, 95% CI 1.40-6.37; $P = .0048$) remained an independent predictor of poorer DFS (**Table 4**).

Discussion

Among 68 curatively treated cases of SDC identified in this study, OS and DFS were not significantly different between SDC ex PA and de novo (OS $P = .28$; DFS

Table 3. Univariate Analyses for Overall Survival and Disease-Free Survival

Univariate analysis

Factor	No. of patients	OS		DFS	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Age at diagnosis, years	68	1.00 (0.96-1.04)	.96	1.00 (0.98-1.03)	.88
Sex					
Female	24	1.00		1.00	
Male	44	2.25 (0.71-7.08)	.64	2.07 (0.98-4.40)	.058
Histologic origin[a]					
ex PA	25	1.00		1.00	
de novo	43	2.00 (0.55-7.26)	.10	1.68 (0.77-3.63)	.19
Tumor location[a]					
Parotid	54	1.00		1.00	
Other	14	1.11 (0.31-4.01)	.45	1.47 (0.66-3.29)	.34
T Stage					
Tis/T1/T2	36	1.00		1.00	
T3/T4/Tx	32	1.35 (0.50-3.64)	.84	1.61 (0.81-3.20)	.40
N Stage[a]					
N0/Nx	34	1.00		1.00	
N1/N2/N3	34	4.04 (1.28-12.8)	**.017**	3.81 (1.49-6.62)	**.0025**
Postoperative radiation					
Yes	51	1.00		1.00	
No	13	0.56 (0.12-2.60)	.46	0.58 (0.20-1.67)	.31
Neck Dissection after primary resection					
Yes	42	1.00		1.00	
No	21	0.35 (0.10-1.25)	.11	0.27 (0.10-0.72)	**.010**
Number of positive lymph nodes	43	1.04 (0.99-1.09)	.16	1.04 (1.01-1.07)	**.008**
Tumor Size	55	1.90 (1.24-2.92)	**.003**	1.36 (1.02-1.81)	**.038**
Facial Nerve Sacrifice					
No	34	1.00		1.00	
Yes	9	1.02 (0.25-4.17)	.98	2.09 (0.82-5.357)	.12
Perineural Invasion					
No	27	[b]		1.00	
Yes	30			2.71 (1.13-6.50)	**.025**
Lymphovascular invasion					
No	33	1.00		1.00	
Yes	20	2.41 (0.83-6.97)	.11	2.46 (1.14-5.29)	**.022**
Margin status					
Negative	38	1.00		1.00	
Positive	18	1.70 (0.54-5.36)	.37	1.60 (0.71-3.63)	.26
HER2 status					
Positive	13	1.00		[a]	
Negative	8	0.54 (0.07-3.91)	.54		

Bolded *P*-values are significant at a .05 level.

Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

[a]Variables included in multivariable analyses for DFS.

[b]Not included due to violation of proportional hazards assumption.

$P = .19$), although 2-year estimates were numerically higher in SDC ex PA (OS 87% vs 81%; DFS 63% vs 57%). Of all 85 SDC cases identified, SDC arising de novo (67%) presented with more advanced disease, aggressive features such as perineural invasion, and were more likely to be treated palliatively, although histologic origin was not associated with treatment intent ($P = .16$). Distant recurrence was the primary mechanism of failure, occurring more frequently in de novo than ex PA (37% vs 20%, $P = .23$). The large number of de novo cases treated palliatively and recurring distantly suggests that SDC ex PA may trend

Table 4. Multivariable Analysis for Disease-Free Survival

Multivariable analysis			
		DFS	
Factor	No of patients[a]	HR (95% CI)	*P*
Histologic origin			
ex PA	25	1.00	
de novo	43	1.58 (0.72-3.44)	.25
T stage			
Tis/T1/T2	36	1.00	
T3/T4/Tx	32	1.28 (0.63-2.57)	.50
N stage			
N0/Nx	34	1.00	
N1/N2/N3	34	2.98 (1.40-6.37)	**.0048**

Bolded *P*-values are significant at a .05 level.
Abbreviations: 95% CI, 95% confidence interval; DFS, disease-free survival; HR, hazard ratio.
[a]Out of patients treated with curative intent (n = 68), 14 patients were excluded due to incomplete data.

toward more favorable prognosis, although differences were not statistically significant.

