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ORIGINAL ARTICLE

Rising Incidence With Modest Survival Improvement in Salivary Duct Carcinoma: A Population-Based Study in the United States, 2000–2022

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ABSTRACT

Background: Salivary duct carcinoma (SDC) is a rare and aggressive malignancy with limited population-based data.

Methods: Incidence trends and survival outcomes were analyzed using the Surveillance, Epidemiology, and End Results database.

Results: A total of 955 cases were identified. The age-adjusted incidence rate increased from 0.158 in 2000 to 1.18 in 2022 (average annual percent change, 10.38%; $p < 0.001$), accelerating after 2012. Increases were more pronounced among females, older patients, regional-stage disease, and tumors > 2 cm. The 5-year disease-specific survival (DSS) and overall survival were 60.6% and 51.2%, respectively. Advanced age, non-parotid site, larger tumor size, lymph node metastasis, advanced stage, and non-surgical management were independent predictors of worse DSS. Patients diagnosed in 2013–2022 showed better DSS compared with those in 2004–2012 (64.7% vs. 52.0%, $p = 0.048$).

Conclusion: SDC incidence has increased rapidly, possibly reflecting improved diagnostic recognition and reclassification, with only modest survival improvement over the past decade.

1 | Introduction

Major salivary gland (MSG) carcinoma comprises a rare and histologically diverse group of malignancies, characterized by substantial heterogeneity in clinical behavior and prognosis [1, 2]. Among the more than 20 recognized histologic subtypes of MSG carcinoma, salivary duct carcinoma (SDC) is a distinct high-grade malignancy first described by Kleinsasser et al. in 1968 that histologically resembles ductal carcinoma of the breast [3–5]. Historically, SDC has been considered an exceedingly rare entity, accounting for approximately 1%–3% of all MSG carcinomas [3–5]. This rarity, together with lack of recognition, has limited accurate assessment of epidemiologic information, including true incidence and demographic and clinical characteristics [6–8].

Since the early 2000s, advances in pathologic diagnosis—particularly the incorporation of androgen receptor (AR) and human epidermal growth factor receptor 2 (HER2) immunohistochemistry—have substantially improved diagnostic accuracy for SDC [4–6, 8]. Concurrently, recent studies have reported relatively higher proportions of SDC, reaching up to 5%–12% of all MSG carcinomas [4, 6]. Despite these observations, population-level incidence analyses that adequately reflect contemporary diagnostic practices remain limited, underscoring the need for an updated epidemiologic assessment of SDC.

SDC has long been recognized as an aggressive malignancy with poor prognosis, with reported 5-year disease-specific survival (DSS) rates of 42%–55% and overall survival (OS) rates of 32%–48% [5–7, 9, 10]. However, potential temporal changes in the epidemiologic and clinicopathologic characteristics of SDC over recent decades may have influenced survival outcomes. In addition, the introduction of molecularly targeted therapies and androgen deprivation–based treatments for recurrent or metastatic SDC raises the possibility that survival outcomes may have potentially improved in the modern treatment era [10].

Accordingly, this study aimed to evaluate contemporary incidence trends and survival outcomes of SDC arising from the MSGs in the United States (US), using data from the Surveillance, Epidemiology, and End Results (SEER) database spanning the period from 2000 to 2022.

2 | Materials and Methods

This study was reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

2.1 | Data Source

Data were obtained from the SEER 17 Registries database (November 2024 submission; covering cases diagnosed between 2000 and 2022). The database includes 17 population-based cancer registries—San Francisco–Oakland, San Jose–Monterey, Los Angeles, Rural Georgia, Greater Georgia, Connecticut, Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, Atlanta (Metropolitan), Kentucky, Louisiana, New Jersey, and California (excluding San Francisco–Oakland, San Jose–Monterey, and Los Angeles)—covering approximately 26.5% of the U.S. population based on the 2020 census. Because the SEER database is publicly available and all patient information is deidentified, institutional review board approval and informed consent were not required for this study.

2.2 | Study Population

The SEER*Stat software was used for case selection. Inclusion criterion was SDC of the MSGs according to the International Classification of Diseases for Oncology, Third Edition (ICD-O-3). SDC of the MSGs were defined by pathological type and its primary sites. Pathological type was based on the WHO classification of salivary gland tumors and ICD-O histology code for SDC (8500). The primary site criteria included the parotid gland (C07.9), submandibular gland (C08.0), sublingual gland (C08.1), overlapping lesion of major salivary glands (C08.8), and major salivary gland, not otherwise specified (NOS) (C08.9).

All eligible cases were included for the evaluation of incidence and temporal trends, whereas cases with missing information on combined summary stage, cause-specific death classification, race, histologic grade, tumor size, scope of regional lymph node surgery, or number of regional nodes positive were excluded from the analyses of survival outcomes and prognostic factors. Data on combined summary stage with expanded regional codes were available in the SEER database from 2004; therefore, analyses of survival outcomes and prognostic factors were performed for cases diagnosed between 2004 and 2022.

2.3 | Study Variables and Definitions

The following information was obtained from the SEER database and included in the analyses: age, sex, race, year of diagnosis (YOD), primary site, histologic grade, combined summary stage with expanded regional codes, tumor size, surgery of the primary site, scope of regional lymph node surgery, number of regional nodes examined, number of regional nodes positive, sequence of surgery and radiation, chemotherapy, SEER cause-specific death classification, vital status, and survival months.

Age was categorized into five groups at 20-year intervals (0–19, 20–39, 40–59, 60–79, and ≥ 80 years). Race was categorized according to SEER classifications as White, Black, Asian/Pacific Islander, and American Indian/Alaska Native. Histologic grade was classified as well differentiated, moderately differentiated, poorly differentiated, or undifferentiated.

Combined summary stage was used as a measure of disease extent instead of TNM stage because it provides a consistent staging framework throughout the study period and is less susceptible to bias introduced by changes in AJCC staging definitions over time. The six categories of the combined summary stage with expanded regional codes, including in situ, localized only, regional by direct extension only, regional lymph node involvement only, regional by both direct extension and lymph node involvement, and distant site(s)/node(s) involvement, were re-categorized into three groups—localized, regional, and distant disease—to simplify the summary stage classification. Localized disease included in situ and localized only. Regional disease included cases with direct extension only, lymph node involvement only, or both direct extension and lymph node involvement. Distant disease included cases with distant site(s) or node(s) involvement.

Radiotherapy and chemotherapy were categorized as yes or no/unknown. Neck surgery was defined based on the scope of regional lymph node surgery and categorized as no neck surgery or neck surgery. Neck surgery categories included removal of 1–3 regional lymph nodes, removal of ≥ 4 regional lymph nodes, sentinel lymph node biopsy (SLNB), SLNB with additional lymph node removal at different times, and SLNB with additional lymph node removal at the same or unspecified time.

2.4 | Outcome Assessment and Statistical Analysis

The primary outcome variables were (1) the incidence and temporal trends of SDC from 2000 to 2022 and (2) survival outcomes, including DSS and OS.

