Survival Outcome of Salivary Gland Carcinoma: A 50-Year Retrospective Study With Long-Term Follow-up

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Purpose: Salivary gland carcinomas (SGCs) can be classified into more than 20 subtypes with various clinical behaviors. The present study aimed to analyze the clinical and pathological features of SGCs and evaluate their long-term prognosis.

Methods: A retrospective cohort study was performed. This study investigated cases of histologically confirmed SGC at the authors' institution from January 1963 to December 2014. Data on sex, age, site, histopathological diagnosis, tumor-node-metastasis classification, postoperative radiotherapy and/or chemotherapy, local and regional recurrence, and distant metastasis (DM) were collected as covariates. The overall survival (OS) rate was analyzed as the outcome. Kaplan-Meier survival analysis and Cox multivariate analysis were used for survival analysis. The cohort was divided into 2 groups—before and after 1989. The clinicopathological characteristics of the 2 groups were compared using the χ^2 test.

Results: The cohort included 1,637 patients who met the admission criteria and had a male-to-female ratio of 0.9:1. The median age was 47 years (range, 8 months to 86 years). The median follow-up time was 54 months (range, 1–432 months). The majority of the tumors occurred in the parotid gland (35.3%), followed by the palate gland (25.2%). Adenoid cystic carcinoma was the most common tumor type (34.3%), and mucoepidermoid carcinoma (29%) was the second most common type. In the 1,637 patients, the neck lymph node metastasis rate was 8.7% at the first surgery, and the overall DM rate was 14.1%. The 5-, 10-, and 15-year OS rates of the 1,637 cases were 93.1%, 87.2%, and 79.3%, respectively. Comparative analysis before and after 1989 showed statistically significant differences in sex, site, histologic subtype, T classification, local and regional recurrence rate, and radiotherapy ($P < .05$), while no significant differences were found in age, N classification, M staging, DM, or chemotherapy.

Conclusions: The OS rates of SGC have improved significantly over the past 30 years. This is attributable to an increase in the proportion of patients diagnosed at the early stage and receiving radiotherapy, as this has led to a reduction in the local and regional recurrence rate and, consequently, an improvement in the survival rates.

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Salivary gland carcinomas (SGCs) are a heterogeneous and highly diverse group of tumors that occur in the major and minor salivary glands. These tumors account for 3% to 10% of the neoplasms of the head and neck region.[1-3] They are the second most common tumors in the oral and maxillofacial region (the most common being oral squamous cell carcinoma).[4] The variety of pathological types of SGCs results in differences in the prognosis of these carcinomas. In general, the short-term survival rate of SGCs is high, but the long-term survival rate progressively decreases, especially in the case of certain high-grade salivary malignancies.[5,6] Therefore, patients with SGCs require more than 10 years of regular follow-up. However, the low incidence of SGCs makes retrospective studies with large samples and long-term follow-up difficult. Very few studies have examined large-scale data for this carcinoma.[7,8]

Some previous studies on SGCs were conducted at our center.[9-11] As one of the top stomatology centers in China, we have conducted a new study to analyze retrospectively the clinical characteristics and prognosis of 1,637 patients with SGCs who were admitted to our hospital in the last 50 years—from 1963 to 2014. The purpose of this study was to analyze the clinicopathologic characteristics and evaluate the prognosis of SGCs. The investigators hypothesize that changes in the clinical features and prognosis of SGCs have occurred over this period. The specific aim of the study is to provide a reference to guide clinical decision-making based on the findings.

Materials and Methods

STUDY DESIGN/SAMPLE

To address the research purpose, the investigators designed and implemented a retrospective cohort study. The study population was composed of patients who presented for the evaluation and management of SGCs between January 1963 and December 2014. Patients diagnosed with primary SGC who had first consulted and undergone surgical excision at our institution were included. Patients were excluded as study subjects if they had received conservative treatment or had been lost to follow-up.

STUDY VARIABLES

The primary predictor variable was time, before and after 1989. The primary outcome variable was survival. The covariates were age, sex, tumor site, histology, pathological tumor-node-metastasis (TNM) classification, treatment modality, recurrence (time from initial surgery to recurrence at the primary site or neck), and metastasis. The major salivary glands involved include the parotid gland, submandibular gland, and sublingual gland, whereas the minor glands include those in the lip and intraoral regions (the palate, tongue, bucca, maxilla, mandible, temporal fossa, and pharyngeal). The treatment modality included surgery with or without postoperative radiotherapy and/or chemoradiotherapy.

Follow-up duration was calculated from the date of surgery until the last known contact with the patient. Subjects were censored at the time of last follow-up or death.

According to the criteria of the World Health Organization's classification of salivary gland tumors published in 2017,[12] all cases were reassessed based on their histologic features by 2 experienced salivary gland pathologists. TNM classification was carried out according to the 2017 criteria of the International Union Against Cancer.[13]

DATA COLLECTION METHODS

Local recurrence and regional failure were assessed by clinical examinations and radiographic imaging, and histopathological examination was only performed when necessary. Prognostic information, such as the presence of local or regional recurrence and distant metastasis (DM), was obtained from the patients' medical records and follow-up telephone calls. Due to the retrospective nature of this study, it was exempted from ethical review by the Peking University School and Hospital of Stomatology Institutional Review Board (approval number PKUSSIRB-202058146).

DATA ANALYSES

The characteristics of the case series were analyzed using SPSS software version 23.0 (SPSS Inc, Chicago, IL). The continuous variable (age) was analyzed using an independent-samples t test. Categorical variables (sex, site, histologic type, TNM classification, local and regional recurrence, DM, radiotherapy, and chemotherapy) were analyzed by Pearson χ^2 test. Kaplan-Meier estimator and Cox multivariate regression were used for survival analysis and identifying covariates associated with outcome. P values less than .05 were considered to indicate statistical significance. All tests were 2-sided and run with a type 1 error ($\alpha = .05$).

Results

COHORT CHARACTERISTICS

Over the 50-year period in which the data were collected, 2,686 underwent surgery. Among them, 1,637 patients met the inclusion criteria and had detailed follow-up data (Table 1). The cohort of 1,637 patients comprised 789 males (48.2%) and 848

females (51.8%), and their age ranged from 8 months to 86 years (median age 47 years).