This cohort's demographic and treatment characteristics were largely similar to prior studies.[3,15,16,21-27] Follow-up time (median: 19.8 months) was shorter than observed in prior studies.[3,15,16,21-27] Overall DFS of 3.1 years was consistent with prior reports, OS of 7.1 years exceeded previous estimates (~3-4 years), and survival estimates at 2 years were slightly higher than prior studies, possibly due to exclusion of patients treated with palliative intent or loss to follow-up.[3,15,16,21-27] The overall distant recurrence rate of 35% was comparable to prior studies.[3,15,16,21-27]

Our findings that SDC ex PA and de novo show similar OS and DFS contributes to the mixed literature on survival differences by histologic origin in SDC. While Boon et al and Nakaguro et al found no association between histologic origin and prognosis, Gilbert et al reported a trend toward worse DFS in de novo cases, which is consistent with numerical trends observed in our cohort.[3,11,15,16] By separating curative versus palliative patients and applying consistent histologic classification, our study adds complementary data on recurrence patterns and clinical outcomes for SDC. In contrast, prior studies often categorized patients inconsistently, for example, by grouping SDC ex PA with SDC de novo or with other subtypes of carcinoma ex PA, potentially obscuring meaningful biological differences.[9,15,25-28]

Similar survival rates observed in SDC ex PA and de novo are somewhat unexpected given mechanistic studies such as Chiosea et al, who found that SDC ex PA has a prolonged premalignant disease course driven by stepwise genetic alterations while SDC de novo is characterized by rapid progression and instability due to mutations in genes such as HRAS and TP53.[8,9,11,17-20] As molecular characterization of SDC advances and more genetic differences between SDC ex PA and de novo tumors are identified as potential drug targets, additional studies are needed to clarify the clinical implications of these genetic mutations on prognosis and treatment.[8,11,19,20]

This study also confirmed established negative prognostic factors, including pathologic nodal metastasis and tumor size, which should continue to guide treatment and patient counseling.[3,5,11,16,25-27] Notably, we found that neck dissection predicted poorer DFS, though this likely reflects confounding by indication as it is a marker of advanced disease. Consistent with prior studies, our findings showed that HER2 status was not associated with worse survival outcomes, though this finding is limited by incomplete data and low rates of HER2-targeted therapy utilization.[3,29-32]

Despite advances in identifying prognostic factors, the high rate of distant recurrence (35%) observed in this cohort as well as in prior studies underscores the need to explore novel treatment paradigms for SDC.[3,26] Although adjuvant therapies such as HER2 and AR-targeted therapy have progressed in recent years, clinical trials on neoadjuvant treatment in SDC remain limited.[33-35] Future research should continue refining prognostic frameworks and evaluate whether earlier systemic therapy could improve outcomes in SDC.

This study has limitations. Referral bias at our institution likely led to a higher proportion of advanced SDC cases. To reduce this bias, patients with advanced disease treated palliatively, mostly de novo cases, were excluded from the main analysis. Despite this exclusion, our results suggest a trend toward worse prognosis in de novo cases, implying that differences in survival may be even greater in a broader cohort that included more advanced de novo cases. Next, the retrospective study design inherently limited comprehensive data collection and increased the risk of subtype misclassification, particularly if PA features were underreported. However, the consistent clinical behavior observed between ex PA and de novo cases is reassuring against misclassification. Additionally, any misclassification of ex PA as de novo would likely bias towards underestimating the survival difference, given that ex PA demonstrated a modestly more favorable prognosis. Lastly, short follow-up and small sample size due to the rarity of SDC limited statistical power, covariate adjustment, and the strength of the conclusions, which were drawn based on non-statistically significant results. Future studies with larger pooled, multi-institution datasets may help overcome these constraints.

