Received: 22 August 2023 | Revised: 29 November 2023 | Accepted: 25 February 2024

DOI: 10.1002/lio2.1234

ORIGINAL RESEARCH

Laryngoscope Investigative Otolaryngology

A 22-year single institution review of 119 cases of salivary duct carcinoma

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Abstract

Objective: Salivary duct carcinoma (SDC) is a rare and aggressive salivary gland malignancy. Herein, we present the largest single-institution review of SDC to date.

Methods: This is a retrospective cohort study of all histologically confirmed cases of SDC seen at our institution from January 1, 2002, to August 1, 2022. Patient demographics, treatment, histological characteristics, tumor staging, and outcomes were extracted from the electronic medical record. Kaplan-Meier and Cox regression survival analyses were performed.

Results: This study included 119 patients with a mean age of 66.2 years. Most primary tumors arose from the parotid gland (72.3%), and 23.5% were noted to be carcinoma ex-pleomorphic adenoma. 57.1% of patients presented with regional lymph node metastasis, whereas 23.5% presented with distant disease. Kaplan–Meier analysis demonstrated a 62.4% 5-year overall survival (OS) and a 69.0% 5-year disease-specific survival (DSS). Univariate analyses indicated that presence of regional lymph node disease (p<.001), distant metastasis (p<.001), perineural invasion ($p = .027$), and lymphovascular invasion ($p = .018$) were predictive of decreased OS and DSS. Trastuzumab administration was not associated with survival in HER-2-positive patients receiving chemotherapy. Multivariate analyses demonstrated that presence of nodal disease (HR 30.337, 95% CI 2.782–330.851, $p = .005$) and carcinoma ex pleomorphic adenoma (HR 5.54, 95% CI 1.024–29.933, $p = .047$) were associated with decreased OS.

Conclusion: Our patients had more favorable survival rates compared to prior studies, which may be due to lower incidence of nodal disease. Factors associated with

Oral Presentation at AHNS 11th Annual Conference on Head and Neck Cancer on July 12 in Montreal, Canada.

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worse survival included nodal and distant metastases, perineural invasion, lymphovascular invasion, and tumor size.

Level of Evidence: Level 3.

KEYWORDS

oropharyngeal cancer, salivary duct carcinoma, salivary gland cancer, survival analysis

1 | INTRODUCTION

Salivary duct carcinoma (SDC) is a rare but aggressive malignancy, comprising less than 2% of salivary gland tumors.[1] Noted for its histologic resemblance to ductal carcinoma of the breast, it most commonly arises in the parotid gland, followed by the submandibular gland, but may also arise from minor salivary glands in the oral cavity and oropharynx.[2,3] Regional metastases and lymph node involvement are frequently observed, thus SDC is often treated with surgical resection with modified radical neck dissection.[1,4] Many patients also receive postoperative radiation therapy and chemotherapy, however, there is little evidence that these adjuvant therapies impact survival beyond improving local regional control.[5–7]

Data on SDC survival vary widely, with studies reporting 5-year overall survival (OS) rates ranging from 30% to 64%.[6–14] Given the rarity of SDC, most of these estimations are derived from small, single-institution studies, except for a few national database investigations. Furthermore, there is still no consensus on the clinical or histological characteristics of SDC that impact survival. Such information would be valuable for both patients and clinicians when prognosticating disease. Thus, the primary aim of our investigation was to perform the largest single-institution review to date of clinical characteristics, treatment, and outcomes in SDC.

2 | MATERIALS AND METHODS

This is a retrospective cohort study of SDC patients seen at the University of California, Los Angeles (UCLA; Los Angeles, CA). Approval was obtained from the Institutional Review Board (IRB#11-002858), and the requirement for informed consent was waived. An internal pathology database was reviewed by a single head and neck pathologist for all histologically confirmed cases of SDC from January 1, 2000, to August 1, 2022. Patient demographics, clinical characteristics, treatment, histopathological characteristics, tumor staging, and outcomes were extracted from the electronic medical record. Histopathological characteristics included margin status, carcinoma ex pleomorphic adenoma origin, human epidermal growth factor receptor (HER-2) positivity, and presence of perineural invasion (PNI), lymphovascular invasion (LVI), and extracapsular spread (ECS). If not explicitly stated in the medical record, tumor staging was retrospectively determined using the salivary gland cancer staging system provided by the American Joint Committee on Cancer.[9]

The primary endpoints of our study included OS and disease-specific survival (DSS), which were calculated from month and year of initial diagnosis. Kaplan Meier analysis was performed to analyze OS and DSS, and comparisons were made via the log-rank test. Cox proportional hazard regression models were fitted and included age, gender, T/N/M stage, PNI, LVI, HER-2 positivity, carcinoma ex pleomorphic adenoma origin, and facial nerve sacrifice. Statistical significance was determined using the threshold of p <.05. Statistics and graphical comparisons were performed using SPSS software (version 28.0; IBM, Armonk, NY).