TUMOR LOCATION AND PATHOLOGICAL TYPES

Carcinomas of the major salivary gland were distributed in the parotid, submandibular, and sublingual glands, while carcinomas of the minor salivary gland were distributed in the palate, buccal mucosa, retromolar region, lip, tongue, maxilla sinus, and other sites (Table 1). The most frequently involved sites were the parotid gland (578/1,637) and the palate (413/1,637). Our case series covered almost all types of salivary gland malignancies, with the exception of secretory carcinoma, which is a new entity of salivary malignant tumor. Adenoid cystic carcinoma (ACC) and mucoepidermoid carcinoma (MEC) were the 2 most common pathologic types and accounted for more than 60% of the carcinomas.

TUMOR STAGING AND TREATMENT

With regard to tumor staging, 1,093 (66.8%) patients had stage T1 or T2 carcinoma, and lymph node metastasis was not detected in the majority of the patients (1,495/1,637; 91.3%). In this cohort, 821 patients received radiation therapy (including implantation of radioactive particles), and 90 patients received chemotherapy and radiation. For patients with T1-T2 stage SGC, Kaplan-Meier survival analysis showed statistically significant differences between surgery alone and surgery combined with postoperative radiotherapy ($P < .01$) (Fig 1). However, for T3-T4 stage patients, there was no statistically significant difference between surgery only and surgery combined with radiotherapy ($P > .05$) (Fig 2).

FOLLOW-UP FINDINGS

The follow-up time ranged from 1 to 432 months, with an average follow-up period of 66.3 months. During the follow-up period, 684 patients had local and/or regional recurrence, with local and regional recurrence rates of 37.0% (606/1,637) and 12.2% (200/1,637), respectively. After more than 5 years of follow-up, 147 (147/606, 24.3%) patients developed local recurrence, and 52 (52/200, 26%) patients developed cervical metastasis. The 3 most common pathologic types associated with cervical metastasis were oncocytic carcinoma (41.2%), squamous cell carcinoma (26.1%), and salivary ductal carcinoma (25.9%). The tumor recurrence rate in patients with ACC as the pathological type was 39.5% (270/684). With regard to metastasis, the overall rate of DM was 14.1%, and ACC accounted for 64.9% of DM cases, followed by adenocarcinoma (9.1%) and carcinoma ex pleomorphic adenoma (6.9%).

SURVIVAL DATA

At the end of the follow-up period, 305 patients had died. Among them, 186 patients succumbed to tumor recurrence, with the most common histologic types being ACC (43.5%) and adenocarcinoma (17.2%). Furthermore, 92 patients died of DM, and 54 of them had the ACC pathological type. The remaining 27 patients died of other causes.

Cox multivariate survival analysis showed that the 5-, 10-, and 15-year survival rates were 93.1%, 87.2%, and 79.3%, respectively. The cumulative survival analysis curve is shown in Figure 3.

Kaplan-Meier univariate survival analysis and Cox models showed that age, sex, pathological type, TNM classification, local and regional recurrence, DM, radiotherapy, and chemotherapy were statistically significant prognostic factors for survival ($P < .05$) (Table 2). A bivariate analysis between time and overall survival (OS) showed time (year of diagnosis) was a statistically significant factor for survival ($P < .001$) (Table 3). However, Cox multiple regression analysis revealed the following independent factors: time ($P < .001$; hazard ratio [HR] = 0.40; confidence interval [CI] = 0.31–0.52), age ($P < .001$; HR = 1.97; CI = 1.50-2.60), ACC ($P = .039$; HR = 1.56; CI = 1.02–2.37), other pathologic types ($P = .011$; HR = 1.70; CI = 1.13–2.56), T classification ($P < .001$; HR = 2.21; CI = 1.71–2.86), N classification ($P < .001$; HR = 3.03; CI = 2.03–4.51), local recurrence ($P < .001$; HR = 2.72; CI = 2.06–3.60), regional recurrence ($P = .019$; HR = 1.51; CI = 1.07–2.13), and DM ($P < .001$; HR = 2.97; CI = 2.28–3.88) (Table 4).

Moreover, we performed Kaplan-Meier univariate analysis of clinicopathological characteristics associated with the crude 5-, 10-, and 15-year survival rates for 1,637 patients (Table 5). The results showed that there were statistically significant differences among people of different ages, genders, pathologic types, and TNM classification ($P < .05$) (Table 5). Besides, the OS rate of patients with local or regional recurrence or DM was lower than that of patients without recurrence or metastasis (Table 5). For the subgroup of postoperative chemotherapy or not, the OS of patients with postoperative chemotherapy and radiotherapy decreased over time ($P < .05$), but there were no statistically significant differences in primary site ($P > .05$) (Table 5).

COMPARATIVE ANALYSIS

The results of the 1963–1989 cohort (453 cases) analysis were compared with the 1990–2014 cohort (1,184 cases) study results. We found statistically significant differences in sex, site, histologic subtype, T classification, local and regional recurrence rate, and radiotherapy rate ($P < .05$), while there was no

Table 1. CLINICOPATHOLOGICAL CHARACTERISTICS OF THE STUDY COHORT (N = 1,637) AND CORRELATION ANALYSIS OF VARIABLES BETWEEN 2 GROUPS