Conclusion

Histologic origin of salivary duct carcinoma was not independently associated with OS or DFS. Although

differences were not statistically significant, 2-year OS and DFS estimates were numerically higher in SDC ex PA than de novo, complementing prior literature on SDC outcomes. Future studies clarifying the prognostic value of histologic origin in SDC may aid clinicians in treatment stratification and patient counseling, especially given the rarity of SDC and emerging molecular insights. Lastly, the predominance of distant metastasis as the primary mechanism of failure for both SDC ex PA and de novo highlights the need to investigate novel treatment paradigms, including neoadjuvant therapies, to improve outcomes.

IRB Approval

This study was approved by the Institutional Review Board of Vanderbilt University Medical Center (Protocol #240685).

Author Contributions

Lily Gao, BA: study design, data collection, data analysis, manuscript composition; **Sindhura Sridhar**, BS: study design, data analysis, manuscript revision; **Daniel R. S. Habib**, BA: data analysis, manuscript revision; **Marina Aweeda**, MD: study design, manuscript revision; **Michael C. Topf**, MD, MSCI: data analysis, clinical expertise, manuscript revision; **Alexander Langerman**, MD: study design, data analysis, clinical expertise, study oversight, manuscript revision.

Disclosures

Competing interests: None.

Funding source: None.

ORCID iD

Lily Gao https://orcid.org/0009-0007-8819-6165
Sindhura Sridhar https://orcid.org/0009-0009-3649-3920
Daniel R. S. Habib https://orcid.org/0000-0003-0504-9076
Marina Aweeda https://orcid.org/0000-0001-9360-9592
Michael C. Topf https://orcid.org/0000-0002-1022-4417
Alexander Langerman https://orcid.org/0000-0003-0866-463X