Incidence rates (IRs) were expressed as age-adjusted rates per 1 000 000 persons with 95% confidence intervals (CIs), standardized to the 2000 US standard population. Age-standardized IRs based on the WHO World Standard Population (2000–2025)

were additionally calculated for the overall incidence analysis to facilitate international comparisons. Both IRs and their 95% CIs were rounded to three decimal places. Temporal trends in incidence were analyzed according to clinicopathological characteristics and quantified using annual percent change (APC) values with corresponding *p* values. In addition, Joinpoint regression analysis was performed to identify statistically significant changes ("joinpoints") in annual incidence trends, and the average annual percent change (AAPC) with its corresponding *p* value for the overall study period was calculated. Joinpoint regression was conducted using a log-linear model with a maximum of two joinpoints, and model selection was performed using the weighted Bayesian information criterion. CIs for APC and AAPC were estimated using the parametric method. Both APC and AAPC values were rounded to two decimal places. Survival outcomes, including DSS and OS, were analyzed using the Kaplan–Meier method, and differences between groups were assessed using the log-rank test.

The secondary outcome variables were demographic and clinicopathological characteristics associated with DSS. The Cox proportional hazards regression model was used to evaluate the impact of demographic and clinicopathological characteristics on the risk of disease-specific mortality. Multivariable models were constructed by including clinically relevant prognostic factors regardless of their significance in univariate analyses. The results of the Cox proportional hazards regression analyses are presented as hazard ratios (HRs) with 95% CIs and corresponding *p* values. If notable findings were identified in the primary analyses, subgroup analyses were subsequently performed for the relevant variables to validate the results and further explore their characteristics.

All statistical analyses and data visualization were conducted using SEER*Stat (version 9.0.42.0; National Cancer Institute, Bethesda, MD, USA), the Joinpoint Regression Program (version 5.1.1; National Cancer Institute), and/or SPSS for Windows (version 22.0; SPSS Inc., Chicago, IL, USA). Statistical significance was defined as a two-sided p value < 0.05.

3 | Results

3.1 | Characteristics and Incidence Rate of SDC Between 2000 and 2022

The characteristics and incidence rates of SDC between 2000 and 2022 are summarized in Table 1. A total of 955 patients were newly diagnosed with SDC between 2000 and 2022, and the overall age-adjusted IR was 0.475 (95% CI, 0.445–0.507) per 1 000 000 persons. When age-standardized using the WHO World Standard Population (2000–2025), the IR was 0.351 (95% CI, 0.329–0.374) per 1 000 000 persons.

Males accounted for 701 cases (73.4%) and females for 254 cases (26.6%), with age-adjusted IRs of 0.780 (95% CI, 0.722–0.841) and 0.233 (95% CI, 0.205–0.264), respectively. The male-to-female IR ratio was 3.3:1.

The distribution of cases by age group was as follows: 22 (2.3%) in patients aged 20–39 years, 215 (22.5%) in those aged 40–59 years, 555 (58.1%) in those aged 60–79 years, and 163 (17.1%) in those aged ≥ 80 years. The corresponding IRs were 0.042 (95% CI, 0.026–0.064), 0.397 (95% CI, 0.345–0.454), 2.053 (95% CI, 1.883–2.234), and 2.625 (95% CI, 2.237–3.060), respectively, demonstrating an increasing trend in IR with age. No cases were identified in patients aged < 20 years.

Regarding race, White, Black, Asian/Pacific Islander, and American Indian/Alaska Native patients accounted for 748 (78.3%), 84 (8.8%), 106 (11.1%), and 9 (0.9%) cases, respectively. The corresponding IRs were 0.467 (95% CI, 0.434–0.502), 0.457 (95% CI, 0.362–0.569), 0.385 (95% CI, 0.159–0.773), and 0.531 (95% CI, 0.434–0.644), respectively. Race was unknown in eight cases (0.8%).

As the primary site, the parotid gland accounted for 732 cases (76.6%; IR, 0.365; 95% CI, 0.339–0.393), followed by the submandibular gland with 142 cases (14.9%; IR, 0.070; 95% CI, 0.059–0.083). Other primary sites, including the sublingual gland, overlapping lesion of major salivary glands, and major salivary gland, NOS, accounted for 81 cases (8.5%; IR, 0.041; 95% CI, 0.033–0.051).

Stage distribution showed that 227 cases (23.8%) had localized disease (IR, 0.114; 95% CI, 0.100–0.130), 411 (43.0%) had regional disease (IR, 0.206; 95% CI, 0.186–0.227), and 264 (27.6%) had distant disease (IR, 0.130; 95% CI, 0.115–0.147). Stage was unknown in 53 cases (5.5%).

Tumor size was ≤ 2.0 cm in 247 cases (25.9%), 2.1–4.0 cm in 437 cases (45.8%), and > 4.0 cm in 200 cases (20.9%). The corresponding IRs were 0.123 (95% CI, 0.108–0.140) for tumors ≤ 2.0 cm, 0.218 (95% CI, 0.197–0.239) for tumors 2.1–4.0 cm, and 0.098 (95% CI, 0.085–0.113) for tumors > 4.0 cm. Tumor size was unknown in 71 cases (7.4%).

Regional lymph node metastasis was present in 531 cases (55.6%) and absent in 417 cases (43.7%). The IR was 0.262 (95% CI, 0.240–0.285) in cases with nodal metastasis and 0.211 (95% CI, 0.191–0.233) in those without nodal involvement. Nodal status was unknown in seven cases (0.7%).

Histologic grade was well differentiated in 14 cases (1.5%), moderately differentiated in 50 (5.2%), poorly differentiated in 314 (32.9%), and undifferentiated in 152 (15.9%). The corresponding IRs were 0.007 (95% CI, 0.004–0.012), 0.026 (95% CI, 0.019–0.034), 0.156 (95% CI, 0.139–0.175), and 0.075 (95% CI, 0.064–0.088), respectively. Histologic grade was unknown in 425 cases (44.5%).

3.2 | Incidence Trend According to Clinicopathological Characteristics, 2000–2022

Between 2000 and 2022, the overall age-adjusted IR of SDC demonstrated a continuous increase over time, rising from 0.158 in 2000 to 1.18 in 2022. The APC was 5.55% from 2000 to 2012 ($p = 0.030$) and increased to 16.47% from 2012 to 2022 ($p < 0.001$), with 2012 identified as a joinpoint. The AAPC for the entire study period was 10.38% ($p < 0.001$) (Figure 1A). When age-standardized using the WHO World Standard Population

TABLE 1 | Characteristics and incidence rates of salivary duct carcinoma between 2000 and 2022.