Characteristics	Total (%)	1963–1989	1990–2014	*P* Value
Age (yr, mean ± SD)	46 ± 16	45 ± 15	47 ± 16	.159
Sex				<.001
Male	789 (48.2)	250 (55.2)	539 (45.5)	
Female	848 (51.8)	203 (44.8)	645 (54.5)	
Site				<.001
Parotid gland	578 (35.3)	197 (43.5)	381 (32.2)	
Submandibular gland	166 (10.1)	50 (11)	116 (9.8)	
Sublingual gland	141 (8.6)	27 (6.0)	114 (9.6)	
Palate	413 (25.2)	95 (21.0)	318 (26.9)	
Retromolar region	88 (5.4)	18 (4.0)	70 (7.6)	
Buccal mucosa	86 (5.3)	21 (4.6)	65 (5.5)	
Tongue	81 (4.9)	20 (4.4)	61 (5.2)	
Lip	24 (1.5)	9 (2.0)	15 (1.3)	
Maxillary sinus	45 (2.7)	15 (3.3)	30 (2.5)	
Others*	15 (0.9)	1 (0.2)	14 (1.2)	
Histologic subtype				<.001
Mucoepidermoid carcinoma	474 (29.0)	130 (28.7)	344 (29.1)	
Adenoid cystic carcinoma	561 (34.3)	143 (12.1)	418 (35.3)	
Carcinoma, eg, pleomorphic adenoma	135 (8.2)	58 (12.8)	77 (6.5)	
Adenocarcinoma, NOS	178 (10.9)	84 (18.5)	94 (7.9)	
Acinic cell carcinoma	79 (4.8)	9 (2.0)	70 (5.9)	
Myoepithelial carcinoma	43 (2.6)	1 (0.2)	42 (3.5)	
Polymorphous adenocarcinoma	21 (1.3)	0 (0)	21 (1.8)	
Basal cell adenocarcinoma	20 (1.2)	1 (0.2)	19 (1.6)	
Salivary duct carcinoma	27 (1.6)	9 (2.0)	18 (1.5)	
Squamous cell carcinoma	23 (1.4)	10 (2.2)	13 (1.1)	
Lymphoepithelial carcinoma	9 (0.5)	1 (0.2)	8 (0.7)	
Epithelial-myoepithelial carcinoma	14 (0.9)	1 (0.2)	13 (1.1)	
Oncocytic adenocarcinoma	17 (1.0)	1 (0.2)	16 (1.4)	
Clear cell carcinoma	17 (1.0)	2 (0.4)	15 (1.3)	
Others†	19 (1.2)	3 (0.7)	16 (1.4)	
T classification				<.001
T1–T2	1,093 (66.8)	282 (62.3)	811 (68.5)	
T3–T4	544 (33.2)	171 (37.7)	373 (31.5)	
N classification				.467
N0	1,495 (91.3)	410 (90.5)	1,085 (91.6)	
N+	142 (8.7)	43 (9.5)	99 (8.4)	
M classification				.864
M0	1,614 (98.6)	447 (98.7)	1,167 (98.6)	
M+	23 (1.4)	6 (1.3)	17 (1.4)	
Local recurrence				<.001
Yes	606 (37.0)	219 (48.3)	387 (32.7)	
No	1,031 (63.0)	234 (51.7)	797 (67.3)	
Regional recurrence				.005
Yes	200 (12.2)	72 (15.9)	128 (10.8)	
No	1,437 (87.8)	381 (84.1)	1,056 (89.2)	
Distant metastasis				.150
Yes	231 (14.1)	73 (16.1)	158 (13.3)	
No	1,406 (85.9)	380 (83.9)	1,026 (86.7)	
Radiotherapy				<.001
Yes	821 (50.2)	142 (31.3)	679 (57.3)	
No	816 (49.8)	311 (68.7)	505 (42.7)	

Table 1. Cont'd

Characteristics	Total (%)	1963–1989	1990–2014	*P* Value
Chemotherapy				.270
Yes	122 (7.5)	39 (8.6)	83 (7.0)	
No	1,515 (92.5)	414 (91.4)	1,101 (93.0)	

Abbreviation: NOS, not otherwise specified; SD, standard deviation.
* Mandible, temporal fossa, and pharyngeal.
† Sebaceous adenocarcinoma, carcinosarcoma, poorly differentiated carcinoma, sialoblastoma, and carcinomas of unclear malignant potential.

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statistically significant difference in age, N and M classification, DM rate, and chemotherapy (Table 1). Furthermore, the 5-, 10-, and 15-year survival rate of the 1963–1989 cohort was 76.4%, 62.7%, and 53.8%, respectively, while the 5-, 10-, and 15-year survival rate of the 1990–2014 cohort was 89.3%, 84.2%, and 71.3%, respectively (Fig 4). The OS rate of the 2 cohorts showed statistically significant differences ($P < .001$) (Table 6).

Discussion

Based on a large sample size of patients that covered nearly all localizations of SGCs, the present retrospective study analyzed the prognosis of patients with this carcinoma and identified the clinicopathological factors that are significantly associated with prognosis. Very few studies have conducted such a multivariable analysis on a large scale and with long-term follow-up data from a single center. Despite its retrospective nature, this study reports important clinical and pathological information along with highly detailed long-term follow-up data. Importantly, it follows up a previous study that was conducted at our center.[11] We believe that the study findings can be used as a reference for clinical decision-making in cases of salivary gland malignancy. The findings reveal the changes in the clinical features of SGCs and their prognosis.

