Head and Neck Pathology (2023) 17:739–750
https://doi.org/10.1007/s12105-023-01551-z

ORIGINAL PAPER

Intraoral Minor Salivary Gland Tumors: A Retrospective, Clinicopathologic, Single-Center Study of 432 Cases in Japan and a Comparison with Epidemiological Data

Katsutoshi Kokubun[1] · Takatoshi Chujo[1] · Kei Yamamoto[1] · Yoshihiko Akashi[1] · Kei Nakajima[1] · Masayuki Takano[2] · Akira Katakura[3] · Kenichi Matsuzaka[1]

Received: 6 March 2023 / Accepted: 30 March 2023 / Published online: 19 April 2023
© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2023

Abstract

Background Intraoral minor salivary gland tumors are relatively rare lesions with histological subtypes not commonly found in major salivary glands. This study aimed to retrospectively evaluate the clinicopathologic features of intraoral minor salivary gland tumors from the Tokyo Dental College Hospital, Japan, and compare them with findings from other epidemiological studies.

Methods We conducted a retrospective clinicopathologic evaluation of 432 cases of intraoral minor salivary gland tumors [161 male (37.3%) and 271 female (62.7%) patients; mean age: 52.5 and 48.6 years for males and females, respectively; age at diagnosis: 7–87 (mean: 50.1) years] from the Tokyo Dental College Hospital between 1975 and 2022, including 283 benign tumors (65.5%) and 149 malignant tumors (34.5%).

Results The most common benign tumor was pleomorphic adenoma ($n=239$), whereas mucoepidermoid carcinoma was the most common malignant tumor ($n=74$). The mean age of patients with benign and malignant tumors was 48.4 and 53.2 years, respectively, with patients with malignant tumors being significantly older ($P=0.0042$). The mean age of patients with malignant tumors was significantly higher in males (56.7 years) than in females (50.9 years) ($P=0.0376$), although the mean age of patients with benign tumors did not differ by sex. Tumors were commonly located in the palate [250 cases (57.9%)]. Benign tumors were more frequent in the palate, upper lip, and buccal mucosa, whereas malignant tumors were more frequent in the palate, floor of the mouth, buccal mucosa, and retromolar area.

Conclusions Understanding the features of intraoral minor salivary gland tumors is useful for diagnosis. Our study provides important epidemiological data (patient differences in age at occurrence, sex, and site of origin) that will inform clinicians and researchers.

Keywords Epidemiology · Minor salivary gland tumors · Mucoepidermoid carcinoma · Oral pathology · Pleomorphic adenoma

Introduction

Salivary gland tumors are rare, comprising 5.0% of all head and neck cancers and 0.5% of all systemic malignancies, with an annual incidence of 0.5–2.0 patients per 100,000 [1, 2]. These tumors are classified into 15 benign and 21 malignant types according to the World Health Organization (WHO) International Histological Classification of Tumors series, which was recently revised in 2022 [3]. Despite their infrequent occurrence, there are a relatively large number of histologic subtypes within these classifications, with various subtypes reported with different malignancy grades even within the same tumor type. This diversity of histology can

✉ Katsutoshi Kokubun
kkokubun@tdc.ac.jp

[1] Department of Pathology, Tokyo Dental College, 2-9-18 Kandamisaki-Cho, Chiyoda-Ku, Tokyo 101-0061, Japan

[2] Department of Oral and Maxillofacial Surgery, Tokyo Dental College, Tokyo, Japan

[3] Department of Oral Pathobiological Science and Surgery, Tokyo Dental College, Tokyo, Japan

make salivary gland tumors difficult to diagnose. The salivary glands are divided into major and minor glands, and tumors arising in the intraoral minor salivary glands make up 32% of all salivary gland tumors [4]. These tumors are regularly encountered in oral pathology work, so accurately diagnosing and treating them is important. Therefore, determining the clinicostatistical frequency of intraoral minor salivary gland tumors is crucial.

The incidence of intraoral minor salivary gland tumors varies among populations, as demonstrated in studies conducted in Asia [5–12], Europe [13–15], North America [16–19], South America [20–26], and Africa [27, 28]. Regional differences in the occurrence of salivary gland tumors may reflect genetic and cultural variations among people from different geographic regions.

According to the 2022 WHO classification system, we aimed to determine the frequency and types of intraoral minor salivary gland tumors by evaluating data on tumors examined at the Tokyo Dental College Hospital, Japan. Additionally, we compared our evaluation results with findings reported in previous studies.

Materials and Methods

Based on clinical record data, including the age and sex of patients and anatomical location of tumors, 432 cases of intraoral minor salivary gland tumors examined at the Tokyo Dental College Hospital between 1975 and 2022 were reviewed. Diagnosis was confirmed via histologic and immunohistochemical descriptions from histopathology reports, and tumors were reclassified based on criteria suggested by the 2022 WHO classification system. When dealing with old case reports that were pathologically diagnosed under the previous classification system, the pathologist performed reclassification on slides stained with hematoxylin and eosin. As required, special stains (mucicarmine and periodic acid-Schiff), immunohistochemical stains and fluorescence in situ hybridization were used to aid in the final diagnosis. The diagnostic criteria for defining salivary gland myoepithelioma were ≤ 1 duct per medium power field or < 5% ducts in the whole section [29]. To ensure accurate diagnoses, the independent opinions of two experienced oral pathologists were compared, and in cases of doubt, a third expert oral pathologist was consulted to obtain a diagnosis by consensus.

Based on the previous literature, the present study included demographic features, anatomic locations of tumors, and histopathology as categories of variables. The patient demographic features included age and sex. The anatomic location of tumors was categorized as tumors located in the lips, sinuses, intrabony locations, and intraoral regions, including the palate, buccal mucosa, floor of the mouth, retromolar area, alveolar ridge, tongue, and vestibule.

We conducted a literature search of articles published in PubMed from 1995 to 2022, focusing specifically on minor salivary gland tumors. Each retrieved article was evaluated for relevance by reading the titles, abstracts, and full texts to identify eligible articles. Reports with fewer than 50 cases per study were excluded due to small sample size.

Data was recorded in Microsoft Excel (Microsoft Inc., Redmond, WA, USA) and analyzed using Prism version 9 (GraphPad Software, CA, USA). Categorical variables were analyzed using standard statistical methods such as count, frequency table, and proportion analyses. Age, a continuous variable, was analyzed using a t test and one-way ANOVA. A Chi squared test was used to analyze the association between subtypes and other variables. P values of < 0.05 were considered statistically significant.