Variables	Patient number (%)	Age-adjusted incidence rate
Overall	955 (100.0%)	0.475 (0.445–0.507)
Sex		
Male	701 (73.4%)	0.780 (0.722–0.841)
Female	254 (26.6%)	0.233 (0.205–0.264)
Age		
< 20 years	0 (0.0%)	0
20–39 years	22 (2.3%)	0.042 (0.026–0.064)
40–59 years	215 (22.5%)	0.397 (0.345–0.454)
60–79 years	555 (58.1%)	2.053 (1.883–2.234)
≥ 80 years	163 (17.1%)	2.625 (2.237–3.060)
Race		
White	748 (78.3%)	0.467 (0.434–0.502)
Black	84 (8.8%)	0.457 (0.362–0.569)
Asian/Pacific Islander	106 (11.1%)	0.385 (0.159–0.773)
American Indian/Alaska Native	9 (0.9%)	0.531 (0.434–0.644)
Unknown	8 (0.8%)	—
Primary site		
Parotid gland	732 (76.6%)	0.365 (0.339–0.393)
Submandibular gland	142 (14.9%)	0.070 (0.059–0.083)
Others[a]	81 (8.5%)	0.041 (0.033–0.051)
Combined summary stage		
Localized	227 (23.8%)	0.114 (0.100–0.130)
Regional	411 (43.0%)	0.206 (0.186–0.227)
Distant	264 (27.6%)	0.130 (0.115–0.147)
Unknown	53 (5.5%)	—
Primary tumor size		
≤ 2.0 cm	247 (25.9%)	0.123 (0.108–0.140)
2.1–4.0 cm	437 (45.8%)	0.218 (0.197–0.239)
> 4.0 cm	200 (20.9%)	0.098 (0.085–0.113)
Unknown	71 (7.4%)	—
Regional lymph node metastasis		
No	417 (43.7%)	0.211 (0.191–0.233)
Yes	531 (55.6%)	0.262 (0.240–0.285)
Unknown	7 (0.7%)	—
Histologic grade		
Well differentiated	14 (1.5%)	0.007 (0.004–0.012)
Moderately differentiated	50 (5.2%)	0.026 (0.019–0.034)
Poorly differentiated	314 (32.9%)	0.156 (0.139–0.175)

(Continues)

TABLE 1 | (Continued)

Variables	Patient number (%)	Age-adjusted incidence rate
Undifferentiated	152 (15.9%)	0.075 (0.064–0.088)
Unknown	425 (44.5%)	—

[a]Sublingual gland, overlapping lesion of major salivary glands, and major salivary gland, not otherwise specified.

(2000–2025), the incidence likewise increased continuously throughout the study period (AAPC = 9.88%; $p < 0.001$), and joinpoint analysis identified 2012 as a significant inflection point (Figure 1B).

When stratified by sex, IRs increased in both males and females, with APCs of 10.47% in males ($p < 0.001$) and 21.40% in females ($p = 0.016$) (Figure 2A). Age-stratified analyses showed increasing IRs across all age groups. The APC was 75.31% for patients aged 20–39 years ($p < 0.001$), 10.36% for those aged 40–59 years ($p < 0.001$), 10.51% for those aged 60–79 years ($p < 0.001$), and 29.42% for those aged ≥ 80 years ($p = 0.006$) (Figure 2B). Race-stratified analyses also demonstrated increasing IRs across most racial groups. From 2000 to 2022, the APC was 10.91% among White individuals ($p < 0.001$), 37.35% among Black individuals ($p = 0.004$), 41.52% among Asian/Pacific Islander individuals ($p = 0.010$), and 34.12% among American Indian/Alaska Native individuals ($p = 0.137$) (Figure 2C). Primary site–specific analyses showed increasing IRs across all sites. The APC from 2000 to 2022 was 10.98% for tumors arising in the parotid gland ($p < 0.001$), 10.09% for those in the submandibular gland ($p < 0.001$), and 35.22% for other sites, including the sublingual gland, major salivary gland, NOS, and overlapping lesion of the major salivary glands ($p = 0.005$) (Figure 2D). Stage-stratified analyses demonstrated increasing IRs across all combined summary stages. Between 2004 and 2022, the APC was 12.61% for localized disease ($p < 0.001$), 13.93% for regional disease ($p < 0.001$), and 9.72% for distant disease ($p < 0.001$) (Figure 2E). Tumor size–specific analyses also showed increasing IRs across all size categories. The APC from 2000 to 2022 was 8.34% for tumors measuring ≤ 2.0 cm ($p < 0.001$), 26.02% for tumors measuring 2.1–4.0 cm ($p = 0.003$), and 9.50% for tumors measuring > 4.0 cm ($p < 0.001$) (Figure 2F).

3.3 | Pattern of Treatment

Among 955 patients diagnosed with SDC between 2000 and 2022, 99 cases (10.4%) did not undergo surgery for the primary tumor. Local tumor excision was performed in 63 cases (6.6%), and less-than-total resection of the salivary gland was performed in 297 cases (31.1%). Total resection was performed in 366 cases (38.3%), and radical resection in 113 cases (11.8%). Parotidectomy, NOS or Surgery, NOS was reported in 17 cases (1.8%) (Table 2). Facial nerve preservation was documented in 634 cases (66.4%), whereas facial nerve sacrifice was reported in 321 cases (33.6%). Neck surgery was performed in 752 cases (78.7%), whereas 178 cases (18.6%) did not undergo neck surgery and the status was unknown in 25 cases (2.6%).

Adjuvant radiotherapy was administered in 686 cases (71.8%), whereas 269 cases (28.2%) were classified as no/unknown for radiotherapy. Chemotherapy was administered in 283 cases (29.6%), whereas 672 cases (70.4%) were classified as no/unknown for chemotherapy.

3.4 | Survival Outcomes and Prognostic Factors Associated With DSS

For the analysis of survival outcomes and prognostic factors, 484 cases were excluded due to missing information on the following variables: combined summary stage ($n = 43$), cause-specific death classification ($n = 6$), race ($n = 8$), histologic grade ($n = 406$), tumor size ($n = 19$), extent of regional lymph node surgery ($n = 1$), and number of regional nodes positive ($n = 1$). Accordingly, 471 cases were included in the final analysis.

Kaplan–Meier analyses showed that the 5-year DSS and OS were 60.6% and 51.2%, respectively, for the analytic cohort ($n = 471$). The 5-year DSS were 82.9%, 63.4%, and 38.7% for localized, regional, and distant disease, respectively ($p < 0.001$) (Figure 3A). The corresponding 5-year OS were 72.8%, 52.6%, and 32.3%, respectively ($p < 0.001$) (Figure 3B).

Results of the Cox regression analysis for disease-specific mortality are summarized in Table 3. In the univariate analysis, the following variables were associated with disease-specific mortality: primary tumor size of 2.1–4.0 cm (HR, 1.948; 95% CI, 1.276–2.973; $p = 0.002$) and > 4.0 cm (HR, 3.004; 95% CI, 1.877–4.807; $p < 0.001$), primary surgery including local tumor excision or less-than-total resection (HR, 0.160; 95% CI, 0.089–0.287; $p < 0.001$) and total or radical resection (HR, 0.247; 95% CI, 0.142–0.429; $p < 0.001$), lymph node metastasis (single: HR, 2.550; 95% CI, 1.398–4.651; $p = 0.002$; multiple: HR, 2.706; 95% CI, 1.854–3.949; $p < 0.001$), combined summary stage of regional (HR, 2.540; 95% CI, 1.500–4.301; $p = 0.001$) and distant disease (HR, 5.376; 95% CI, 3.215–8.988; $p < 0.001$), adjuvant radiotherapy (HR, 0.621; 95% CI, 0.434–0.890; $p = 0.009$), and YOD between 2013 and 2022 (HR, 0.723; 95% CI, 0.521–0.997; $p = 0.050$).