References

1. El-Naggar AK, Chan JKC, Takata T, Grandis JR, Slootweg PJ. The fourth edition of the head and neck World Health Organization blue book: editors' perspectives. *Hum Pathol*. 2017;66:10-12. doi:10.1016/j.humpath.2017.05.014
2. Nakaguro M, Tada Y, Faquin WC, Sadow PM, Wirth LJ, Nagao T. Salivary duct carcinoma: updates in histology, cytology, molecular biology, and treatment. *Cancer Cytopathol*. 2020;128(10):693-703. doi:10.1002/cncy.22288
3. E B, M B, W vanB, et al. A clinicopathological study and prognostic factor analysis of 177 salivary duct carcinoma patients from The Netherlands. *Int J Cancer*. 2018;143:758-766.
4. Zhang D, Li L. Prognostic models for estimating survival of salivary duct carcinoma: a population-based study. *Eur Arch Oto-rhino-laryngol*. 2023;280(4):1939-1954. doi:10.1007/s00405-022-07755-3
5. Salovaara E, Hakala O, Bäck L, et al. Management and outcome of salivary duct carcinoma in major salivary glands. *Eur Arch Otrhinolaryngol*. 2013;270(1):281-285. doi:10.1007/s00405-012-1997-4
6. Nakano K, Sato Y, Sasaki T, et al. Combination chemotherapy of carboplatin and paclitaxel for advanced/metastatic salivary gland carcinoma patients: differences in responses by different pathological diagnoses. *Acta Otolaryngol*. 2016;136(9):948-951. doi:10.3109/00016489.2016.1170876
7. Takase S, Kano S, Tada Y, et al. Biomarker immunoprofile in salivary duct carcinomas: clinicopathological and prognostic implications with evaluation of the revised classification. *Oncotarget*. 2017;8(35):59023-59035. doi:10.18632/oncotarget.19812
8. Chiosea SI, Thompson LDR, Weinreb I, et al. Subsets of salivary duct carcinoma defined by morphologic evidence of pleomorphic adenoma, PLAG1 or HMGA2 rearrangements, and common genetic alterations. *Cancer*. 2016;122(20):3136-3144. doi:10.1002/cncr.30179
9. Key S, Chia C, Hasan Z, Sundaresan P, Riffat F, Dwivedi RC. Molecular factors in carcinoma Ex pleomorphic adenoma: systematic review and meta-analysis. *Laryngoscope*. 2024;134(3):1042-1053. doi:10.1002/lary.30993
10. Utsumi Y, Nakaguro M, Tada Y, Nagao T. High-grade salivary carcinomas: a current insight on diagnostic pathology and the key to clinical decision making. *Semin Diagn Pathol*. 2024;41(4):197-206. doi:10.1053/j.semdp.2024.04.002
11. Nakaguro M, Sato Y, Tada Y, et al. Prognostic implication of histopathologic indicators in salivary duct carcinoma: proposal of a novel histologic Risk Stratification Model. *Am J Surg Pathol*. 2020;44(4):526-535. doi:10.1097/PAS.0000000000001413
12. Qian K, Di L, Guo K, Zheng X, Ji Q, Wang Z. Cervical lymph node metastatic status and adjuvant therapy predict the prognosis of salivary duct carcinoma. *J Oral Maxillofac Surg*. 2018;76(7):1578-1586. doi:10.1016/j.joms.2018.01.033
13. Laughlin BS, Ebrahimi S, Voss MM, et al. Clinicopathologic factors and their association with outcomes of salivary duct carcinoma: a multicenter experience. *Adv Radiat Oncol*. 2023;8(4):101204. doi:10.1016/j.adro.2023.101204
14. Griffith CC, Thompson LDR, Assaad A, et al. Salivary duct carcinoma and the concept of early carcinoma ex pleomorphic adenoma. *Histopathology*. 2014;65(6):854-860. doi:10.1111/his.12454
15. Lewis JE, McKinney BC, Weiland LH, Ferreiro JA, Olsen KD. Salivary duct carcinoma. *Cancer*. 1996;77(2):223-230. doi:10.1002/(SICI)1097-0142(19960115)77:2<223::AID-CNCR1>3.0.CO;2-N
16. Gilbert MR, Sharma A, Schmitt NC, et al. A 20-year review of 75 cases of salivary duct carcinoma. *JAMA Otolaryngol Head Neck Surg*. 2016;142(5):489-495. doi:10.1001/jamaoto.2015.3930
17. Katabi N, Ghossein R, Ho A, et al. Consistent *PLAG1* and *HMGA2* abnormalities distinguish carcinoma ex-pleomorphic

adenoma from its de novo counterparts. *Hum Pathol*. 2015; 46(1):26-33. doi:10.1016/j.humpath.2014.08.017