3 | RESULTS

We identified a total of 119 patients with SDC from January 1, 2000, to August 1, 2022. Demographics, clinical characteristics, and treatment of the cohort are reported in Table 1. The mean age at diagnosis was 66.2 years, and 34.5% of identified patients were female. Most tumors arose from the parotid gland (72.3%), followed by the submandibular gland (20.2%), and almost half of patients presented with stage T3 or T4 disease. Lymph node involvement was common—at least one positive lymph node was observed in over half of cases. Almost all patients underwent surgical resection (95.8%), and 88.4% received either adjuvant chemoradiation or radiation therapy. Many chemotherapeutic regimens included a combination of platinum-based agents (79.6%) and taxanes (51.0%), and most HER-2 positive patients receiving chemotherapy also received trastuzumab (87.5%) (Table 2). On histopathological evaluation, 60% of tumors were HER-2 positive and 90.4% were androgen receptor (AR) positive (Table 1). Almost a quarter of tumors appeared to be carcinoma ex pleomorphic adenoma. PNI was observed in 72.3% of cases, LVI in 65.1%, and ECS in 53.1%. Negative margins were obtained in 71.1% of surgical resections.

Our cohort demonstrated a 5-year OS of 62.4% and a 5-year DSS of 69.0%, with a median OS of 7.5 years and a median DSS of 8.9 years (Figure 1). Univariate Kaplan Meier analyses revealed that presence of nodal involvement, distal metastasis, PNI, and LVI were significantly associated with decreased OS and DSS (Table 3, Figure 2, all p <.05). Tumor size was associated with decreased DSS ($p = .034$) but did not impact OS ($p = .173$). Margin status was not associated with survival (p >.05). Trastuzumab therapy did not seem to impact survival in HER-2-positive patients receiving chemotherapy (p >.05). On multivariate analysis, after controlling for age, gender, tumor

TABLE 1 Patient clinical and histopathologic characteristics.

Clinical characteristics	*N* (%)
Age at diagnosis, mean (range)	66.2 (30–90)
Male	66.0 (35–88)
Female	66.5 (30–90)
Sex ($n = 119$)	
Male	78 (65.5%)
Female	41 (34.5%)
Smoking history ($n = 119$)	
Positive	47 (39.5%)
Negative	57 (47.9%)
Unknown	15 (12.6%)
Alcohol use ($n = 119$)	
Positive	36 (30.3%)
Negative	66 (55.5%)
Unknown	17 (14.3%)
Primary tumor site ($n = 119$)	
Parotid	86 (72.3%)
Submandibular gland	24 (20.2%)
Tongue	1 (0.8%)
Hard palate	2 (1.7%)
Parapharyngeal space	4 (3.4%)
Buccal mucosa	1 (0.8%)
Unknown	1 (0.8%)
Procedure ($n = 119$)	
Surgical resection	114 (95.8%)
Biopsy only	5 (4.2%)
Facial nerve sacrifice ($n = 91$)	
Yes	33 (36.3%)
No	58 (63.7%)
Adjuvant therapy ($n = 95$)	
Chemotherapy and radiation therapy	46 (48.4%)
Radiation only	35 (36.8%)
Chemotherapy only	3 (3.2%)
None	11 (11.6%)
T stage ($n = 119$)	
Tis	2 (1.7%)
T1	23 (19.3%)
T2	27 (22.7%)
T3	19 (16.0%)
T4a	32 (26.9%)
T4b	4 (3.4%)
Tx	12 (10.1%)
N stage ($n = 119$)	
N0	36 (30.3%)
N1	7 (5.9%)
N2a	22 (18.5%)
N2b	22 (18.5%)
N2c	1 (0.8%)
N3a	6 (5.0%)
N3b	10 (8.4%)
Nx	15 (12.6%)
M stage ($n = 119$)	
M0	70 (58.8%)
M1	28 (23.5%)
Unknown	21 (17.8%)
Histopathologic characteristics	*N* (%)
Perineural invasion ($n = 94$)	
Yes	68 (72.3%)
No	26 (27.7%)
Carcinoma ex pleomorphic adenoma ($n = 119$)	
Yes	28 (23.5%)
No	91 (76.5%)
Lymphovascular invasion ($n = 86$)	
Yes	56 (65.1%)
No	30 (34.9%)
Extracapsular spread ($n = 64$)	
Yes	34 (53.1%)
No	30 (46.9%)
HER-2 status ($n = 105$)	
Positive	63 (60.0%)
Negative	42 (40.0%)
AR status ($n = 83$)	
Positive	75 (90.4%)
Negative	8 (9.6%)
Margin status ($n = 83$)	
Positive	24 (28.9%)
Negative	59 (71.1%)