Results

Frequency of Tumors

Of 432 cases, 283 (65.5%) and 149 (34.5%) patients had benign and malignant tumors, respectively (Table 1). The incidence of malignant salivary gland tumors was compared during 1980, 1990, 2000, and 2010s was 36%, 38%, 37%, and 27%, respectively. The majority of the histological subtypes were pleomorphic adenoma ($n = 239$, 55.3%), mucoepidermoid carcinoma ($n = 74$, 17.1%), and adenoid cystic carcinoma ($n = 52$, 12.0%). Pleomorphic adenoma was the most common benign tumor (84.5%), followed by salivary gland myoepithelioma (8.1%) and cystadenoma of the salivary gland (3.5%). Mucoepidermoid carcinoma was the most common malignancy (49.7%), followed by adenoid cystic carcinoma (34.9%), carcinoma ex pleomorphic adenoma (4.7%), and acinic cell carcinoma (4.0%).

Frequency of Tumors According to Sex

Table 2 shows the distribution of tumors by sex. Among all patients, 161 (37.3%) were male and 271 (62.7%) were female (ratio: approximately 1.0:1.7). Males and females had benign tumors in 101 (35.7%) and 182 (64.3%) cases, respectively, and malignant tumors in 60 (40.3%) and 89 (59.7%) cases, respectively. The incidence of malignant tumors was higher in males than in females, with 60 of 161 (37.3%) and 89 of 271 (32.8%) cases, respectively. Regarding histological subtypes, pleomorphic adenomas accounted for 152 (63.6%) of all benign tumors, but many other benign tumors were more common in females. Mucoepidermoid carcinoma occurred significantly more frequently in females, with a male-to-female ratio of 1.0:2.1. However, the male-to-female

Table 1 Frequency of intraoral minor salivary gland tumors according to the recent WHO classification

Histological subtype	Number of cases	% of group	% of total
Benign tumors			
Pleomorphic adenoma	239	84.5	55.3
Basal cell adenoma	4	1.4	0.9
Oncocytoma	1	0.4	0.2
Salivary gland myoepithelioma	23	8.1	5.3
Cystadenoma of salivary gland	10	3.5	2.3
Ductal papilloma	3	1.1	0.7
Sialadenoma papilliferum	3	1.1	0.7
Subtotal	283	100.0	65.5
Malignant tumors			
Mucoepidermoid carcinoma	74	49.7	17.1
Adenoid cystic carcinoma	52	34.9	12.0
Acinic cell carcinoma	6	4.0	1.4
Secretory carcinoma	1	0.7	0.2
Polymorphous adenocarcinoma	3	2.0	0.7
Salivary duct carcinoma	1	0.7	0.2
Myoepithelial carcinoma	2	1.3	0.5
Epithelial-myoepithelial carcinoma	3	2.0	0.7
Carcinoma ex pleomorphic adenoma	7	4.7	1.6
Subtotal	149	100.0	34.5
Total (benign and malignant)	432	100.0	100.0

Table 2 Frequency of intraoral minor salivary gland tumors according to sex

Histological subtype	Male	Female	M:F ratio
Benign tumors			
Pleomorphic adenoma	87	152	1:1.7
Basal cell adenoma	1	3	1:3
Oncocytoma	0	1	–
Salivary gland myoepithelioma	8	15	1:9
Cystadenoma of salivary gland	3	7	1:2.3
Ductal papilloma	0	3	–
Sialadenoma papilliferum	2	1	2:1
Subtotal	101	182	1:1.8
Malignant tumors			
Mucoepidermoid carcinoma	24	50	1:2.1
Adenoid cystic carcinoma	30	22	1.4:1
Acinic cell carcinoma	0	6	–
Secretory carcinoma	0	1	–
Polymorphous adenocarcinoma	0	3	–
Salivary duct carcinoma	0	1	–
Myoepithelial carcinoma	1	1	1:1
Epithelial-myoepithelial carcinoma	2	1	2:1
Carcinoma ex pleomorphic adenoma	3	4	1:1.3
Subtotal	60	89	1:1.5
Total (benign and malignant)	161	271	1:1.7
Incidence of malignant tumors (%)	37.3	32.8	

ratio for adenoid cystic carcinoma was 1.4:1.0. There were no significant differences in the distribution of the ratio of malignant tumor and histological subtype between the sexes.

Frequency of Tumors According to Age

The mean patient age [± standard deviation] at the time of tumor diagnosis was 50.1 ± 16.8 years (age range: 7–87 years). The majority of cases were diagnosed in patients aged in their 30 s to 60 s, with two peaks in the 40 s and 60 s (Table 3, Fig. 1).

The mean age of benign tumor diagnosis was 48.4 ± 16.7 years (age range: 7–87 years). Pleomorphic adenoma and salivary gland myoepithelioma (benign tumors) were diagnosed at mean ages of 47.4 and 48.3 years, respectively, whereas other tumors were diagnosed at 56.1–63.8 years. Pleomorphic adenoma was the most common histological subtype diagnosed among patients aged in their 30 s to 60 s. The mean age of malignant tumor diagnosis was 53.2 years ± 16.5, which was 4.8 years later than mean benign tumor diagnosis and significantly different ($P = 0.0042$). The mean age at diagnosis varied by histological subtype, ranging from 47.8 years for mucoepidermoid carcinoma to 59.0 years for carcinoma ex pleomorphic adenoma, and including 58.4 years for adenoid cystic carcinoma and 52.0 years for acinic cell carcinoma, with a significant difference observed for mucoepidermoid carcinoma relative to the other subtypes ($P = 0.0027$).

The mean age of male and female patients differed significantly ($P = 0.0206$), with male patients having a higher mean age (52.5 years) than female patients (48.6 years). Among patients with malignant tumors, males had a significantly higher mean age of 56.7 years compared with 50.9 years for females ($P = 0.0376$).