In the multivariate analysis, age ≥ 80 years (HR, 4.829; 95% CI, 1.123–20.757; $p = 0.034$), non-parotid primary site (HR, 1.562; 95% CI, 1.034–2.360; $p = 0.034$), primary tumor size > 4.0 cm (HR, 1.887; 95% CI, 1.135–3.138; $p = 0.014$), primary surgery including local tumor excision or less-than-total resection (HR, 0.180; 95% CI, 0.064–0.502; $p = 0.001$) and total or radical resection (HR, 0.221; 95% CI, 0.077–0.635; $p = 0.005$), lymph node metastasis (single: HR, 3.669; 95% CI, 1.807–7.451; $p < 0.001$; multiple: HR, 3.483; 95% CI, 2.049–5.920; $p < 0.001$), combined summary stage of regional (HR, 2.154; 95% CI, 1.216–3.817; $p = 0.009$) and distant disease (HR, 4.262; 95% CI, 2.381–7.628; $p < 0.001$), and YOD between 2013 and 2022 (HR, 0.568; 95% CI,

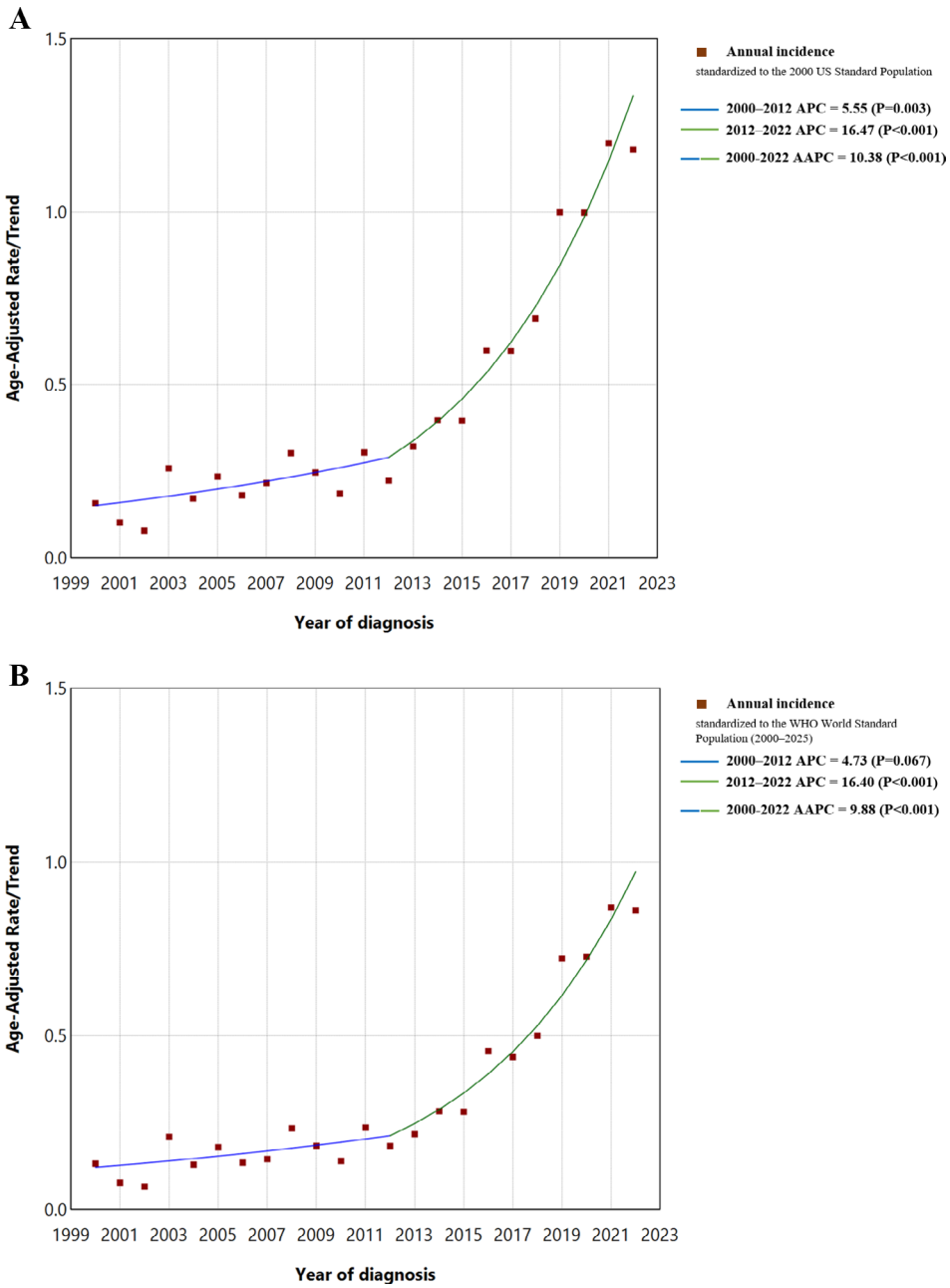

FIGURE 1 | Overall incidence trend of salivary duct carcinoma between 2000 and 2022. The incidence rate increased markedly over time, with a more pronounced rise after 2012. AAPC, average annual percentage change; APC, annual percentage change. [Color figure can be viewed at wileyonlinelibrary.com]

0.405–0.798; $p = 0.001$) remained independently associated with disease-specific mortality.

3.5 | Subgroup Analysis According to Diagnostic Period

Given that YOD, which is not a conventional prognostic factor, was independently associated with disease-specific mortality in the primary analyses, subgroup analyses stratified by diagnostic period were performed. These analyses aimed to determine whether survival outcomes differed between the two diagnostic periods (2004–2012 vs. 2013–2022) and to explore potential clinicopathological characteristics associated with the observed differences in survival between diagnostic periods.

Kaplan–Meier analyses demonstrated better survival outcomes in the more recent diagnostic period. The 5-year DSS were 52.0% for cases diagnosed in 2004–2012 and 64.7% for those diagnosed in 2013–2022 ($p = 0.048$) (Figure 4A). The corresponding 5-year OS were 42.7% and 55.4%, respectively ($p = 0.099$) (Figure 4B).