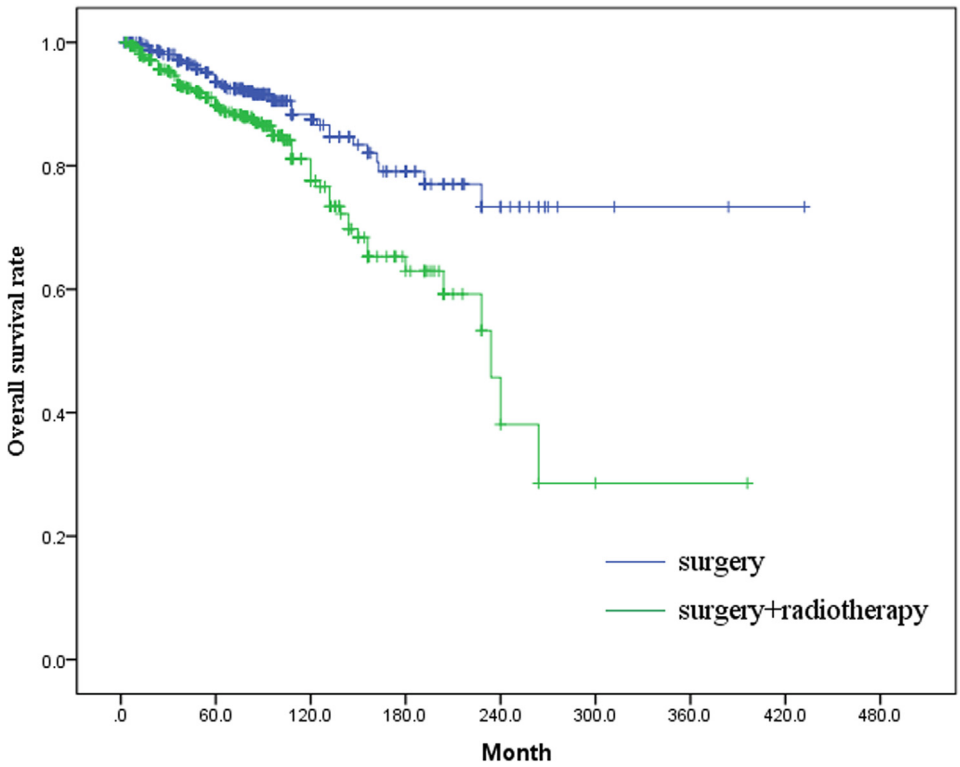

FIGURE 1. Overall survival rate of T1- and T2-stage patients, stratified by surgery only and surgery combined with postoperative radiotherapy.

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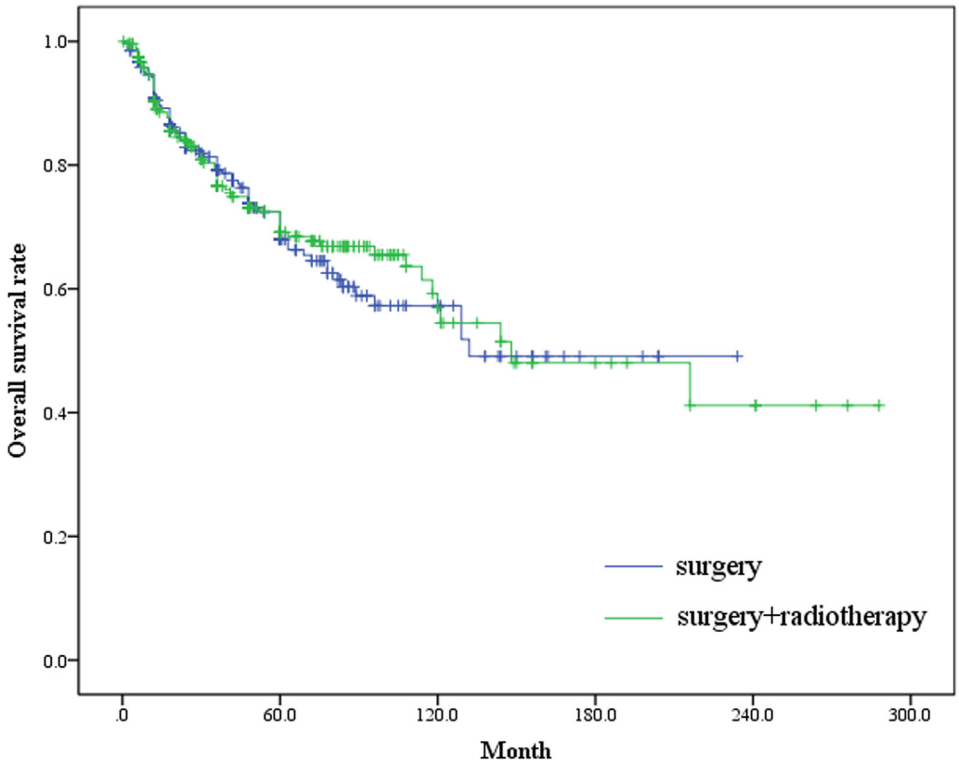

FIGURE 2. Overall survival rate of T3- and T4-stage patients, stratified by surgery only and surgery combined postoperative radiotherapy.

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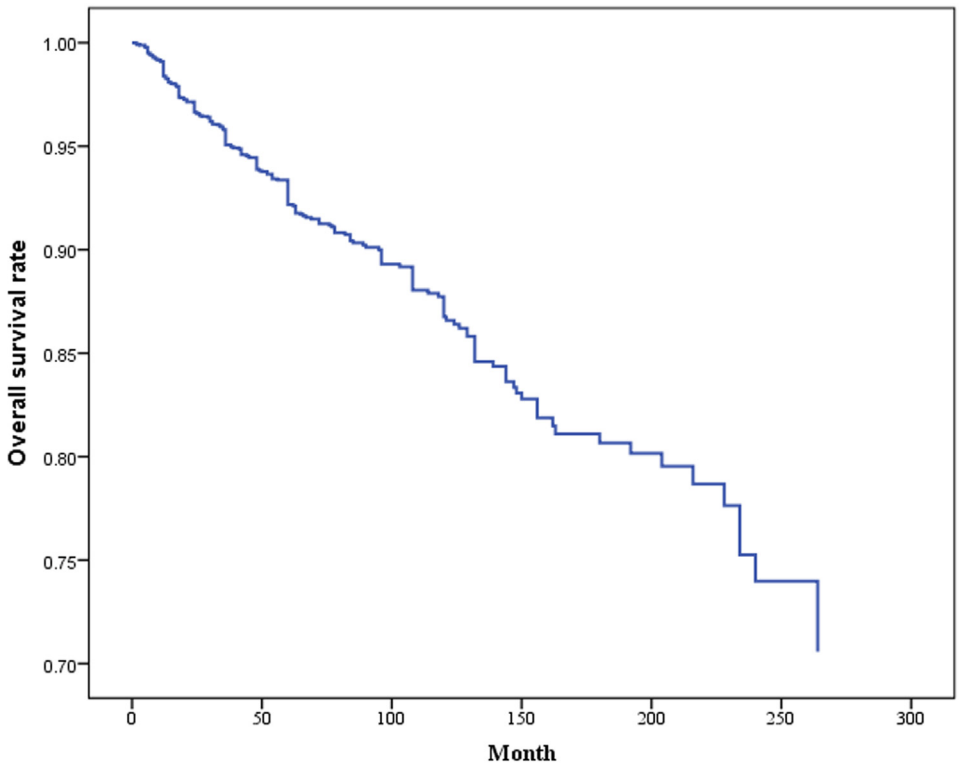

FIGURE 3. Overall survival rate of salivary gland carcinoma.