Frequency of Tumors by Anatomical Region

Table 4 and Fig. 2 shows the distribution of tumors according to histological subtype and anatomical site. The most common tumor site was the palate (250 cases, 57.9%), followed by the upper lip (67 cases, 15.5%) and buccal mucosa (36 cases, 8.3%). The most common benign tumor site was the palate (180 cases, 63.6%), followed by the upper lip (59 cases, 20.8%), and buccal mucosa (22 cases, 7.8%). The most common malignant tumor site was the palate (70 cases, 47.0%), followed by the floor of the mouth (16 cases, 10.7%), buccal mucosa (14 cases, 9.4%), and retromolar area (13 cases, 8.7%). In the major tumor type, 159 (66.5%) of all pleomorphic adenomas occurred on the palate, whereas 51

Table 3 Diagnosis age distribution of intraoral minor salivary gland tumors

Histological subtype	Age group (years)									Mean age (years old)		
	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	Male	Female	Total
Benign tumors												
Pleomorphic adenoma	1	8	29	45	45	43	47	19	2	49.4	46.3	47.4
Basal cell adenoma	0	0	0	0	1	1	0	2	0	56.0	66.3	63.8
Oncocytoma	0	0	0	0	0	0	1	0	0	–	64.0	64.0
Salivary gland myoepithelioma	0	1	4	3	3	3	6	2	1	51.5	46.5	48.3
Cystadenoma of salivary gland	0	0	0	2	1	2	4	1	0	54.0	57.0	56.1
Ductal papilloma	0	0	0	0	1	0	1	1	0	–	61.3	61.3
Sialadenoma papilliferum	0	0	0	0	1	0	1	1	0	59.0	64.0	60.7
Subtotal	1	9	33	50	52	49	60	26	3	50	47.5	48.4
Malignant tumors												
Mucoepidermoid carcinoma	0	4	9	10	17	14	13	5	2	53.0	45.3	47.8
Adenoid cystic carcinoma	0	0	0	6	9	10	17	7	3	58.7	58.0	58.4
Acinic cell carcinoma	0	0	1	0	1	1	3	0	0	–	52.0	52.0
Secretory carcinoma	0	0	0	0	0	0	1	0	0	–	69.0	69.0
Polymorphous adenocarcinoma	0	0	0	0	1	1	0	1	0	–	57.0	57.0
Salivary duct carcinoma	0	0	0	0	0	0	1	0	0	–	66.0	66.0
Myoepithelial carcinom	0	0	0	0	0	0	2	0	0	69.0	63.0	66.0
Epithelial-myoepithelial carcinoma	0	0	0	0	1	0	0	2	0	60.0	76.0	65.3
Carcinoma ex pleomorphic adenoma	0	0	0	1	1	0	4	1	0	59.0	59.0	59.0
Subtotal	0	4	10	17	30	26	41	16	5	56.7	50.9	53.2
Total (begin and malignant)	1	13	43	67	82	75	101	42	8	52.2	48.6	50.1

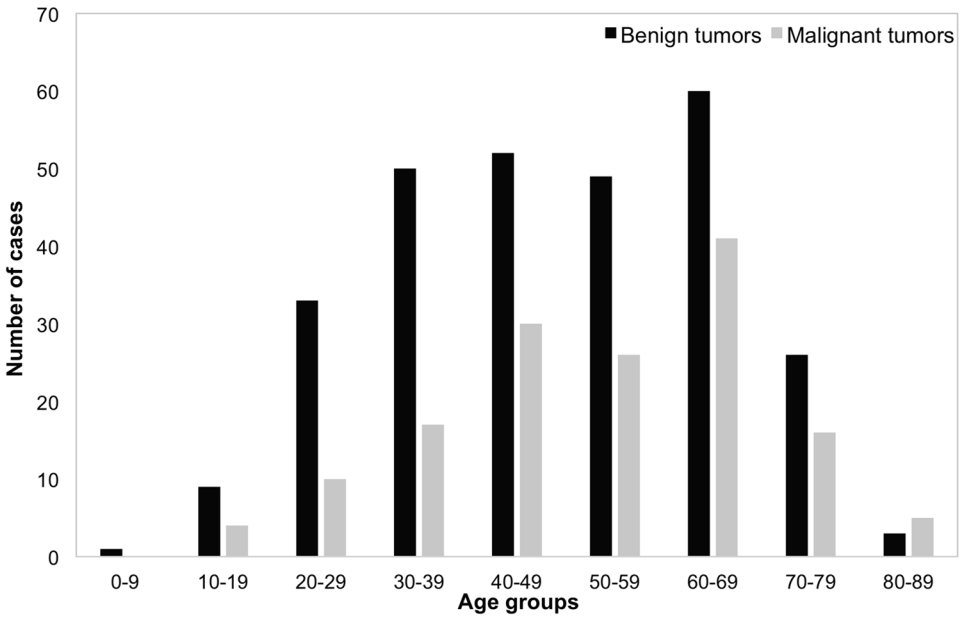

Fig. 1 Distribution of 432 intraoral minor salivary gland tumors based on age group

cases (21.3%) involved tumors on the upper lip. Mucoepidermoid carcinoma also occurred most frequently on the palate (40 cases, 54.1%), followed by the buccal mucosa and retromolar area (9 cases each, 12.2%). Adenoid cystic carcinoma most frequently occurred on the palate (18 cases, 34.6%), followed by the floor of the mouth (12 cases, 23.1%). The anatomical distribution of histological subtypes differed significantly among all cases ($P < 0.0001$).

The incidence of benign tumors was highest on the upper lip (88.1%), followed by the palate (72.0%) and the buccal

Table 4 Anatomical distribution of intraoral minor salivary gland tumors. Count and percentage (in parentheses) data are shown