Clinicopathological characteristics according to diagnostic period are summarized in Table 4. Overall, demographic characteristics, including sex, age, and race, were comparable between the two periods. No significant differences were observed in tumor characteristics, including primary tumor site, tumor size,

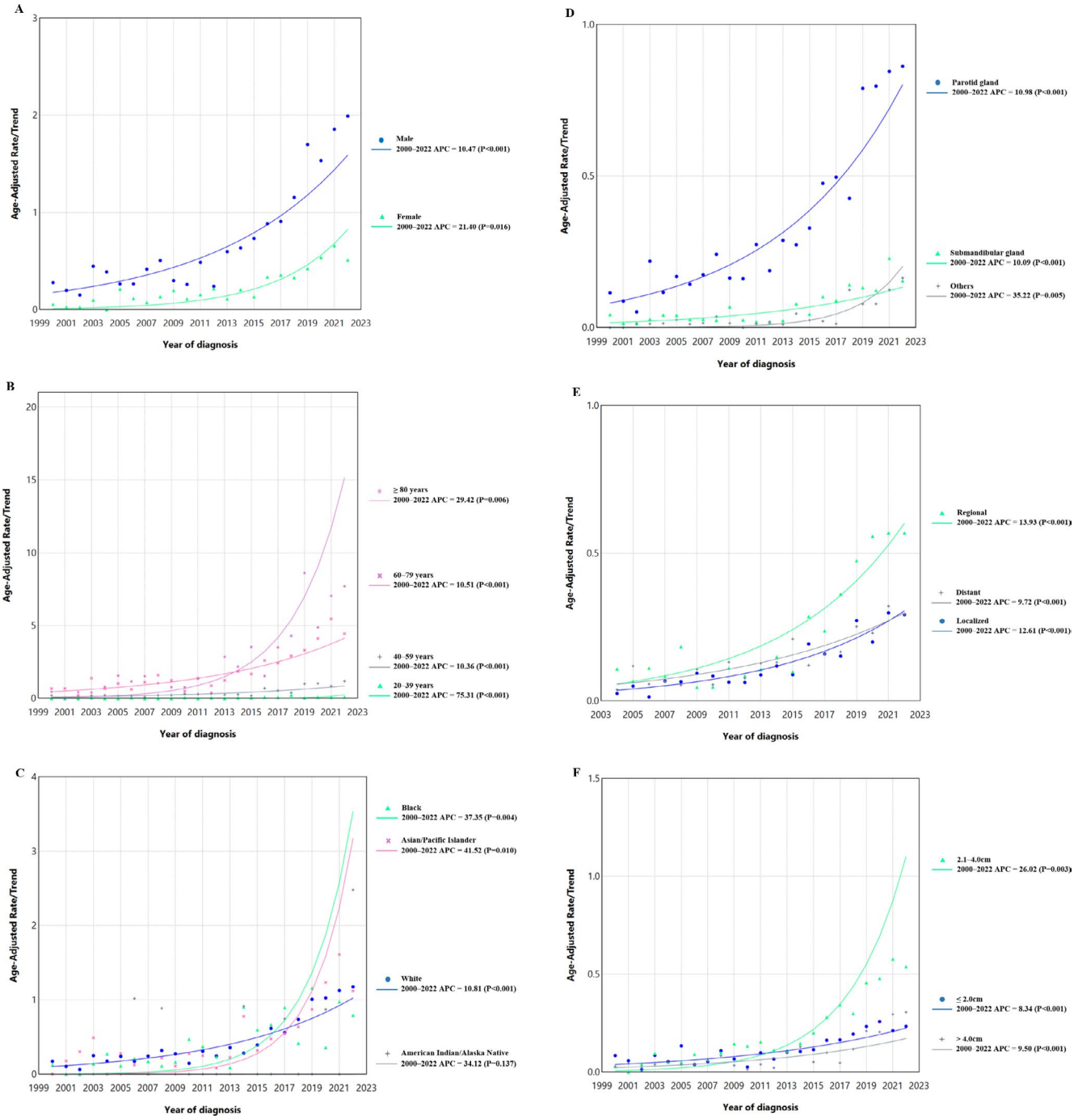

FIGURE 2 | Incidence trends of salivary duct carcinoma by sex (A), age (B), race (C), primary site (D), combined summary stage (E), and tumor size (F) between 2000 and 2022. An increasing trend is observed across all subgroups, with more pronounced increases among females, older individuals, regional-stage disease, and tumors > 2 cm. APC, annual percentage change. [Color figure can be viewed at wileyonlinelibrary.com]

lymph node metastasis, or combined summary stage at diagnosis. Similarly, treatment patterns, including primary tumor surgery, neck surgery, adjuvant radiotherapy, and chemotherapy, did not differ significantly between the two periods.

4 | Discussion

This study represents one of the largest population-based analyses specifically evaluating incidence trends and survival outcomes of SDC. Our findings demonstrate that the incidence of SDC has significantly increased in the US between 2000 and 2022, whereas survival outcomes have shown modest improvement, with DSS and OS remaining relatively poor.

4.1 | Characteristics of Newly Diagnosed SDC Between 2000 and 2022

From a demographic perspective, the present analysis demonstrated a significant increase in SDC incidence with advancing age, suggesting that SDC predominantly affects older

TABLE 2 | Pattern of treatment.

Variables	Patient number (%)
Surgery for Primary tumor	
No surgery	99 (10.4%)
Local tumor excision	63 (6.6%)
Less than total resection of the salivary gland	297 (31.1%)
Total resection of the salivary gland	366 (38.3%)
Radical resection of the salivary gland	113 (11.8%)
Parotidectomy, NOS/Surgery, NOS	17 (1.8%)
Facial nerve management	
Spared	634 (66.4%)
Sacrificed	321 (33.6%)
Neck surgery	
No	178 (18.6%)
Yes	752 (78.7%)
Unknown	25 (2.6%)
Adjuvant radiation	
No/unknown	269 (28.2%)
Yes	686 (71.8%)
Chemotherapy	
No/unknown	672 (70.4%)
Yes	283 (29.6%)

Abbreviation: NOS, not otherwise specified.

individuals, consistent with previous reports [5, 8, 10]. In addition, the pronounced male predominance observed in this study aligns with prior findings, which have reported male-to-female ratios ranging from approximately 3:1–5:1 [3–5]. Although the frequent expression of AR in SDC has been proposed as a potential explanation for this sex disparity, the underlying biological mechanisms remain incompletely understood [11, 12].

Despite the male predominance in IR, the temporal increase in incidence was more pronounced among females (APC 21.40% vs. 10.47% in males). This observation may, in part, be attributable to an increased recognition of SDC arising from pleomorphic adenoma (carcinoma ex pleomorphic adenoma, Ca ex PA). Given that pleomorphic adenoma is more prevalent in women and that recent epidemiologic studies have demonstrated a rising incidence of pleomorphic adenoma predominantly among female patients, this trend may have contributed to the increasing incidence of SDC as Ca ex PA in women [13–15]. Furthermore, sex-related differences in healthcare utilization—such as more frequent engagement in routine medical evaluations and cross-sectional imaging among women—may also partially explain this disproportionate increase [16, 17].