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Table 2. BIVARIATE ANALYSES BETWEEN THE COVARIATES AND OVERALL SURVIVAL RATE OF PATIENTS FROM 1963 TO 2014

	Median Survival, mo (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age (yr)		<.001		<.001
≤60	-		Reference	
>60	156.00 (119.70-192.30)		2.11 (1.62-2.75)	
Sex		<.001		<.001
Male	228.00 (199.00-257.00)		Reference	
Female	-		0.63 (0.50-0.80)	
Primary site		.260		.262
Major gland	-		Reference	
Minor gland	264.00 (207.15-320.85)		0.87 (0.69-1.11)	
Pathologic type		<.001		<.001
MEC	-		Reference	
ACC	163.00 (116.43-209.58)		3.25 (2.20-4.81)	
Others*	-		2.90 (1.95-4.32)	
T classification		<.001		<.001
T1–T2	-		Reference	
T3–T4	144.00 (86.98-201.02)		3.47 (2.73-4.40)	
N classification		<.001		<.001
N0	-		Reference	
N+	60.00 (31.18-88.83)		5.56 (4.17-7.42)	
M classification		<.001		<.001
M0	-		Reference	
M+	36.00 (14.95-57.05)		7.55 (3.97-14.35)	
Local recurrence		<.001		<.001
No	-		Reference	
Yes	156.00 (113.30-198.70)		4.00 (3.06-5.22)	
Regional recurrence		<.001		<.001
No	-		Reference	
Yes	76.00 (37.56-114.11)		3.80 (2.93-4.92)	
Distant metastasis		<.001		<.001
No	-		Reference	
Yes	108.46 (87.50-128.50)		4.48 (3.54-5.68)	
Radiotherapy		.020		.021
No	-		Reference	
Yes	228.00 (195.64-260.36)		1.32 (1.04-1.68)	
Chemotherapy		<.001		<.001
No	-		Reference	
Yes	132.00 (93.50-170.51)		2.46 (1.80-3.37)	

Abbreviations: ACC, adenoid cystic carcinoma; CI, confidence interval; HR, hazard ratio; MEC, mucoepidermoid carcinoma.
* Other pathological types of salivary gland malignancy.

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Table 3. BIVARIATE ANALYSIS BETWEEN TIME AND OVERALL SURVIVAL RATE

Characteristic	Median Survival, mo (95% CI)	*P* Value	HR (95% CI)	*P* Value
Time		<.001		<.001
1963-1989	216.00 (153.06-278.94)		Reference	
1990-2014	240.00 (216.36-263.64)		0.42 (0.33-0.54)	

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

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Table 4. MULTIVARIATE COX MODEL OF THE PRIMARY PREDICTOR AND TIME ADJUSTED AS INDICATED BASED ON THE RESULTS OF TABLES 1 AND 3

Characteristic	Number	HR	95% CI	*P* Value
Year				
1963-1989	453	Reference		
1990-2014	1,184	0.40	0.31-0.52	<.001
Age (yr)				
≤60	1,295	Reference		
>60	342	1.97	1.50-2.60	<.001
Sex				
Male	789	Reference		
Female	848	0.82	0.64-1.10	.127
Pathologic type				
MEC	474	Reference		
ACC	561	1.56	1.02-2.37	.039
Others*	602	1.70	1.13-2.56	.011
T classification				
T1–T2	1,093	Reference		
T3–T4	544	2.21	1.71-2.86	<.001
N classification				
N0	1,495	Reference		
N+	142	3.03	2.03-4.51	<.001
M classification				
M0	1,614	Reference		
M+	23	1.27	0.64-2.52	.492
Local recurrence				
No	1,031	Reference		
Yes	606	2.72	2.06-3.60	<.001
Regional recurrence				
No	200	Reference		
Yes	1,437	1.51	1.07-2.13	.019
Distant metastasis				
No	1,406	Reference		
Yes	231	2.97	2.28-3.88	<.001
Radiotherapy				
No	816	Reference		
Yes	821	1.04	0.80-1.35	.771
Chemotherapy				
No	1,515	Reference		
Yes	122	1.11	0.80-1.54	.546

Abbreviations: ACC, adenoid cystic carcinoma; CI, confidence interval; HR, hazard ratio; MEC, mucoepidermoid carcinoma.

* Other pathological types of salivary gland malignancy.

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The 5-, 10-, and 15-year survival rates of the 1,637 patients were 93.1%, 87.2%, and 79.3%, respectively.

To understand the changes in prognosis, we compared the 1963–1989 and 1990–2014 cohorts. Over 3 decades, the proportion of patients at early stage had significantly increased. Furthermore, the proportion of patients receiving postoperative radiotherapy increased from 31.3% to 57.3%. The local and regional recurrence rates had decreased, but the DM rates remained unchanged.

With regard to the anatomic location and pathological subtypes, it has been reported that tumors of the major salivary glands are more common than those of the minor salivary glands.[14] The present findings showed that the incidence of major SGCs was slightly higher than that of minor SGCs. In addition, the parotid gland (with a reported incidence rate of 82.2%) was the most common site in major salivary glands, while in the minor salivary glands, the palate is the most common site (with an incidence rate of 51.4%).[15] The incidence rate of parotid SGC (578/885, 65.3%) in our study was lower than that published in the literature, while the incidence rate of palate SGC (413/752, 54.9%) was similar to that reported in the literature. With regard to the distribution of pathological subtypes, MEC and ACC were the 2 most common pathological types of salivary gland malignant tumors.[15-17] This was in line with our study results, as ACC and MEC accounted for 63.2% (1,035/1,637) of all the pathological types (ACC = 34.3%, MEC = 29%).