Histological subtype	Palate		Upper lip		Buccal mucosa		Floor of the mouth		Retromolar area		Lower lip		Alveolar ridge		Intrabony location		Tongue		Sinuses		Vestibule		Total	
Benign tumors																								
Pleomorphic adenoma	159	(66.5)	51	(21.3)	18	(7.5)	2	(0.8)	3	(1.3)	4	(1.7)	1	(0.4)	0		0		0		1	(0.4)	239	(100.0)
Basal cell adenoma	1	(25.0)	1	(25.0)	1	(25.0)	0	(0.0)	0		1	(25.0)	0		0		0		0		0		4	(100.0)
Oncocytoma	0		0		0		1	(100.0)	0		0		0		0		0		0		0		1	(100.0)
Salivary gland myoepithelioma	17	(73.9)	4	(17.4)	1	(4.3)	0	(0.0)	0		0		0		0		0		0		1	(4.3)	23	(100.0)
Cystadenoma of salivary gland	1	(10.0)	2	(20.0)	1	(10.0)	2	(20.0)	0		2	(20.0)	0		0		2	(20.0)	0		0		10	(100.0)
Ductal papilloma	1	(33.3)	0	(0.0)	1	(33.3)	1	(33.3)	0		0		0		0		0		0		0		3	(100.0)
Sialadenoma papilliferum	1	(33.3)	1	(33.3)	0		0	(0.0)	1	(33.3)	0		0		0		0		0		0		3	(100.0)
Subtotal	180	(63.6)	59	(20.8)	22	(7.8)	6	(2.1)	4	(1.4)	7	(2.5)	1	(0.4)	0		2	(0.7)	0		2	(0.7)	283	(100.0)
Malignant tumors																								
Mucoepidermoid carcinoma	40	(54.1)	2	(2.7)	9	(12.2)	3	(4.1)	9	(12.2)	3	(4.1)	3	(4.1)	3	(4.1)	0	(0.0)	2	(2.7)	0		74	(100.0)
Adenoid cystic carcinoma	18	(34.6)	2	(3.8)	3	(5.8)	12	(23.1)	3	(5.8)	1	(1.9)	3	(5.8)	4	(7.7)	4	(7.7)	2	(3.8)	0		52	(100.0)
Acinic cell carcinoma	1	(16.7)	2	(33.3)	0		1	(16.7)	1	(16.7)	1	(16.7)	0		0		0		0		0		6	(100.0)
Secretory carcinoma	1	(100.0)	0		0		0	(0.0)	0		0		0		0		0		0		0		1	(100.0)
Polymorphous adenocarcinoma	3	(100.0)	0		0		0	(0.0)	0		0		0		0		0		0		0		3	(100.0)
Salivary duct carcinoma	0		0		1	(100.0)	0	(0.0)	0		0		0		0		0		0		0		1	(100.0)
Myoepithelial carcinoma	2	(100.0)	0		0		0	(0.0)	0		0		0		0		0		0		0		2	(100.0)
Epithelial-myoepithelial carcinoma	1	(33.3)	0		0		0	(0.0)	0		1	(33.3)	1	(33.3)	0		0		0		0		3	(100.0)
Carcinoma ex pleomorphic adenoma	4	(57.1)	2	(28.6)	1	(14.3)	0	(0.0)	0		0		0		0		0		0		0		7	(100.0)
Subtotal	70	(47.0)	8	(5.4)	14	(9.4)	16	(10.7)	13	(8.7)	6	(4.0)	7	(4.7)	7	(4.7)	4	(2.7)	4	(2.7)	0		149	(100.0)
Total (benign and malignant)	250	(57.9)	67	(15.5)	36	(8.3)	22	(5.1)	17	(3.9)	13	(3.0)	8	(1.9)	7	(1.6)	6	(1.4)	4	(0.9)	2	(0.5)	432	(100.0)

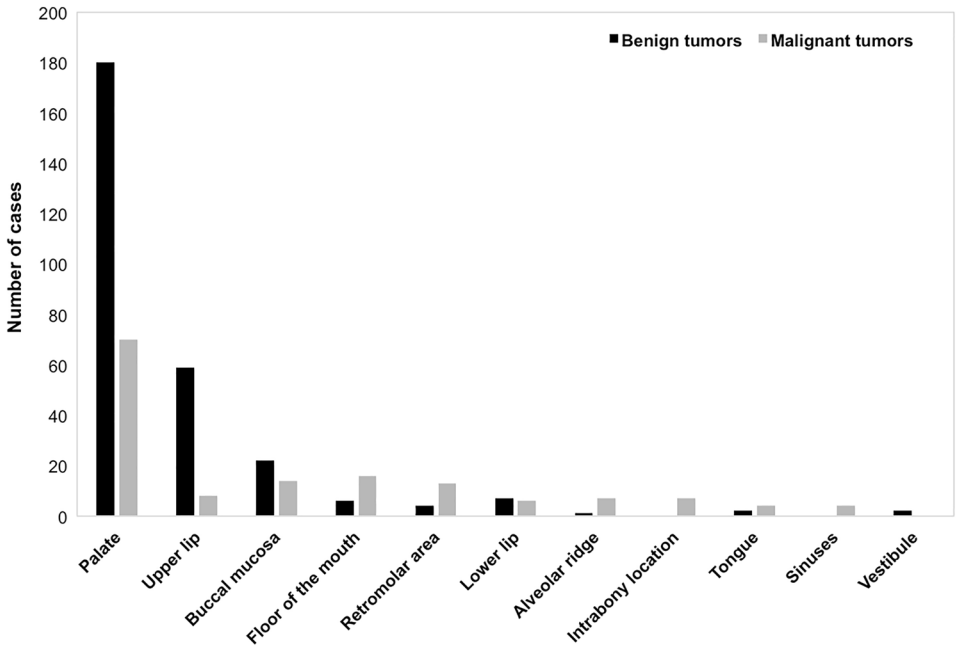

Fig. 2 Distribution of 432 intraoral minor salivary gland tumors based on their anatomical location

Table 5 Anatomical distribution of benign and malignant intraoral minor salivary gland tumors

	Benign tumors		Malignant tumors		
Anatomic site	Number	Percent	Number	Percent	Total
Palate	180	72.0	70	28.0	250
Upper lip	59	88.1	8	11.9	67
Buccal mucosa	22	61.1	14	38.9	36
Floor of the mouth	6	27.3	16	72.7	22
Retromolar area	4	23.5	13	76.5	17
Lower lip	7	53.8	6	46.2	13
Alveolar ridge	1	12.5	7	87.5	8
Intrabony location	0	0.0	7	100.0	7
Tongue	2	33.3	4	66.7	6
Sinuses	0	0.0	4	100.0	4
Vestibule	2	100.0	0	0.0	2

mucosa (61.1%) (Table 5). The incidence of malignant tumors was highest in intrabony locations (100%), sinuses (100%), the alveolar ridge (87.5%), the retromolar area (76.5%), and the floor of the mouth (72.7%). The anatomical distribution of the ratio of benign and malignant tumor was significantly different among all the cases ($p < 0.0001$).

Discussion

Salivary gland tumors can originate from the major salivary glands, i.e., the parotid, submandibular, and sublingual glands, and numerous intraoral minor salivary glands in the oral cavity. Clinical studies on both major and minor salivary gland tumors have been reported [4, 13, 15, 24, 25, 30], and studies examining only minor salivary gland tumors have been conducted [5–12, 14, 16–23, 26–28]. The present study was conducted at a dental school with patients that mainly presented with oral lesions, so the incidence of parotid gland tumors was lower than that in studies performed at medical schools or cancer centers. Therefore, we focused our clinicopathological study on intraoral minor salivary gland tumors.

The proportion of malignant tumors among intraoral minor salivary gland tumors varies widely across different centers, ranging from 28.9% to 86.7% (Table 6). In Japan, reported rates of malignant tumors range from 32.9% to 38.0% [5, 6], tending to be lower than in many other countries, consistent with the present findings. In contrast, the incidence of malignancy in India tends to be very high, ranging from 74.6% to 86.7% [9, 11], whereas in Brazil, it ranges from 28.9% to 65.0% [20, 22–26]. Thus, different trends are observed in different countries and regions. Notably, data from cancer centers show a higher percentage of malignant tumors than benign tumors, ranging from 65.0% to 86.7% [11, 16, 22]. This is likely because patients with malignant tumors are typically referred to cancer centers for treatment.