From a clinicopathological perspective, a substantial proportion of patients in this cohort presented with advanced disease; more than 50% had lymph node metastasis and over 70% were diagnosed at regional or distant stages. These findings underscore the aggressive biological behavior of SDC and are consistent with its well-established propensity for early regional and distant dissemination [6, 7, 10]. Moreover, although facial nerve status at the time of diagnosis could not be directly determined from the SEER database, approximately one-third of patients underwent sacrifice of at least one branch of the facial nerve. This observation suggests that SDC is not only characterized by early regional and distant spread, but also exhibits marked local invasiveness. Supporting this, previous studies have reported that facial nerve palsy is present at diagnosis in approximately

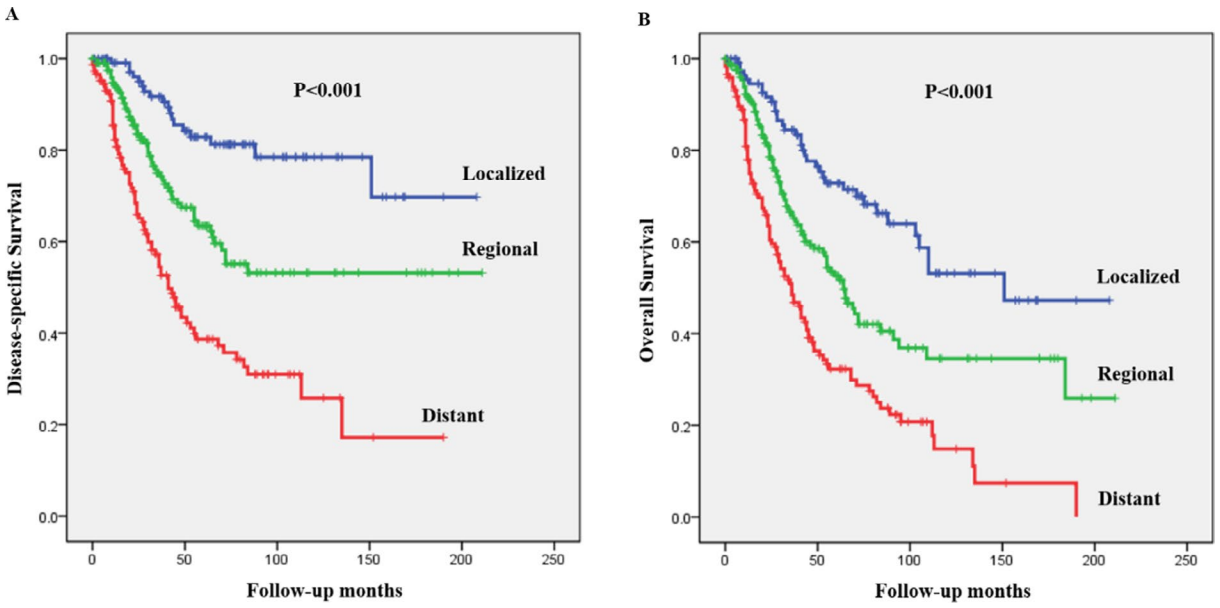

FIGURE 3 | Kaplan–Meier curves for disease-specific survival (A) and overall survival (B) according to combined summary stage. Survival outcomes differ significantly according to stage ($p < 0.001$). [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 | Cox regression analysis for disease-specific mortality.

	Univariate			Multivariate		
Variables	**HR**	**CI**	***p***	**HR**	**CI**	***p***
Sex						
Female (reference)	1	—	—	1	—	—
Male	1.279	0.890–1.837	0.183	1.200	0.823–1.750	0.343
Age						
20–39 years (reference)	1	—	—	1	—	—
40–59 years	2.111	0.507–8.792	0.305	2.307	0.549–9.704	0.254
60–79 years	2.320	0.571–9.423	0.239	2.515	0.610–10.364	0.202
≥ 80 years	3.877	0.926–16.241	0.064	4.829	1.123–20.757	0.034
Primary site						
Parotid (reference)	1	—	—	1	—	—
Non-parotid	1.022	0.694–1.507	0.911	1.562	1.034–2.360	0.034
Primary tumor size						
≤ 2.0 cm (reference)	1	—	—	1	—	—
2.1–4.0 cm	1.948	1.276–2.973	0.002	1.486	0.954–2.314	0.080
> 4.0 cm	3.004	1.877–4.807	< 0.001	1.887	1.135–3.138	0.014
Surgery for primary tumor						
No surgery (reference)	1	—	—	1	—	—
Local tumor excision or less than total resection of the salivary gland	0.160	0.089–0.287	< 0.001	0.180	0.064–0.502	0.001
Total or radical resection of the salivary gland	0.247	0.142–0.429	< 0.001	0.221	0.077–0.635	0.005
Facial nerve management						
Spared (reference)	1	—	—	1	—	—
Sacrificed	1.189	0.866–1.631	0.284	1.057	0.732–1.525	0.768
Neck surgery						
No (reference)	1	—	—	1	—	—
Yes	0.865	0.551–1.358	0.528	1.468	0.648–3.325	0.358
Histologic grade						
Well or Moderate (reference)	1	—	—	1	—	—
Poorly or Undifferentiated	1.626	0.939–2.815	0.083	0.943	0.535–1.662	0.839
Regional lymph node metastasis						
No (reference)	1	—	—	1	—	—
Single	2.55	1.398–4.651	0.002	3.669	1.807–7.451	< 0.001
Multiple	2.706	1.854–3.949	< 0.001	3.483	2.049–5.920	< 0.001
Combined summary stage						
Localized (reference)	1	—	—	1	—	—
Regional	2.540	1.500–4.301	0.001	2.154	1.216–3.817	0.009
Distant	5.376	3.215–8.988	< 0.001	4.262	2.381–7.628	< 0.001

(Continues)

TABLE 3 | (Continued)

Variables	Univariate			Multivariate		
	HR	CI	*p*	HR	CI	*p*
Adjuvant radiation						
No/unknown (reference)	1	—	—	1	—	—
Yes	0.621	0.434–0.890	0.009	0.810	0.516–1.271	0.360
Chemotherapy						
No/unknown (reference)	1	—	—	1	—	—
Yes	1.583	1.150–2.180	0.005	1.250	0.864–1.809	0.237
Year of diagnosis						
2004–2012 (reference)	1	—	—	1	—	—
2013–2022	0.723	0.521–0.997	0.050	0.568	0.405–0.798	0.001

Abbreviations: CI, confidence interval; HR, hazard ration.

30% of patients, and facial nerve resection is required in 42.1%–55.5% of cases during surgical management, further highlighting the locally aggressive nature of this malignancy [7, 8, 18, 19].

4.2 | Increasing Incidence of SDC

Although the overall incidence of SDC during the study period was still low, the IR significantly increased 7.5 times, from 0.158 in 2000 to 1.18 in 2022, with an AAPC of 10.38%. This increase could initially be attributed to improved life expectancy and population aging, given that SDC predominantly affects older individuals. Nevertheless, because the present analyses were based on age-adjusted IRs, demographic aging alone is unlikely to fully explain the observed increase. Importantly, the increasing trend was consistently observed across nearly all demographic and clinical subgroups, rather than being confined to older patients.

One plausible explanation for this increasing incidence is improved pathologic recognition of SDC. Historically, SDC was frequently misclassified as adenocarcinoma, NOS, now termed salivary gland carcinoma, NOS in the most recent WHO classification, or other high-grade salivary gland malignancies due to overlapping morphologic features and limited diagnostic criteria [20, 21]. However, since the early 2000s, the routine use of immunohistochemical markers—particularly AR and HER2—has substantially enhanced diagnostic accuracy [4, 20, 21]. In fact, a recent study evaluating 79 tumors initially diagnosed as adenocarcinoma, NOS between 1986 and 2017 reported that 39% of cases were reclassified as SDC upon reassessment using contemporary histologic and immunohistochemical criteria [22]. This finding suggests that a proportion of tumors previously categorized as adenocarcinoma, NOS are now more accurately identified as SDC, thereby contributing to the observed increase in incidence. Supporting this interpretation, we conducted an additional exploratory analysis using the same SEER database and observed a decreasing trend in the incidence of adenocarcinoma, NOS over the present study period (Figure S1). These findings are consistent with recent observations by Jansen et al., who also suggested that contemporary diagnostic reclassification and improved diagnosis contributed substantially to the increasing recognition of SDC in recent decades [23]. Nevertheless, this possibility should be formally validated in future studies specifically designed to evaluate temporal diagnostic shifts among salivary gland carcinoma subtypes. We are currently planning a follow-up study to further address this hypothesis.