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

staging, and histologic features, we found that presence of nodal involvement was independently associated with decreased OS (HR 30.337, 95% CI 2.782–330.851, $p = .005$) and DSS (HR 27.76, 95% CI 1.93–399.39, $p = .015$), while carcinoma-ex pleomorphic adenoma was associated with decreased OS (HR 5.54, 95% CI 1.024–29.933, $p = .047$) (Table 4).

4 | DISCUSSION

Disease characterization and prognostication remain difficult in SDC given the relative rarity of this malignancy and the limited availability of larger cohort analyses. Thus, our study was performed to provide more robust data on clinical, histological, and treatment characteristics

TABLE 2 Chemotherapy agents utilized in SDC.

Agent	*N* (%)
All SDC ($n = 49$)	
Platinum-based chemotherapy	39 (79.6%)
Taxanes	25 (51.0%)
5-FU	5 (10.2%)
Anti-androgen	1 (2.0%)
Other	8 (16.3%)
HER-2 (+) SDC ($n = 24$)	
Trastuzumab	21 (87.5%)
Pertuzumab	1 (4.2%)

Note: Platinum-based chemotherapy: cisplatin (9), carboplatin (31) Taxanes: paclitaxel (7), docetaxel (18). Anti-androgen: bioalutamide. Other: sunitinib (1), lapatinib (2), capecitabine (1), navelbine (1), nivolumab (2), tucatinib (1), gemcitabine (1), cetuximab (1).

that impact survival and is the largest single-institution investigation of SDC to our knowledge. The cohort's 5-year OS and DSS of 62.4% and 69.0%, respectively, are among the highest reported in the literature.[4,6–8,10] We found that increased tumor size, nodal involvement, distant metastases, PNI, and LVI were all associated with decreased survival on univariate analysis. Nodal involvement and carcinoma-ex pleomorphic adenoma were negative prognostic factors on multivariable analysis. Our findings are largely consistent with previous studies evaluating prognostic factors in SDC and further emphasize the importance of regional lymph node involvement on survival.[6–11,15–17]

SDC is an aggressive disease, and many cases are identified at advanced stages. Median OS widely varies (3.1 years in Gilbert's single-institution series of 75 patients, and 6.6 years in Jayaprakash's national database study examining 228 patients).[6,7] Our cohort demonstrated a median OS of 7.5 years and 5-year OS of 62.4%. Our higher survival rates may be due to our lower proportion of nodal disease (57.1% in our cohort vs. 72% in Gilbert's cohort).[6] Similarly to Gilbert et al, we found nodal disease to be an independent prognosticator of decreased survival in our study. In Otsuka's multi-institutional study examining 141 patients, 3-year OS was 70.5%, and incidence of nodal disease was 48%.[10] Across multiple studies, postoperative treatment failure is often linked to inability to achieve locoregional control.[4,5,11]

Prognostic significance of HER-2 expression remains uncertain at present. HER-2 positivity was observed in 60% of cases in our cohort. This is in contrast to a recent meta-analysis by Egebjerg et al. which estimated the prevalence of HER-2 positivity in SDC at 43% and the single-institution series by Gilbert et al. which estimated prevalence at 31%.[6,13] In multiple studies including our own, HER-2 was not found to be associated with survival.[6,13,14] Nonetheless, the significance of HER-2 in SDC has garnered considerable interest, primarily due to its clinical utility in breast cancer. HER-2 status in breast cancer has been shown to improve identification of responders to targeted immunotherapy with trastuzumab, which may prolong survival.[13,14] In our study, 87.5% of HER-2-positive patients undergoing chemotherapy also received trastuzumab, although trastuzumab was not associated with survival in this subgroup. While the median DSS of patients receiving trastuzumab was greater than those who did not (4.8 vs. 1.0 years), this difference was not statistically significant. Trastuzumab has shown promise in SDC management in limited case reports and small retrospective studies, although there have been no large studies or randomized trials investigating its impact on SDC survival to date.[18–22] Nonetheless, most eligible patients at our institution still underwent trastuzumab therapy, and our results may have been influenced by the lack of randomization and the size disparity between comparison groups ($n = 24$ trastuzumab recipients vs. $n = 2$ non-recipients).