The most frequent histological subtype of intraoral minor salivary gland tumors is pleomorphic adenoma, followed by mucoepidermoid carcinoma and adenoid cystic carcinoma [5–8, 10, 12, 13, 15, 17, 18, 20, 21, 23–26, 28]. This tendency was also observed in the present study.

In intraoral minor salivary gland tumors, pleomorphic adenomas are the most common subtype among benign tumors, whereas other histological subtypes are rare [5–10, 12–15, 17–28]. Salivary gland myoepithelioma was the

Table 6 Clinicopathological characteristics of intraoral minor salivary gland tumors reported in epidemiological studies published in English since 1995

First author and reference	Year	Country	Total number of cases	% of malignant cases	Histological subtype (%)			Male			Female				Mean age		
					Pleomorphic adenoma	Mucoepidermoid carcinoma	Adenoid cystic carcinoma	Benign	Malignant	Incidence of malignant tumors (%)	Benign	Malignant	Incidence of malignant tumors (%)	M:F ratio	Benign	Malignant	Total
Loyola[20]	1995	Brazil	164	38	53.0	17.1	13.4	43	27	38.6	56	34	37.8	1:1.3	39.9	43.5	41.5
Rivera-Bastidas[21]	1996	Venezuela	62	45	38.7	29.0	9.7	10	11	52.4	24	17	41.5	1:1.8	38	42	NS
Kusama[5]	1997	Japan	129	38	57.4	19.4	13.2	29	24	45.3	51	25	32.9	1:1.4	44.5	54.3	47.1
Lopes[22]	1999	Brazil	196	65	33.2	38.8	17.3	29	69	70.4	39	59	60.2	1:1	NS*	NS	NS
Jansisyanont[16]	2002	United States	80	76.3	21.3	41.3	8.8	10	21	67.7	9	40	81.6	1:1.6	60	54	NS
Toida[6]	2005	Japan	82	32.9	65.9	9.8	12.2	13	15	53.6	42	12	22.2	1:1.9	49.4	55.4	51.4
Yih[17]	2005	United States	213	44	43.7	21.1	10.3	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Jaber[27]	2006	Libya	75	61.3	30.7	25.3	17.3	NS	NS	NS	NS	NS	NS	1:1.4	44.1	44.3	44.2
Pires[19]	2007	United States	546	44.1	33.2	22.9	6.4	115	94	45.0	190	147	43.6	1:1.6	58	62.4	60.2
Buchner[18]	2007	United States	380	41	39.2	21.8	6.3	NS	NS	NS	NS	NS	NS	1:1.7	NS	NS	NS
Wang[7]	2007	China	737	53.9	37.7	12.3	19.4	165	216	56.7	175	181	50.8	1.1:1	40.7	55.4	NS
Jones[13]	2008	UK	455	37.8	40.4	13.0	11.4	116	64	35.6	167	108	39.3	1:1.5	NS	NS	NS
Dhanuthai[8]	2009	Thailand	311	52.7	42.8	22.8	18.3	51	93	64.6	78	85	52.1	1:1.4	40.01	42.96	41.6
Jaafari-Ashkavandi[10]	2011	Iran	82	46.3	43.9	12.2	28.0	22	22	50.0	36	46	56.1	1:1.3	35	48.8	41.4
Vani[9]	2011	India	185	74.6	22.2	34.1	14.6	22	25	53.2	73	62	45.9	1.1:1	40.36	48.06	46.11
Vaidya[11]	2012	India	104	86.7	16.3	18.3	45.2	NS	NS	NS	NS	NS	NS	1:1	NS	NS	45
Lukšić[15]	2012	Croatia	212	59	39.6	8.5	29.2	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Wyszynska-Pawelec[14]	2012	Poland	57	63.2	29.8	14.0	31.6	7	14	66.7	13	23	63.9	1:1.8	48.3	51.3	NS
Wang[12]	2015	China	485	44.7	37.1	12.2	16.3	107	93	46.5	161	124	43.5	1:1.4	47.6	51.5	49.3
Abrahão[23]	2016	Brazil	170	48	44.1	13.5	11.2	30	36	54.5	53	51	49.0	1:1.6	47	55	51
da Silva[24]	2018	Brazil	1114	53.77	34.1	15.5	10.4	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Mahomed[28]	2020	South Africa	553	43	51.9	10.5	12.8	122	79	39.3	193	159	45.2	1:1.8	39.76	49.81	44.1
Cunha[25]	2020	Brazil	159	28.9	63.5	10.7	5.7	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Bruzinga[26]	2021	Brazil	480	30.7	51.0	14.6	9.0	100	48	32.4	172	99	36.5	1:1.8	45.22	46.29	45.32
Present study	2023	Japan	432	34.5	55.3	17.1	12.0	101	60	37.3	182	89	32.8	1:1.7	48.4	53.2	50.1

**NS* not stated

second most common benign tumor in our study and in previous studies [5, 7, 10, 12, 14, 15, 28]. Other studies have identified cystadenoma of the salivary gland as the second most common benign tumor [6, 18, 20, 21, 23, 24, 27], although basal cell adenoma [8, 9, 13, 22] and canalicular adenoma [17, 19, 25, 26] have also been reported, but their frequency was much lower than that of pleomorphic adenomas.

Among malignant tumors, mucoepidermoid carcinoma [5, 8, 9, 13, 16–27] and adenoid cystic carcinoma [6, 7, 10–12, 14, 15, 28] were reported as the most common histological subtypes, with slight variations across studies. These two types were also found to be the highly prevalent in the present study. Other high-grade tumors, such as salivary duct carcinoma and myoepithelial carcinoma, were observed in the present study and previous studies [7–9, 12, 13, 18, 19, 22, 25, 26, 28], indicating the need for careful diagnosis of these highly malignant intraoral minor salivary gland tumors.

Intraoral minor salivary glands have been reported to occur more frequently in females than in males [5, 6, 8, 10, 12–14, 16, 18–21, 23, 26–28]. This trend was also observed in the present study. Both males and females had more benign tumors than malignant tumors in previous studies [5, 12, 13, 19, 20, 26, 28], and this was also the case in our study. The incidence of malignant tumors is often reported to be higher in males [5–9, 12, 14, 19–23], and the malignancy frequency was slightly higher in males (37.3%) than in females (32.8%) in the current study.