18. Kobayashi K, Saito Y, Kage H, et al. CDK12 alterations and ARID1A mutations are predictors of poor prognosis and therapeutic targets in high-grade salivary gland carcinoma: analysis of the National Genomic Profiling Database. *Jpn J Clin Oncol*. 2023;53(9):798-807. doi:10.1093/jjco/hyad066
19. Santana T, Pavel A, Martinek P, et al. Biomarker immunoprofile and molecular characteristics in salivary duct carcinoma: clinicopathological and prognostic implications. *Hum Pathol*. 2019;93:37-47. doi:10.1016/j.humpath.2019.08.009
20. Mueller SA, Gauthier MA, Blackburn J, et al. Molecular patterns in salivary duct carcinoma identify prognostic subgroups. *Modern Pathol*. 2020;33(10):1896-1909. doi:10.1038/s41379-020-0576-2
21. Afzelius LE, Cameron WR, Svensson C. Salivary duct carcinoma—a clinicopathologic study of 12 cases. *Head Neck Surg*. 1987;9(3):151-156. doi:10.1002/hed.2890090304
22. Han EJ, Mukdad LA, Alhiyari Y, Nakhla MN, Sajed DP, St. John MA. A 22-year single institution review of 119 cases of salivary duct carcinoma. *Laryngoscope Investig Otolaryngol*. 2024;9(2):e1234. doi:10.1002/lio2.1234
23. Jaehne M, Roeser K, Jaekel T, Schepers JD, Albert N, Löning T. Clinical and immunohistologic typing of salivary duct carcinoma: a report of 50 cases. *Cancer*. 2005;103(12): 2526-2533. doi:10.1002/cncr.21116
24. Hosal AS, Fan C, Barnes L, Myers EN. Salivary duct carcinoma. *Otolaryngol Head Neck Surg*. 2003;129(6):720-725. doi:10.1016/S0194-59980301386-X
25. Ran J, Zou H, Li X, Guo F, Xu W, Han W. A population-based competing risk survival analysis of patients with salivary duct carcinoma. *Ann Transl Med*. 2020;8(21):1355. doi:10.21037/atm-20-1849
26. Otsuka K, Imanishi Y, Tada Y, et al. Clinical outcomes and prognostic factors for salivary duct carcinoma: a multi-institutional analysis of 141 patients. *Ann Surg Oncol*. 2016; 23(6):2038-2045. doi:10.1245/s10434-015-5082-2
27. Jayaprakash V, Merzianu M, Warren GW, et al. Survival rates and prognostic factors for infiltrating salivary duct carcinoma: analysis of 228 cases from the Surveillance, Epidemiology, and End Results database. *Head Neck*. 2014;36(5):694-701. doi:10.1002/hed.23350
28. Patel EJ, Oliver JR, Liu C, Tam M, Givi B. Outcomes of carcinoma ex pleomorphic adenoma compared to de novo adenocarcinoma of major salivary glands. *J Surg Oncol*. 2021;123(2):446-455. doi:10.1002/jso.26289
29. Williams CYK, Townson AT, Terry N, Schmitt NC, Sharma A. Role of HER2 in prognosis of salivary duct carcinoma: a systematic review and meta-analysis. *Laryngoscope*. 2023; 133(3):476-484. doi:10.1002/lary.30214
30. Limaye SA, Posner MR, Krane JF, et al. Trastuzumab for the treatment of salivary duct carcinoma. *Oncologist*. 2013;18(3):294-300. doi:10.1634/theoncologist.2012-0369
31. Kano S, Kawakita D, Honma Y, et al. The impact of HER2-Low expression in salivary duct carcinoma: clinicopathologic features, survival outcomes, and association with androgen receptor-targeted therapy. *Oral Oncol*. 2025;165: 107280. doi:10.1016/j.oraloncology.2025.107280
32. Han MW, Roh JL, Choi SH, et al. Prognostic factors and outcome analysis of salivary duct carcinoma. *Auris Nasus Larynx*. 2015;42(6):472-477. doi:10.1016/j.anl.2015.04.005
33. Park S, Jung HA, Lee SH, et al. A phase II trial of neoadjuvant nivolumab, docetaxel, and cisplatin followed by surgery and radiation therapy for resectable high-grade salivary gland carcinoma. *J Clin Oncol*. 2024;42(16_suppl):e18061. doi:10.1200/JCO.2024.42.16_suppl.e18061
34. Takahashi H, Tada Y, Saotome T, et al. Phase II trial of trastuzumab and docetaxel in patients with human epidermal growth factor receptor 2-positive salivary duct carcinoma. *J Clin Oncol*. 2019;37(2):125-134. doi:10.1200/JCO.18.00545
35. Weijers JAM, Verhaegh GW, Lassche G, et al. A randomized phase II trial on the addition of dutasteride to combined androgen blockade therapy versus combined androgen blockade therapy alone in patients with advanced or metastatic salivary duct carcinoma—the DUCT study protocol. *BMC Cancer*. 2024;24(1):1174. doi:10.1186/s12885-024-12889-0