Other histopathological features investigated in our study include AR positivity, PNI, carcinoma ex pleomorphic adenoma, LVI, and extracapsular spread. Over 90% of tumors were AR-positive, consistent with reported rates in the literature.[3,23,24] While AR status has not exhibited significant prognostic implications, it may serve as a diagnostic marker, aiding in the distinction of SDC from other salivary malignancies. Rates of PNI (72.3%) and LVI (65.1%) were also high in our cohort and were associated with decreased OS and DSS. These rates are similar to the PNI (69%) and LVI (61%) rates presented in the study by Gilbert and colleagues. As in our study, PNI and LVI were associated with decreased survival in the studies by Gilbert and Roh.[6,11] Our prevalence of cases of carcinoma ex-pleomorphic adenoma was only 23.5% compared to the 41% noted in Gilbert's report, and our study did note an association with decreased OS following multivariate adjustment in contrast to Gilbert's report which found no association with survival. This observation may be attributed to the relatively large proportion of ex-pleomorphic SDC presenting with nodal involvement in our study. While ex-pleomorphic status is often linked to a more favorable prognosis due to lower rates of regional lymph node metastasis, over half of ex-pleomorphic adenoma cases in our study presented with nodal involvement.[25]

The mainstay of SDC treatment remains surgical resection, and almost all patients in this study underwent primary resection. Given aggressive nature of SDC and high prevalence of PNI, an important question is whether resection with clear margins or facial nerve sacrifice confer survival benefits. Negative margins were obtained in 71.1% of surgical resections in this cohort, although margin status was not associated with survival. These findings are largely consistent with previous work showing that while margin status is associated with high-risk pathologic features such as PNI and LVI, it is not an independent predictor of survival.[26] Obtaining negative margins may also be limited by the proximity of the facial nerve, and there is uncertainty whether the benefit of facial nerve sacrifice outweighs the morbidity of this procedure. 36.3% of our patients had facial nerve sacrifice during surgery, but this was not associated with survival benefit, a finding that was corroborated in the study by Otsuka.[10] The study by Gilbert indicated facial nerve sacrifice was associated with worse survival, however. Due to conflicting data, and the known high prevalence of PNI, further investigation on the benefit of aggressive upfront surgery is warranted.