Pleomorphic adenomas were reported to be more common in females in previous studies [7, 9, 10, 12, 13, 18, 19, 23, 25, 26]. Consistent with these findings, pleomorphic adenomas were also more common in females in our study. Mucoepidermoid carcinoma and adenoid cystic carcinoma, which are typical malignant tumors, have also been reported to be more common in females in previous studies [7, 10, 12, 13, 18, 19, 23, 25, 26]. However, in our study, mucoepidermoid carcinoma was more common in females than males while adenoid cystic carcinoma was more common in males than females. This finding is consistent with previous studies that have reported adenoid cystic carcinoma to be more common in males [9].

Intraoral minor salivary gland tumors are generally more prevalent in middle-aged and older adults, with an average age of 40–50 years reported [5, 6, 8–12, 20, 23, 26–28]. The mean age of all patients in the present study was 50.1 years, and there was a statistically significant difference in the mean age of benign tumor occurrence (48.4 years) and malignant tumor occurrence (53.2 years), with benign tumors widely distributed across all age groups and malignant tumors more likely to occur in older age groups (Fig. 1). Many studies have also found that the mean age of patients with malignant tumors is higher than that of patients with benign tumors [5–10, 12, 20, 23, 26–28]. However, malignancies can occur in very young patients, with some cases reported in patients younger than 10 years [8, 21] and in their teens [6, 7, 9, 10, 12, 13, 18, 20, 22, 26].

Mucoepidermoid carcinoma, a common malignant tumor, had a younger average age of occurrence (47.8 years) than other malignant tumors in the present study, with most patients diagnosed in their 40 s, although some cases presented in patients in their teens (4 cases) and 20 s (9 cases). In previous studies, mucoepidermoid carcinoma also had a younger mean age of occurrence than other malignancies [7, 9, 10, 12, 18, 19, 26], with cases reported in patients aged under 10 and in their teens [7–9, 12, 13, 18, 26].

The age of onset for malignant tumors was found to be significantly higher in males compared with females in the present study. This finding is consistent with previous studies, including in Japan, indicating that females tend to develop malignant tumors at a younger age than males [6, 20].

The palate is the most frequently affected site for intraoral minor salivary glands, accounting for approximately 50% of all cases, followed by the lips and buccal mucosa, whereas the floor of the mouth, retromolar area, and tongue are less common sites [6–8, 10, 12–16, 18–28]. In the present study, the palate was the most common site (57.9%), followed by the upper lip and buccal mucosa. Consistent with previous findings, pleomorphic adenomas were predominately located on the palate (66.5%) [5–9, 12, 15, 17–21, 23–26, 28]. Similar to the current study, the palate has been reported as the most common pleomorphic adenoma site, followed by the upper lip or lips [5, 6, 8, 9, 15, 17–19, 24–26, 28]. Mucoepidermoid carcinomas were also most commonly found on the palate in our patients, as reported in previous studies [5–9, 12, 15, 17–21, 23–26, 28]. Adenoid cystic carcinoma occurred most frequently on the palate (34.6%), but was also found on the floor of the mouth (23.1%). Previous studies have suggested that the floor of the mouth is the second most common occurrence site after the palate [5, 9, 18, 19, 23], whereas other studies have suggested the buccal mucosa [6, 17, 21], alveolar ridge [8, 26], and sinuses [12, 28] as the next most common sites.

The distribution of benign and malignant intraoral minor salivary gland tumors varies by site of occurrence (Table 7). Benign tumors are often found on the palate [5–8, 10, 12–15, 18–21, 23–28] and in the buccal mucosa [6, 8, 10, 12–15, 18–21, 23, 25, 26]. In the present study, benign tumors were also more common in the palate and buccal mucosa. The consensus is that the smaller the salivary gland, the greater the chance that a neoplasm is malignant. Malignancy rates are high in the tongue [5, 7, 9, 10, 12, 14, 15, 22, 24, 27, 28], floor of the mouth [5–7, 9, 10, 14, 19, 22, 27, 28], retromolar area [7–9, 13, 14, 16, 18, 24], alveolar ridge [7–10, 15, 19, 23], and intrabony locations [5, 8–10, 12, 13, 16, 24], with

Table 7 Anatomical distribution of intraoral minor salivary gland tumors reported in epidemiological studies published in English since 1995

First author and reference	Year	Country	Palate		Buccal mucosa		Floor of the mouth		Retromolar area		Upper lip		Lower lip	
			Benign	Malignant	Benign	Malignant	Benign	Malignant	Benign	Malignant	Benign	Malignant	Benign	Malignant
Loyola[20]	1995	Brazil	77	46	17	5	NS	NS	NS	8	NS	NS	NS	NS
Rivera-Bastidas[21]	1996	Venezuela	19	15	3	3	3	2	2	2	NS	NS	NS	NS
Kusama[5]	1997	Japan	60	17	6	7	1	13	3	7	NS	NS	NS	NS
Lopes[22]	1999	Brazil	54	74	0	13	0	5	3	9	NS	NS	NS	NS
Jansisyanont[16]	2002	United States	17	26	0	13	0	0	0	5	2	4	0	4
Toida[6]	2005	Japan	44	20	6	4	0	1	1	0	4	2	0	0
Jaber[27]	2006	Libya	15	11	5	6	0	8	2	5	4	5	1	1
Pires[19]	2007	United States	96	85	57	41	2	19	0	0	86	20	27	11
Buchner[18]	2007	United States	117	89	34	20	4	9	1	19	58	6	8	10
Wang[7]	2007	China	263	234	31	46	1	36	2	17	27	13	4	8
Jones[13]	2008	UK	135	92	39	16	2	6	1	7	79	14	8	6
Dhanuthai[8]	2009	Thailand	104	82	11	6	4	4	1	12	13	2	NS	NS
Jaafari-Ashkavandi[10]	2011	Iran	34	19	7	2	0	2	0	0	1	1	0	1
Vani[9]	2011	India	31	60	1	13	3	19	1	5	5	2	NS	NS
Lukšić[15]	2012	Croatia	60	52	11	11	NS	NS	NS	NS	NS	NS	NS	NS
Wyszynska-Pawelec[14]	2012	Poland	14	12	7	4	0	2	0	2	0	2	0	1
Wang[12]	2015	China	225	89	21	16	2	0	NS	NS	5	5	NS	NS
Abrahão[23]	2016	Brazil	48	47	16	11	2	7	NS	NS	16	6	NS	NS
da Silva[24]	2018	Brazil	307	324	61	86	9	16	3	38	101	33	15	14
Mahomed[28]	2020	South Africa	207	108	22	39	0	4	NS	NS	NS	NS	NS	NS
Cunha[25]	2020	Brazil	62	39	19	3	1	0	0	0	NS	NS	NS	NS
Bruzinga[26]	2021	Brazil	194	103	21	12	5	5	4	4	22	5	4	2
Present study	2023	Japan	180	70	22	14	6	16	4	13	59	8	7	6