In terms of recurrence outcome, the overall recurrence rate (including local and regional recurrence) in the present study was 41.7%. The recurrence interval was 15 days to 348 months. In comparison, the overall recurrence rate was determined as 40.2% in the previous study conducted at our center.[11] ACC is known as a relentlessly growing tumor that is characterized by multiple local recurrences and perineural invasion. According to the literature, the ACC recurrence rate in Australia was 54%,[18] while a United Kingdom patient series reported a recurrence rate of 100% over a 30-year follow-up period.[19] The recurrence rate of ACC in the present study was 48.1% (270/561); this is mostly consistent with the findings of the Australian study.[18] Furthermore, the present findings show that ACC and MEC were prone to recurrence and accounted for 58.8% of all recurrences, with ACC comprising 42.0% of the recurrences.

The cervical lymph node metastasis rate in the present cohort was 8.7% (142/1,637). In comparison, the UK series mentioned earlier reported a cervical metastasis rate of 11%,[19] while Yu and Ma's team at our center reported a slightly higher cervical metastasis rate of 15.3%.[11] Over the follow-up period, cervical metastasis was reported in 200 cases, between 15 days and 228 months after surgery in this study. Oncocytic carcinoma, squamous cell carcinoma, and salivary ductal carcinoma were the 3 most common pathologic types associated with cervical metastasis. Thus, based on these findings, we suggest that elective neck dissection be performed for patients with clinical stage N0 carcinomas who have the abovementioned pathological types.

Table 5. KAPLAN-MEIER ANALYSIS OF THE CLINICOPATHOLOGICAL CHARACTERISTICS ASSOCIATED WITH THE CRUDE 5-, 10-, AND 15-YR SURVIVAL RATES (N = 1,637)

	Year of Diagnosis	5-Yr OS (%)	10-Yr OS (%)	15-Yr OS (%)	Median Survival, Number of mo (95% CI)	*P* Value (Log-Rank)
Age (yr)	1963–2014					<.001
≤60		87.5	77.9	67.9	-	
>60		73.9	66.8	44.9	156.0 (119.7-192.3)	
Sex	1963–2014					<.001
Male		81.5	71.1	60.1	220.1 (188.0-252.3)	
Female		88.4	79.1	67.3	-	
Primary site	1963–2014					.260
Major gland		82.9	75.5	65.4	-	
Minor gland		87.5	73.6	63.5	264.0 (207.2-320.8)	
Pathologic type	1963–2014					<.001
MEC		92.5	91.0	90.3	-	
ACC		85.4	65.9	49.3	163.0 (116.4-209.6)	
Others*		80.1	75.5	66.5	-	
T classification	1963–2014					<.001
T1–T2		92.2	83.7	71.9	-	
T3–T4		70.6	57.7	48.7	144.4 (87.0-201.0)	
N classification	1963–2014					<.001
N0		88.4	78.2	67.6	-	
N+		50.1	42.1	-	60.0 (31.2-88.8)	
M classification	1963–2014					<.001
M0		85.6	76.1	64.8	-	
M+		21.1	-	-	36 (15.0-57.0)	
Local recurrence	1963–2014					<.001
Yes		73.9	61.0	47.1	156.0 (113.3-198.7)	
No		93.0	87.5	83.7	-	
Regional recurrence	1963–2014					<.001
Yes		63.8	54.7	53.3	76.0 (37.6-114.4)	
No		86.7	77.4	65.1	-	
Distant metastasis	1963–2014					<.001
Yes		64.0	44.1	25.5	108.0 (87.5-128.5)	
No		89.5	82.9	77.1		
Radiotherapy	1963–2014					.021
Yes		83.7	72.2	69.8	228.0 (195.6-260.4)	
No		86.4	78.5	59.1	-	
Chemotherapy	1963–2014					<.001
Yes		67.3	51.7	44.1	132.0 (93.5-170.5)	
No		86.7	77.7	66.5	-	

Abbreviations: ACC, adenoid cystic carcinoma; CI, confidence interval; MEC, mucoepidermoid carcinoma; OS, overall survival.
* Other pathological types of salivary gland malignancy.

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According to the present data on DM, from the time of first visit to the end of follow-up, the DM rate was 14.1% (231/1,637). Twenty-five cases had metastasis at the time of admission. The pathological type that was most prone to metastasis was ACC, which accounted for 64.9% of DM cases. The rate of DM of ACC was 26.7%, which was higher than the DM rates of 15% and 18% reported in the previous literature.[20,21] In the present cohort, the most commonly involved site in DM was the lung, which comprised 81.0% (187/231) of all DM sites. Furthermore, 30 patients had multiple metastases in the lung as well as other locations, such as bone, brain, and liver. The time to DM diagnosis ranged from 1 year prior to visit to 252 months after the surgical procedure. Of the patients who developed DM, 125 (54.1%) patients died of DM, and 2 died of other causes. Our findings show that about half of the patients who developed DM survived. In view of the slow progression of this disease entity and the fact that patients with DM can