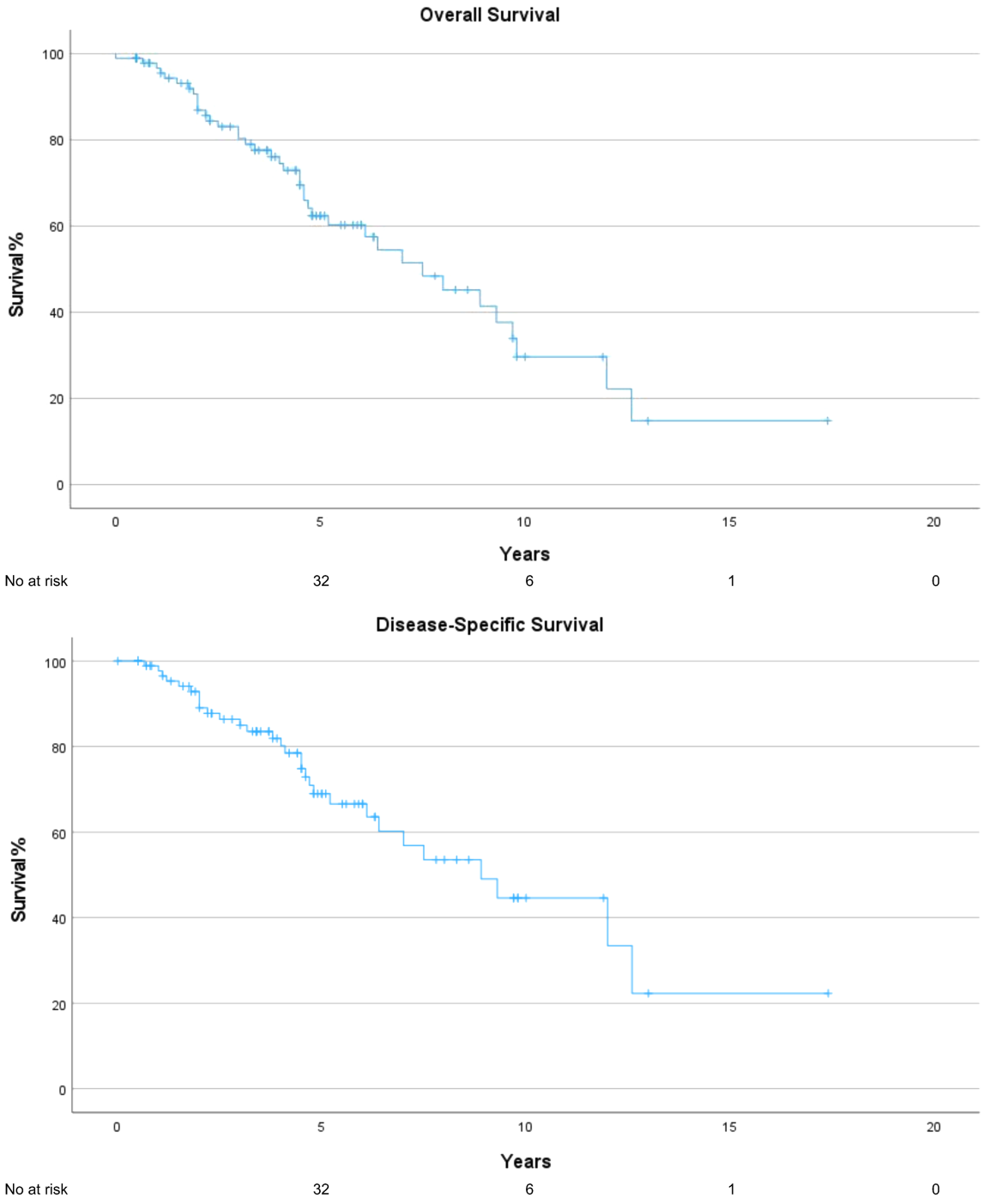

FIGURE 1 Kaplan–Meier analysis of overall survival and disease-specific survival.

Our study showed a higher prevalence of not only adjuvant radiation compared to the literature but also a higher prevalence of additional chemotherapy use. 88.4% of our patients received adjuvant therapy, of which 48.4% received chemoradiation. 81% of Gilbert's cohort received adjuvant therapy, of which 40% received chemoradiation.[6] On the other hand, 58.5% of patients in Osborn's national cancer database study received adjuvant therapy and 71% of patients in Jayaprakash's SEER study received adjuvant therapy.[7,8] Despite the use of adjuvant therapy in the aforementioned studies, none indicated adjuvant therapy's association with survival prolongation.[6–8] There was also no standardized chemotherapy regimen observed among our cohort, although more than half included a combination of a platinum-based agent (e.g., cisplatin, carboplatin) paired with a taxane drug (e.g., paclitaxel, docetaxel). In SDC, cytotoxic chemotherapy primarily plays a palliative role in patients with metastatic or recurrent disease. Due to the rarity of SDC, there is a scarcity of prospective studies determining the optimal regimen of chemotherapy agents.[27] Specifically, the use utility of adjuvant chemotherapy needs further

TABLE 3 Univariate analyses of overall survival and disease-specific survival.