First author and reference	Year	Country	Alveolar ridge		Intrabony location		Tongue		Sinuses		Vestibule		Others	
			Benign	Malignant	Benign	Malignant	Benign	Malignant	Benign	Malignant	Benign	Malignant	Benign	Malignant
Loyola[20]	1995	Brazil	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Rivera-Bastidas[21]	1996	Venezuela	0	0	2	2	NS	NS	NS	NS	NS	NS	3	3
Kusama[5]	1997	Japan	0	0	0	3	0	1	0	0	0	0	NS	NS
Lopes[22]	1999	Brazil	2	7	0	0	3	16	0	0	0	0	0	0
Jansisyanont[16]	2002	United States	0	0	0	9	0	0	0	0	0	0	NS	NS
Toida[6]	2005	Japan	0	0	0	0	0	0	0	0	0	0	NS	NS
Jaber[27]	2006	Libya	0	0	1	3	1	7	0	0	0	0	0	0
Pires[19]	2007	United States	5	31	NS	NS	NS	NS	NS	NS	25	14	7	16

Table 7 (continued)

First author and reference	Year	Country	Alveolar ridge		Intrabony location		Tongue		Sinuses		Vestibule		Others	
			Benign	Malignant	Benign	Malignant	Benign	Malignant	Benign	Malignant	Benign	Malignant	Benign	Malig-nant
Buchner[18]	2007	United States	0	0	NS	0	2	3	0	0	0	0	0	0
Wang[7]	2007	China	0	11	0	0	5	31	NS	NS	NS	NS	7	1
Jones[13]	2008	UK	2	7	0	1	2	5	NS	NS	NS	NS	15	18
Dhanuthai[8]	2009	Thailand	9	37	4	17	NS	NS	NS	NS	NS	NS	NS	NS
Jaafari-Ashkavandi[10]	2011	Iran	0	1	1	5	0	7	0	0	0	0	NS	NS
Vani[9]	2011	India	2	24	0	10	0	1	NS	NS	1	0	3	4
Lukšić[15]	2012	Croatia	0	7	0	0	0	2	1	35	0	0	6	13
Wyszynska-Pawelec[14]	2012	Poland	0	0	0	0	0	2	0	0	0	0	0	11
Wang[12]	2015	China	NS	NS	0	19	4	25	0	1	NS	NS	3	8
Abrahão[23]	2016	Brazil	2	8	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
da Silva[24]	2018	Brazil	NS	NS	0	25	4	32	NS	NS	NS	NS	NS	NS
Mahomed[28]	2020	South Africa	NS	NS	NS	NS	1	15	10	31	NS	NS	37	30
Cunha[25]	2020	Brazil	0	0	0	0	1	1	0	0	0	0	0	0
Bruzinga[26]	2021	Brazil	6	7	NS	NS	2	1	NS	NS	NS	NS	14	8
Present study	2023	Japan	1	7	0	7	2	4	0	4	2	0	0	0

*NS = not stated.

reports of rates of over 80%. Lower lip tumors are more likely to be malignant than upper lip tumors, as reported in several studies [7, 10, 13, 16, 18, 19, 24, 26]. In the present study, infrequently occurring tumor sites, such as the floor of the mouth and retromolar area showed a trend toward a higher incidence of malignancy. Malignancy was also more common in the lower lip than in the upper lip. These findings highlight the need to consider the possibility of malignancy in less common tumor locations.

Conclusion

Intraoral minor salivary gland tumors are infrequently found during routine diagnosis. However, pleomorphic adenoma, mucoepidermoid carcinoma, and adenoid cystic carcinoma are the most common benign and malignant tumors. Malignant tumors occur at an older age in males than in females, and sites with fewer tumors tend to have a high incidence of malignancy. Among all intraoral minor salivary gland tumor subtypes, the palate, lips, and buccal mucosa are the most common occurrence sites. Further large-scale studies would help to determine the prevalence of sex, age, and occurrence site and their association with malignancy frequency. These data will assist in formulating a differential diagnosis prior to biopsy and help facilitate patient management with obtaining a biopsy and treatment plan.

Acknowledgements This work was supported by the KAKENHI program of the Japan Society for the Promotion of Science (Grant No.: 20K10125).

Authors' contributions KK conceived the research project, collected and analyzed data, and contributed to the drafting of the manuscript. KM contributed to the drafting of the manuscript. TC, KY, YA, KN, MT, and AK collected and analyzed data and reviewed the manuscript. All the authors approved the final version of the manuscript.

Funding This study was not supported by any funding.

Data Availability Not applicable.

Code Availability Not applicable.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical Approval For this type of study formal consent is not required.

Informed Consent For this type of study informed consent is not required.

Consent for Publication For this type of study consent for publication is not required.

Consent to Participate Not applicable.