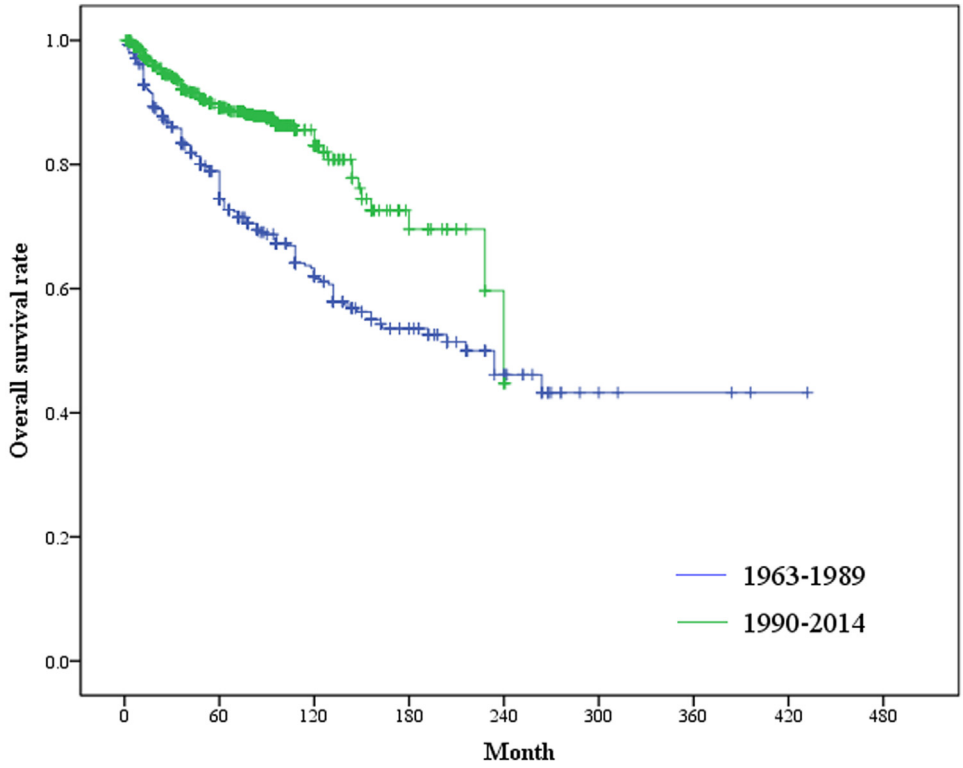

FIGURE 4. Overall survival rate of the 1963–1989 and 1990–2014 cohorts.

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remain asymptomatic for a long period of time, surgeons should employ an active approach in managing the primary lesion.

The National Comprehensive Cancer Network's guidelines for the treatment of salivary gland tumors recommend complete surgical resection with or without adjuvant radiation and/or chemotherapy, according to the surgical margin, pathological type, clinical stage, and other factors.[22] With regard to neck dissection, lymph node dissection or radical radiotherapy should be performed in patients with clinically- or radiologically-positive cervical nodes in a case-by-case manner.[23] It has been reported in a review of 7,342 patients that compared with surgery alone, adjuvant radiotherapy resulted in improved survival in several histologic subgroups, while adjuvant chemoradiotherapy demonstrated no survival advantage.[24] In the present study, for patients with stage T1–T2 tumors, surgery combined with radiotherapy had a worse prognosis than surgery alone. This is probably because most patients who received radiotherapy after surgery had cervical lymph node metastasis or highly malignant tumors. With regard to stage T3–T4 tumors, there was no significant difference in outcomes between surgery and surgery combined with radiotherapy. There is a lack of consensus about the

Table 6. KAPLAN-MEIER ANALYSIS OF SURVIVAL

	5-Yr OS (%)	10-Yr OS (%)	15-Yr OS (%)	Median Survival, Number of mo (95% CI)	*P* Value (Log-Rank)
Year of diagnosis					<.001
1963–1989	76.4	62.7	53.8	216.0 (153.1-278.9)	
1990–2014	89.3	84.2	71.3	240.0 (216.4-263.6)	

Abbreviations: CI, confidence interval; OS, overall survival.

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treatment of DM at present, and systemic therapy is usually recommended for progressive DM. In recent years, targeted therapies for metastatic SGC have shown promising curative effects.[25,26] In recent study, 335 patients survived with carcinoma at the end point of this study. That is, in these 335 patients, the primary tumor had not been removed entirely or DM had occurred. Among them, 233 patients had received radiotherapy, of whom 30 were treated with chemoradiotherapy. Based on these findings, we recommend that adjuvant radiotherapy and chemotherapy be considered in patients with positive surgical margins or distant metastases.

With regard to factors related to survival in SGC patients, our findings show that time (years), age, pathological type, T and N classification, local and regional recurrences, and DM are significant prognostic factors for survival, while sex, anatomical location, radiotherapy, and chemotherapy are not independent significant factors. These results are nearly consistent with previous research findings.[27-29]

The 5- and 10-year survival rates were reported as 69.6% and 55.8%, respectively,[11] while the crude 5- and 10-year survival rates of the 1990–2014 cohort were 89.3% and 84.2%, respectively; these values indicate a significant improvement in survival over the years. With regard to T staging, compared with the data before 1989, the data obtained after 1989 showed relatively early tumor stage, a significantly higher rate of implementation of radiotherapy, and a lower local recurrence rate. That is, patients treated after 1989 had earlier T stage, significantly higher rates of radiotherapy, and lower rates of local recurrence than those treated before 1989. These findings indicate that the nature of the disease and the biological behavior of the tumors have not changed, but its diagnosis and treatment have improved significantly, as indicated by the increase in the cumulative survival rate. This can be attributed to the significant increase in the proportion of patients who consulted the clinic in the early stages (T1–T2), as early detection and early treatment are key factors that affect prognosis. Thus, strengthening the early surveillance of tumors is beneficial for treatment. In addition, over the years, our understanding of SGCs has gradually deepened, and we have formed a more systematic understanding of this disease. The resulting improvement in the quality of treatment may also have contributed to the improved survival rates and decreased local recurrence rates. There has also been immense progress in the skill levels of maxillofacial surgeons and multidisciplinary therapy over the last 3 decades. Finally, increased public awareness about the disease and improved living standards over the last few years may also have contributed to the improved survival rate.

This study has several important limitations. The World Health Organization has updated the Pathology and Genetics Classification of Head and Neck Tumors according to the histologic classification and molecular pathological features of salivary gland tumors, and, among the many changes, a new type of SGC, secretory carcinoma, has been added.[12] The tumors included in this study were reclassified according to this latest classification, and the cases in this cohort covered all types of tumor except secretory carcinomas. We hope to further supplement our database of cases in future clinical work to provide evidence for the clinical diagnosis and treatment of this entity. In addition, the postoperative therapy regimen was not examined in detail. In the future, we will strive to improve the follow-up system to provide more valuable information.

In conclusion, we found a significant improvement in the OS of SGC patients over the last few decades. Early detection and early treatment are the key factors for prognosis. Oncocytic carcinoma, squamous cell carcinoma, and salivary ductal carcinoma showed a propensity for cervical lymph node metastasis; therefore, concurrent neck dissection is necessary for such histologic subtypes. High rates of local and neck recurrence were found at 5 years after surgery, so patients at this postsurgical stage require close follow-up.