Variable	Overall survival median years	*p*	DSS median years	*p*
Age at diagnosis	—	0.555	—	0.489
Sex				
Male	7.5	0.228	7.5	0.508
Female	9.7		12.0	
Smoking history				
Yes	6.4	0.380	6.4	0.172
No	8.9		8.9	
Alcohol use				
Yes	5.2	0.657	12.6	0.735
No	7.0		7.5	
Primary tumor site				
Parotid	8.0	0.885	12.0	0.648
Submandibular gland	7.5		7.5	
Tongue	—		—	
Hard palate	—		—	
Parapharyngeal space	4.7		4.7	
Buccal mucosa	—		—	
T stage				
Tis	—	0.173	—	0.034
T1	—		—	
T2	7.5		7.5	
T3	9.8		—	
T4a	8.0		12.0	
T4b	4.5		4.5	
N stage				
N0	12.0	<0.001	12.0	<0.001
N1	12.6		12.6	
N2a	7.0		—	
N2b	4.0		4.1	
N2c	—		—	
N3a	2.2		2.5	
N3b	4.6		4.6	
M stage				
M0	9.8	<0.001	12.0	<0.001
M1	4.0		4.5	
Perineural invasion				
Yes	6.4	0.027	7.0	0.042
No	9.8		—	
Carcinoma ex pleomorphic adenoma				
Yes	5.2	0.760	—	0.834
No	7.5		8.9	
Lymphovascular invasion				
Yes	4.7	0.018	4.8	0.017
No	9.7		12.0	
Extracapsular spread				
Yes	6.4	0.066	6.4	0.081
No	9.7		12.0	
HER-2 status				
Positive	6.4	0.492	7.0	0.176
Negative	8.0		—	
AR status				
Positive	6.1	0.496	7.0	0.550
Negative	7.0		12.0	
Margin status				
Positive	8.0	0.733	12.6	0.541
Negative	9.3		9.3	
Procedure				
Surgical resection	8.0	<0.001	9.3	0.011
Biopsy only	1.9		2.0	
Facial nerve sacrifice				
Yes	8.0	0.925	9.3	0.838
No	8.9		—	
Adjuvant therapy				
Chemotherapy and radiation therapy	4.8	0.238	6.4	0.058
Radiation only	9.8		12.0	
Chemotherapy only	3.0		—	
None	8.9		8.9	
Trastuzumab[a]				
Yes	4.6	0.759	4.8	0.710
No	1.8		1.0	

Note: — Unable to calculate due to survival >50%.
Abbreviations: AR, androgen receptor; DSS, disease-specific survival; HER-2, Human-epidermal-growth factor receptor 2.
[a]HER-2 (+) patients receiving chemotherapy ($n = 24$).

investigation, as it has received less attention and study in SDC patients.[4,6,7,11,15–17,27]

Strengths of this study include a larger sample size compared to previous single institution reports and central pathology confirmation of SDC cases. However, our results should be interpreted in the