Similarly, changes in the diagnostic approach to Ca ex PA may have contributed to the apparent rise in SDC incidence. Approximately 20%–59% of SDCs are known to arise from preexisting pleomorphic adenomas, and SDC represents the most common malignant component of Ca ex PA [5, 6, 8]. The 2017 WHO classification recommends that Ca ex PA should not be considered a standalone diagnostic entity; instead, the specific histologic subtype of the malignant component should be reported [24, 25]. Consequently, the adoption of this classification may have led to increased reporting of SDC arising within Ca ex PA. In the present study, the increase in incidence was more pronounced in tumors larger than 2 cm compared with those measuring ≤2 cm. Given that malignant transformation in Ca ex PA typically occurs in long-standing pleomorphic adenomas, these tumors are more likely to present at a relatively larger size at diagnosis. This observation may therefore support the hypothesis that a substantial proportion of newly identified SDCs arise through malignant transformation within preexisting pleomorphic adenomas rather than de novo carcinogenesis. Supporting this interpretation, a prior study have shown that only 20.5% of SDCs arising from Ca ex PA were classified as T1 (≤2 cm), whereas the majority presented as T2 or higher-stage tumors (>2 cm) [26]. A similar pattern has also been reported in a study on parotid cancer based on the National Cancer Database, which demonstrated that T2 or higher-stage tumors were more prevalent in Ca ex PA and SDC, whereas T1 tumors were more common in other histologic subtypes, including mucoepidermoid carcinoma, adenoid cystic carcinoma, and acinic cell carcinoma [27].

Furthermore, the timing of these advances in pathologic classification broadly coincides with the joinpoint identified in the present study, which demonstrated a marked acceleration in SDC incidence around 2012. Taken together, these observations

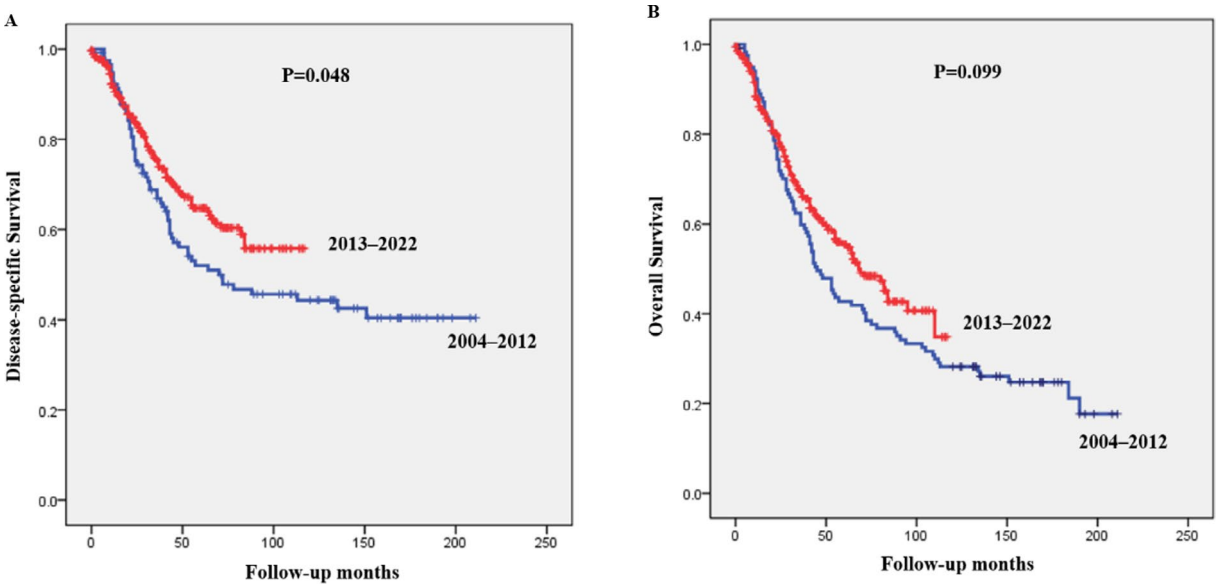

FIGURE 4 | Kaplan–Meier curves for disease-specific survival (A) and overall survival (B) according to year of diagnosis. Cases diagnosed in 2013–2022 shows better disease-specific survival ($p = 0.048$) compared with those diagnosed in 2004–2012, whereas overall survival dose not differ significantly ($p = 0.099$). [Color figure can be viewed at wileyonlinelibrary.com]

support the possibility that the increasing incidence of SDC may, at least in part, reflect evolving pathologic classification and improved diagnostic recognition in the contemporary era. However, this interpretation remains speculative and cannot be directly validated using the present dataset. Future studies are warranted to investigate temporal changes in diagnostic practices and the proportion of SDC arising from Ca ex PA, thereby further clarifying the mechanisms underlying the observed epidemiologic trends.

4.3 | Survival Outcomes of SDC

In this study, the 5-year DSS and OS were 60.6% and 51.2%, respectively, for the analytic cohort ($n = 471$). These outcomes are comparable to, or slightly better than, those reported in previous studies, which have documented 5-year DSS and OS rates ranging from approximately 42%–64% and 30%–48%, respectively [4, 5, 9, 10, 28]. However, despite advances in surgical techniques and adjuvant treatment strategies over recent decades, as well as the marked increase in SDC incidence, the overall prognosis of SDC remains relatively poor. This unfavorable prognosis is largely attributable to the high propensity of SDC for distant metastasis and subsequent distant failure [8, 18, 29, 30].

In contrast to head and neck squamous cell carcinoma (HNSCC), for which neoadjuvant and adjuvant systemic therapies are widely used to reduce distant failure, no systemic agent has yet demonstrated a clear benefit in the neoadjuvant or adjuvant setting for SDC or other MSG carcinomas [10, 18, 21, 31]. Nevertheless, SDC is characterized by a high prevalence of potentially targetable molecular alterations, including HER2 overexpression (approximately 30%–80%) and AR expression (70%–100%) [4, 5, 10, 20, 32]. Over the past two decades, substantial progress has been made in the development of HER2-targeted therapies and AR pathway inhibition, with reported overall response rates of approximately 50%–70% and 20%–60%, respectively, in recurrent or metastatic disease [5, 10, 31]. Despite these encouraging results, these therapies have been used primarily in the palliative setting. Therefore, although molecularly targeted therapies may improve disease control in advanced SDC, their impact on reducing distant failure and improving long-term survival remains uncertain.