References

1. Spiro RH (1998) Management of malignant tumors of the salivary glands. Oncology 12:671–680
2. To VSH, Chan JYW, Tsang RKY, Wei WI (2012) Review of salivary gland neoplasms. I S R N Otolaryngol. https://doi.org/10.5402/2012/872982
3. WHO Classification of Tumours Online (2023). World Health Organization https://tumourclassification.iarc.who.int/welcome/. Accessed Jan 19, 2023
4. Alsanie I, Rajab S, Cottom H et al (2022) Distribution and frequency of salivary gland tumours: an international multicenter study. Head Neck Pathol 16:1043–1054. https://doi.org/10.1007/s12105-022-01459-0
5. Kusama K, Iwanari S, Aisaki K, Wada M, Ohtani J, Itoi K, Hanai K, Shimizu K, Komiyama K, Kudo I, Moro I (1997) Intraoral minor salivary gland tumors: a retrospective study of 129 cases. J Nihon Univ Sch Dent 39:128–132. https://doi.org/10.2334/josnusd1959.39.128
6. Toida M, Shimokawa K, Makita H, Kato K, Kobayashi A, Kusunoki Y, Hatakeyama D, Fujitsuka H, Yamashita T, Shibata T (2005) Intraoral minor salivary gland tumors: a clinicopathological study of 82 cases. Int J Oral Maxillofac Surg 34:528–532. https://doi.org/10.1016/j.ijom.2004.10.010
7. Wang D, Li Y, He H, Liu L, Wu L, He Z (2007) Intraoral minor salivary gland tumors in a Chinese population: a retrospective study on 737 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 104:94–100. https://doi.org/10.1016/j.tripleo.2006.07.012
8. Dhanuthai K, Boonadulyarat M, Jaengjongdee T, Jiruedee K (2009) A clinico-pathologic study of 311 intra-oral salivary gland tumors in Thais. J Oral Pathol Med 38:495–500. https://doi.org/10.1111/j.1600-0714.2009.00791.x
9. Vani NV, Ponniah I (2011) The frequency and distribution pattern of minor salivary gland tumors in a government dental teaching hospital, Chennai, India. Oral Surg Oral Med Oral Pathol Oral Radiol 111:e32–e39. https://doi.org/10.1016/j.tripleo.2010.08.019
10. Jaafari-Ashkavandi Z, Ashraf MJ, Afandak N (2011) A clinicopathologic study of 82 intraoral minor salivary gland tumors. Iran Red Crescent Med J 13:674–677. https://doi.org/10.5812/kowsar.20741804.2244
11. Vaidya AD, Pantvaidya GH, Metgudmath R, Kane SV, D'Cruz AK (2012) Minor salivary gland tumors of the oral cavity: A case series with review of literature. J Cancer Res Ther 8(Suppl. 1):S111–S115. https://doi.org/10.4103/0973-1482.92224
12. Wang XD, Meng LJ, Hou TT, Zheng C, Huang SH (2015) Frequency and distribution pattern of minor salivary gland tumors in a Northeastern Chinese population: A retrospective study of 485 patients. J Oral Maxillofac Surg 73:81–91. https://doi.org/10.1016/j.joms.2014.08.019
13. Jones AV, Craig GT, Speight PM, Franklin CD (2008) The range and demographics of salivary gland tumours diagnosed in a UK population. Oral Oncol 44:407–417. https://doi.org/10.1016/j.oraloncology.2007.05.010
14. Wyszyńska-Pawelec G, Gontarz M, Zapała J, Szuta M (2012) Minor salivary gland tumours of upper aerodigestive tract: A clinicopathological study. Gastroenterol Res Pract. https://doi.org/10.1155/2012/780453
15. Lukšić I, Virag M, Manojlović S, Macan D (2012) Salivary gland tumours: 25 years of experience from a single institution in Croatia. J Craniomaxillofac Surg 40:e75–e81. https://doi.org/10.1016/j.jcms.2011.05.002
16. Jansisyanont P, Blanchaert RH, Ord RA (2002) Intraoral minor salivary gland neoplasm: a single institution experience of 80 cases. Int J Oral Maxillofac Surg 31:257–261. https://doi.org/10.1054/ijom.2002.0223

17. Yih WY, Kratochvil FJ, Stewart JCB (2005) Intraoral minor salivary gland neoplasms: review of 213 cases. J Oral Maxillofac Surg 63:805–810. https://doi.org/10.1016/j.joms.2005.02.021
18. Buchner A, Merrell PW, Carpenter WM (2007) Relative frequency of intra-oral minor salivary gland tumors: a study of 380 cases from northern California and comparison to reports from other parts of the world. J Oral Pathol Med 36:207–214. https://doi.org/10.1111/j.1600-0714.2007.00522.x
19. Pires FR, Pringle GA, de Almeida OP, Chen SY (2007) Intra-oral minor salivary gland tumors: a clinicopathological study of 546 cases. Oral Oncol 43:463–470. https://doi.org/10.1016/j.oraloncology.2006.04.008
20. Loyola AM, de Araújo VC, de Sousa SOM, de Araújo NS (1995) Minor salivary gland tumours. A retrospective study of 164 cases in a Brazilian population. Eur J Cancer B Oral Oncol 31B:197–201. https://doi.org/10.1016/0964-1955(95)00001-X
21. Rivera-Bastidas H, Ocanto RA, Acevedo AM (1996) Intraoral minor salivary gland tumors: a retrospective study of 62 cases in a Venezuelan population. J Oral Pathol Med 25:1–4. https://doi.org/10.1111/j.1600-0714.1996.tb01214.x
22. Lopes MA, Kowalski LP, da Cunha SG, Paes de Almeida O (1999) A clinicopathologic study of 196 intraoral minor salivary gland tumours. J Oral Pathol Med 28:264–267. https://doi.org/10.1111/j.1600-0714.1999.tb02036.x
23. Abrahão AC, de Santos Netto J, Pires FR, Santos TC, Cabral MG (2016) Clinicopathological characteristics of tumours of the intraoral minor salivary glands in 170 Brazilian patients. Br J Oral Maxillofac Surg 54:30–34. https://doi.org/10.1016/j.bjoms.2015.10.035
24. da Silva LP, Serpa MS, Viveiros SK, Sena DAC, de Carvalho Pinho RF, de Abreu Guimarães LD, de Sousa Andrade ES, Dias Pereira JR, Silveira MMFD, Sobral APV, de Sousa SCOM, de Souza LB (2018) Salivary gland tumors in a Brazilian population: A 20-year retrospective and multicentric study of 2292 cases. J Craniomaxillofac Surg 46:2227–2233. https://doi.org/10.1016/j.jcms.2018.09.028
25. Cunha JLS, Coimbra ACP, Silva JVR, Nascimento IS, Andrade ME, Oliveira CR, Almeida OP, Soares CD, Sousa SF, Albuquerque-Júnior RL (2020) Epidemiologic analysis of salivary gland tumors over a 10-years period diagnosed in a northeast Brazilian population. Med Oral Patol Oral Cir Bucal 25:e516–e522. https://doi.org/10.4317/medoral.23532
26. Bruzinga FFB, Fernandes FCF, Dias FR, Lima MG, de Souza PEA, de Aguiar MCF, Grossmann SMC (2023) Clinical and demographic features of minor salivary gland tumors: A collaborative study of 480 cases. Oral Dis 29:1028–1038. https://doi.org/10.1111/odi.14119
27. Jaber MA (2006) Intraoral minor salivary gland tumors: a review of 75 cases in a Libyan population. Int J Oral Maxillofac Surg 35:150–154. https://doi.org/10.1016/j.ijom.2005.07.006
28. Mahomed Y, Meer S (2020) Primary epithelial minor salivary gland tumors in South Africa: A 20-year review. Head Neck Pathol 14:715–723. https://doi.org/10.1007/s12105-019-01111-4
29. Gnepp DR, Brandwein MS, Henley JD (2009) Salivary and lacrimal glands Diagnostic surgical pathology of the head and neck Saunders, 2nd edn. Elsevier, Amsterdam, pp 449–453
30. Mckenzie J, Lockyer J, Singh T, Nguyen E (2023) Salivary gland tumours: an epidemiological review of non-neoplastic and neoplastic pathology. Br J Oral Maxillofac Surg 61:12–18. https://doi.org/10.1016/j.bjoms.2022.11.281

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.