References

1. Eveson JW, Cawson RA: Salivary gland tumours. A review of 2410 cases with particular reference to histological types, site, age and sex distribution. J Pathol 146(1):51–58, 1985
2. Fonseca FP, Carvalho Mde V, de Almeida OP, et al: Clinicopathologic analysis of 493 cases of salivary gland tumors in a Southern Brazilian population. Oral Surg Oral Med Oral Pathol Oral Radiol 114(2):230–239, 2012
3. Gatta G, Guzzo M, Locati LD, McGurk M, Prott FJ: Major and minor salivary gland tumours. Crit Rev Oncol Hematol 152: 102959, 2020
4. McHugh JB, Visscher DW, Barnes EL: Update on selected salivary gland neoplasms. Arch Pathol Lab Med 133(11):1763–1774, 2009
5. Carrillo JF, Vázquez R, Ramírez-Ortega MC, Cano A, Ochoa-Carrillo FJ, Oñate-Ocaña LF: Multivariate prediction of the probability of recurrence in patients with carcinoma of the parotid gland. Cancer 109(10):2043–2051, 2007
6. Schwentner I, Obrist P, Thumfart W, Sprinzl G: Distant metastasis of parotid gland tumors. Acta Otolaryngol 126(4):340–345, 2006
7. Bjørndal K, Krogdahl A, Therkildsen MH, et al: Salivary gland carcinoma in Denmark 1990-2005: Outcome and prognostic factors. Results of the Danish head and neck cancer group (DAHANCA). Oral Oncol 48(2):179–185, 2012
8. Terhaard CH, Lubsen H, Van der Tweel I, et al: Salivary gland carcinoma: Independent prognostic factors for locoregional control, distant metastases, and overall survival: Results of the Dutch head and neck oncology cooperative group. Head Neck 26(8):681–693, 2004
9. Gao M, Hao Y, Huang MX, et al: Salivary gland tumours in a northern Chinese population: A 50-year retrospective study of 7190 cases. Int J Oral Maxillofac Surg 46(3):343–349, 2017

10. Gao M, Hao Y, Huang MX, et al: Clinicopathological study of distant metastases of salivary adenoid cystic carcinoma. Int J Oral Maxillofac Surg 42(8):923–928, 2013
11. Yu GY, Ma DQ: Carcinoma of the salivary gland: A clinicopathologic study of 405 cases. Semin Surg Oncol 3(4):240–244, 1987
12. Sloan P, Gale N, Hunter K, et al: Malignant surface epithelial tumours. In: El-Naggar AK, Chan JK, Grandis JR, Takata T, Slootweg PJ, eds. *WHO classification of head and neck tumours*. 4th ed. Lyon, IARC; 2017, pp 108–131
13. William M, Snehal G, John A, Brian O, Jatin P: Staging head and neck cancer. In: Mahul B, ed. *AJCC cancer staging manual*. 8th ed. New York, Springer; 2017, pp 55–65
14. Spiro RH: Salivary neoplasms: Overview of a 35-year experience with 2,807 patients. Head Neck Surg 8(3):177–184, 1986
15. Jones AV, Craig GT, Speight PM, Franklin CD: The range and demographics of salivary gland tumours diagnosed in a UK population. Oral Oncol 44(4):407–417, 2008
16. Lewis AG, Tong T, Maghami E: Diagnosis and management of malignant salivary gland tumors of the parotid gland. Otolaryngol Clin North Am 49(2):343–380, 2016
17. Badlani J, Gupta R, Balasubramanian D, Smith J, Luk P, Clark J: Primary salivary gland malignancies: A review of clinicopathological evolution, molecular mechanisms and management. ANZ J Surg 88(3):152–157, 2018
18. DeAngelis AF, Tsui A, Wiesenfeld D, Chandu A: Outcomes of patients with adenoid cystic carcinoma of the minor salivary glands. Int J Oral Maxillofac Surg 40(7):710–714, 2011
19. Jones AS, Hamilton JW, Rowley H, Husband D, Helliwell TR: Adenoid cystic carcinoma of the head and neck. Clin Otolaryngol Allied Sci 22(5):434–443, 1997
20. Mimica X, McGill M, Hay A, et al: Distant metastasis of salivary gland cancer: Incidence, management, and outcomes. Cancer 126(10):2153–2162, 2020
21. Ali S, Bryant R, Palmer FL, et al: Distant metastases in patients with carcinoma of the major salivary glands. Ann Surg Oncol 22(12):4014–4019, 2015
22. Pfister DG, Spencer S, Adelstein D, et al: Head and neck Cancers, version 2.2020, NCCN clinical Practice guidelines in oncology. J Natl Compr Canc Netw 18(7):873–898, 2020
23. Green B, Rahimi S, Brennan PA: Current management of the neck in salivary gland carcinomas. J Oral Pathol Med 46(3): 161–166, 2017
24. Ferrell JK, Mace JC, Clayburgh D: Contemporary treatment patterns and outcomes of salivary gland carcinoma: A National cancer database review. Eur Arch Otorhinolaryngol 276(4):1135–1146, 2019
25. Tchekmedyian V, Sherman EJ, Dunn L, et al: Phase II study of Lenvatinib in patients with progressive, recurrent or metastatic adenoid cystic carcinoma. J Clin Oncol 37(18):1529–1537, 2019
26. Fushimi C, Tada Y, Takahashi H, et al: A prospective phase II study of combined androgen blockade in patients with androgen receptor-positive metastatic or locally advanced unresectable salivary gland carcinoma. Ann Oncol 29(4):979–984, 2018
27. Spiro RH, Huvos AG: Stage means more than grade in adenoid cystic carcinoma. Am J Surg 164(6):623–628, 1992
28. Bhattacharyya N, Fried MP: Nodal metastasis in major salivary gland cancer: Predictive factors and effects on survival. Arch Otolaryngol Head Neck Surg 128(8):904–908, 2002
29. Hocwald E, Korkmaz H, Yoo GH, et al: Prognostic factors in major salivary gland cancer. Laryngoscope 111(8):1434–1439, 2001