4.4 | Prognostic Factors for SDC

Multivariable analysis identified several demographic and clinicopathological factors associated with disease-specific mortality, including advanced age (≥ 80 years), non-parotid primary site, large tumor size (> 4 cm), lymph node metastasis, advanced stage, and non-surgical management of the primary tumor. These findings are largely consistent with those reported in previous large-scale studies on SDC [7, 9, 18, 33]. A SEER-based study published in 2014, which analyzed 228 cases of SDC, identified primary tumor size and lymph node metastasis as independent predictors of poor prognosis [9]. Similarly, a multi-institutional study of 141 patients reported that age ≥ 65 years, lymph node metastasis, and primary tumors arising from the minor salivary glands or sublingual gland were independently associated with worse survival outcomes [18].

In contrast to findings commonly reported in HNSCC and other MSG carcinomas, adjuvant radiotherapy was not identified as a significant prognostic factor in the present study. Although some small retrospective series have suggested a potential benefit of postoperative radiotherapy, the available evidence remains limited due to small sample sizes and methodological heterogeneity [29, 34]. In contrast, larger studies involving more than 100 patients—including those based on the National Cancer Database ($n = 495$), the SEER database ($n = 228$), the Nationwide Network and Registry of Histo- and Cytopathology in the Netherlands ($n = 177$), and a Japanese multi-institutional cohort ($n = 141$)—have not demonstrated a clear survival benefit associated with

TABLE 4 | Clinicopathological characteristics according to year of diagnosis.

Variables	2004–2012 ($n = 120$)	2013–2022 ($n = 351$)	p
Sex			
Female	40 (33.3%)	88 (25.1%)	0.096
Male	80 (66.7%)	263 (74.9%)	
Age			
20–39 years	3 (2.5%)	8 (2.3%)	0.356
40–59 years	33 (27.5%)	78 (22.2%)	
60–79 years	70 (58.3%)	202 (57.6%)	
≥ 80 years	14 (11.7%)	63 (18.0%)	
Race			
White	104 (86.7%)	277 (78.9%)	0.162
Black	7 (5.8%)	29 (8.3%)	
Asian/Pacific Islander	7 (5.8%)	42 (12.0%)	
American Indian/Alaska Native	2 (1.7%)	3 (0.9%)	
Primary site			
Parotid	92 (76.7%)	285 (81.2%)	0.292
Non-parotid	28 (23.3%)	66 (18.8%)	
Primary tumor size			
≤ 2.0 cm	40 (33.3%)	91 (25.9%)	0.190
2.1–4.0 cm	59 (49.2%)	177 (50.4%)	
> 4.0 cm	21 (17.5%)	83 (23.4%)	
Regional lymph node metastasis			
No	51 (42.5%)	134 (38.2%)	0.403
Yes	69 (57.5%)	217 (61.8%)	
Combined summary stage			
Localized	30 (25.0%)	88 (25.1%)	0.358
Regional	47 (39.2%)	160 (45.6%)	
Distant	43 (35.8%)	103 (29.3%)	
Surgery for primary tumor			
No surgery	4 (3.3%)	20 (5.7%)	0.152
Local tumor excision or less than total resection of the salivary gland	53 (44.2%)	126 (35.9%)	
Total or radical resection of the salivary gland	59 (49.2%)	200 (57.0%)	
Parotidectomy, NOS/Surgery, NOS	4 (3.3%)	5 (1.4%)	
Neck surgery			
No	20 (16.7%)	41 (11.7%)	0.160
Yes	100 (83.3%)	310 (88.3%)	
Adjuvant radiation			

(Continues)

TABLE 4 | (Continued)

Variables	2004–2012 ($n = 120$)	2013–2022 ($n = 351$)	p
No/unknown	26 (21.7%)	80 (22.8%)	0.799
Yes	94 (78.3%)	271 (77.2%)	
Chemotherapy			
No/unknown	88 (73.3%)	242 (68.9%)	0.365
Yes	32 (26.7%)	109 (31.1%)	

postoperative radiotherapy in SDC [7, 9, 18, 33]. However, these findings should be interpreted with caution, as patients receiving adjuvant radiotherapy are more likely to present with advanced disease and adverse pathological features. Moreover, detailed pathological risk factors and indications for adjuvant treatment are not comprehensively captured in the SEER database, raising the possibility of residual confounding. Therefore, the true survival impact of adjuvant radiotherapy in SDC cannot be reliably determined based on the currently available retrospective evidence alone. Nevertheless, the lack of a consistently demonstrated survival benefit suggests that the role of adjuvant radiotherapy in SDC remains uncertain, and this uncertainty should be considered when developing adjuvant treatment strategies for this aggressive malignancy.

4.5 | Improvement in Survival in the Contemporary Era

A notable finding of the present study was that YOD (2013–2022) was independently associated with a reduced risk of disease-specific mortality. Kaplan–Meier survival analyses further demonstrated that DSS was significantly improved in the more recent diagnostic period (2013–2022) compared with the earlier period (2004–2012). However, the distributions of demographic characteristics, tumor stage, and treatment patterns were comparable between the two periods. Therefore, the factors underlying the observed improvement in survival remain unclear. Several unmeasured factors, including advances in systemic therapy, supportive care, and other aspects of cancer management, may potentially have contributed to these findings [10, 21, 31, 35, 36]. Further studies with more detailed treatment and molecular data are needed to clarify the factors associated with temporal improvements in survival among patients with SDC.

5 | Limitations

This study has several limitations. First, a substantial number of cases were excluded from the survival analyses because of missing histologic grade information, which may have introduced selection bias and limited the generalizability of the prognostic analyses. Second, the SEER database does not provide detailed histopathological information, including resection margin status, lymphovascular invasion, perineural invasion, and molecular characteristics. In addition, detailed information regarding treatment indications and strategies, such as the extent of surgery and the use of adjuvant radiotherapy or chemotherapy, is unavailable. These limitations precluded evaluation of the impact of these factors on survival and may have resulted in residual confounding in the prognostic analyses.

Despite these limitations, this study provides comprehensive population-based data on the epidemiology and prognosis of SDC. Furthermore, the major prognostic factors identified in the present study were largely consistent with those reported in previous institutional and population-based studies, supporting the validity of the findings. Given the rarity of SDC, the present study provides valuable contemporary evidence regarding its incidence trends and survival outcomes at the population level.

In conclusion, this population-based study demonstrates a marked and continuous increase in the incidence of SDC in the US over the past two decades, possibly reflecting improved diagnostic recognition and evolving pathologic classification. Despite this epidemiologic expansion, survival outcomes have shown only modest improvement and remain suboptimal, highlighting a persistent gap between disease burden and effective therapeutic advancement. These findings highlight the continued need for improved disease-specific treatment strategies and further research into the evolving epidemiology and management of SDC.

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Ethics Statement

This study used de-identified publicly available data from the SEER database; therefore, institutional review board approval and informed consent were not required.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in Surveillance, Epidemiology, and End Results (SEER) Program at https://seer.cancer.gov/. These data were derived from the following resources available in the public domain: - SEER database, https://seer.cancer.gov/.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Overall incidence trend of adenocarcinoma, not otherwise specified, from 2000 to 2022. The incidence rate decreased significantly over time, with an annual percentage change of −3.08% ($p < 0.001$). APC, annual percentage change.