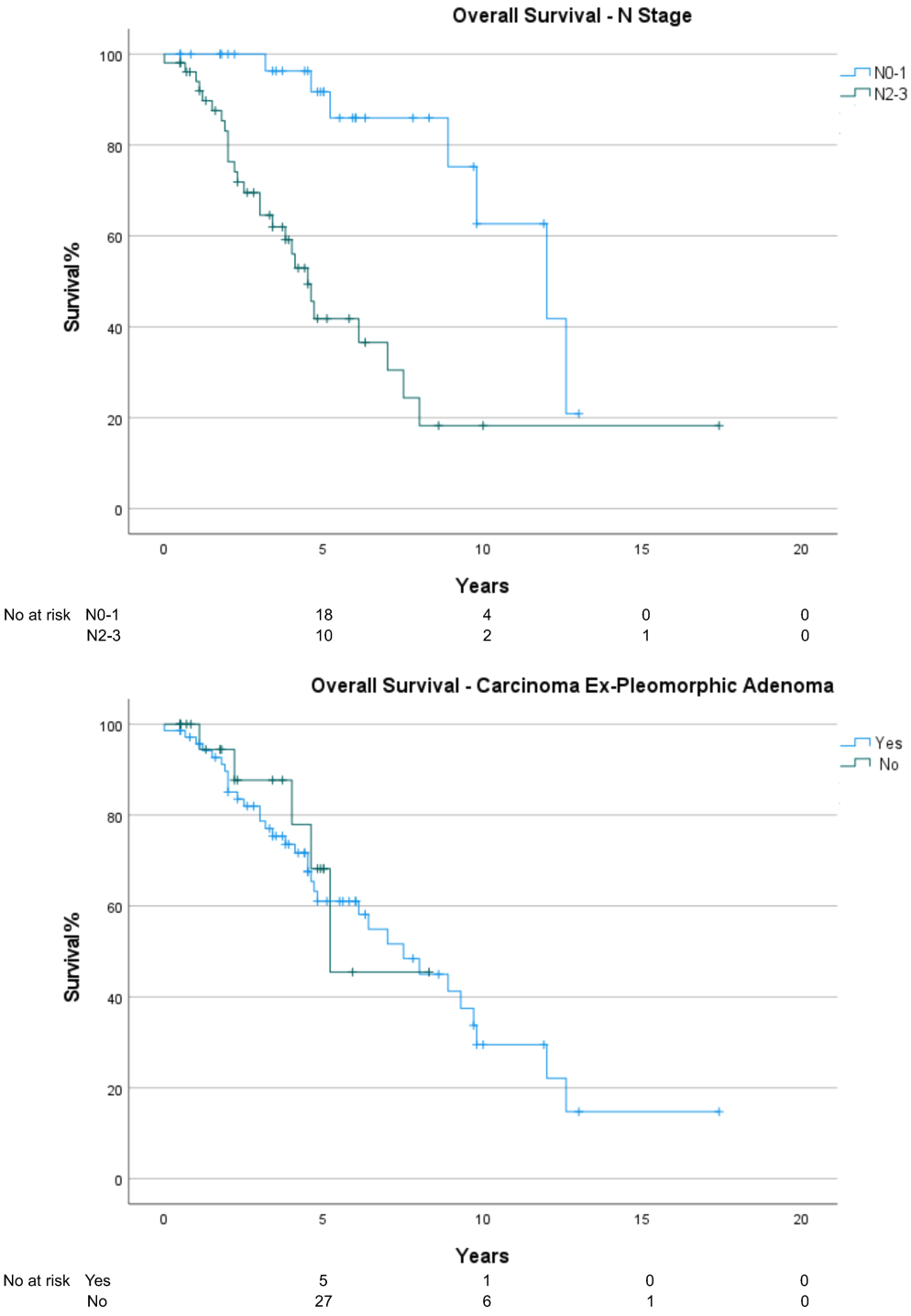

FIGURE 2 Comparison of overall survival by lymph node involvement and carcinoma ex-pleomorphic adenoma origin.

context of potential limitations. This was a retrospective study and many cases presented prior to the establishment of an electronic medical record. Thus, gaps in data were not uncommon, and several patients were lost to follow-up without documentation of their post-operative care or outcomes. Histopathological data was also not always complete, and details on adjuvant therapy such as radiation dosing or treatment length were frequently unavailable. Nonetheless, this study still represents the largest single-institution analysis of SDC outcomes to date and provides additional insight on clinical and histopathological factors associated with survival.

5 | CONCLUSION

SDC is a rare malignancy that typically presents in the parotid glands of older males. We present the largest single-institution review of clinical and histologic features in SDC to date. Our patients had more favorable survival rates compared to prior studies (5-year OS of 62.4%), which may be due to lower incidence of nodal metastases and higher rates of adjuvant therapy. Factors associated with worse survival included nodal and distant metastases, PNI, LVI, and increased tumor size. HER-2 positivity was not associated with differences in

TABLE 4 Multivariate analysis of overall survival and disease-specific survival.

	Overall survival		Disease-specific survival	
Variable	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age at diagnosis	0.956 (0.876–1.042)	0.304	0.960 (0.877–1.052)	0.382
Sex	3.045 (0.701–13.233)	0.137	4.555 (0.866–23.976)	0.074
T stage	1.818 (0.387–8.546)	0.449	1.549 (0.314–7.629)	0.591
N stage	30.337 (2.782–330.851)	0.005	27.756 (1.929–399.385)	0.015
M stage	0.516 (0.127–2.091)	0.354	0.551 (0.119–2.554)	0.446
Perineural invasion	1.868 (0.286–12.212)	0.514	1.479 (0.231–9.486)	0.680
Lymphovascular invasion	1.355 (0.181–10.118)	0.767	1.719 (0.191–15.476)	0.629
Carcinoma ex-pleomorphic adenoma	5.535 (1.024–29.933)	0.047	4.818 (0.858–27.052)	0.074
HER-2 status	1.126 (0.269–4.718)	0.871	1.644 (0.342–7.908)	0.535
Facial nerve sacrifice	0.348 (0.069–1.761)	0.202	0.240 (0.041–1.390)	0.111

Abbreviations: HR, hazard ratio; HER-2, human-epidermal-growth factor receptor 2.

survival, and facial nerve sacrifice did not appear to affect survival rates despite high prevalence of PNI. Further research and understanding into how these factors impact survival will help clinicians guide SDC patients toward appropriate therapy and allow for better prognostication.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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How to cite this article: 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 Investigative Otolaryngology*. 2024;9(2):e1234. doi:10.1002/lio2.1234