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Review

Salivary gland tumours: an epidemiological review of non-neoplastic and neoplastic pathology

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Abstract

Salivary gland tumours (SGT) demonstrate geographical variation. The primary objective of this study was to determine the types, frequency, distribution, and demographics of non-neoplastic and neoplastic salivary gland pathology at Waikato Hospital, New Zealand (NZ) over a 10-year period. Following this we conducted a 10-year retrospective review of SGT epidemiology from international literature. In total 825 patients were identified, 31% (256/825) with non-neoplastic salivary gland pathology, 34% (284/825) with benign neoplastic pathology, 14% (118/825) with primary malignant lesions, 18% (146/825) with metastatic SGTs, and 3% (21/825) with lymphoma. Patients had a mean (range) age of 58 (3–102) years, were predominantly male (58%, 476/825), and NZ European (65%, 536/825). Tumours were most prevalent in the parotid gland (85%, 484/569), of which 44% (211/484) were malignant. Pleomorphic adenoma was the most common benign (71%, 203/284) and overall (36%, 203/569) tumour, while mucoepidermoid carcinoma (25%, 29/118) and squamous cell carcinoma (SCC) (73%, 106/146) were the most common primary malignant and metastatic SGTs, respectively. Our literature review identified 18 studies consisting of 33,933 patients, of whom 71% (24,013/33,933) had benign SGTs. Pleomorphic adenoma (68%, 16404/24013) and mucoepidermoid carcinoma (29%, 2826/9621) were the most common benign and malignant SGTs, respectively. Low numbers of non-neoplastic and metastatic SGTs were reported in the literature. This research provides a greater understanding of differences in their global distribution. Consistent with previous literature, pleomorphic adenoma and mucoepidermoid carcinoma were the most common benign and malignant SGTs. In NZ, we found high rates of malignant SCC to the parotid gland, consistent with the epidemiology of non-melanoma skin cancer in the country.

Keywords: Salivary gland tumours; Epidemiology; New Zealand

Introduction

Salivary gland tumours (SGTs) are rare, constituting 5% of all head and neck cancers and 0.5% of total body malignancies, with an annual incidence of 0.5–2 patients/100,000 people.[1,2] The majority occur in the parotid gland (70%) and they are less common in minor salivary (20%), submandibular (10%), and sublingual (<1%) glands.[1] SGTs have diverse histomorphology, with 33 different tumours recognised by the World Health Organization's (WHO) , making diagnosis and treatment challenging.[3,4]

Eighty per cent of all SGTs are benign,[5] and these are most prevalent in the third to fourth decade, with a slight female predilection (M:F ratio 1:1.33).[6,7] Benign SGTs have reduced histomorphological variability with 10 tumours recognised.[4] Pleomorphic adenoma is the most prevalent, accounting for 65% of all tumours and 50% of benign SGTs.[5]

With regards to malignant SGTs, the smaller the salivary gland the higher the risk of malignancy, with nearly 100% of sublingual and 60% of minor salivary gland tumours diagnosed as malignant.[5] Malignant tumours are more prevalent in the fourth to fifth decade, with a slight predilection in males (M:F ratio 1.34:1),[5,7] Mucoepidermoid (MEC) and adenoid cystic carcinoma (AdCC) are the most prevalent malignant SGTs, making up 25% and 15%, respectively.[8] Metastatic epithelial tumours such as squamous cell carcinoma (SCC) and melanoma account for 10% of all SGTs,

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occurring primarily in the parotid gland (80%), with an increased prevalence in Australasia.[9]

The salivary glands can also be affected by a range of non-neoplastic conditions that often present similarly to tumours, making diagnosis difficult and errors serious. Non-neoplastic disorders range from developmental, inflammatory, infectious, granulomatous, traumatic conditions and cystic lesions.[10] Non-neoplastic salivary gland pathology most commonly occurs in patients in their second to fourth decade with a slight female predilection (M:F ratio1:1.2), primarily affecting the submandibular gland.[10] The most common non-neoplastic pathologies are sialadenitis and mucoceles.[10] To our knowledge, however, few studies have collected epidemiological data on non-neoplastic SGTs.

Due to their rarity, histological heterogeneity, and classification changes of SGTs, epidemiological studies are difficult,[11] but epidemiological data is important for diagnosis and management.[12,13] The aim of this research therefore was to determine the types, frequency, distribution, and demographic characteristics of non-neoplastic and neoplastic SGTs in a large New Zealand (NZ) hospital. This was conducted alongside a 10-year literature review of international epidemiological studies of SGTs.

Methods

Ethics consent was obtained by the New Zealand Health and Disability Commission and approved by the Waikato District Health Board and Māori Research Committee.

The authors conducted a review of the Waikato Hospital pathology database from 1 January 2010 to 31 December 2020. Patients were included if they had a histological diagnosis of a SGT, as per the relevant WHO classification (3rd or 4th editions).[4,14] Immunohistochemical analysis was performed when haematoxylin-eosin staining was not sufficient to establish a diagnosis. All samples were examined by a specialist pathologist, with malignant tumours reviewed at the head and neck cancer multi-disciplinary meeting. Patients were excluded if their records were incomplete. Epidemiological data, including sex, age, ethnicity, tumour location, and histological classification, were recorded.

A literature search was conducted for the period between January 2010 and December 2020. The databases of the National Library of Medicine, Washington, DC (MEDLINE/PubMed), ScienceDirect, Scopus, and the Cochrane Central Register of Controlled Trials were used. The authors used the keywords ((Salivary gland) AND (Epidemiology)) with no restriction on article type. The reference lists of the included papers were reviewed to search for additional papers. Studies eligible for inclusion included recent publications (between 2010 and 2021), English literature, and epidemiological data on benign or malignant tumours, with or without non-neoplastic SGTs. Articles were excluded if they did not collect data on both benign and malignant tumours based on the WHO or International Classification of Diseases classification of SGT. Two authors independently searched all sources and reviewed the titles, abstracts, and full texts to identify eligible articles. Duplicated reports on the same patients were excluded. Discrepancies between the two investigators were resolved through discussion and consensus.

Data collated included name of the first author, year of publication, country of the study population, patient's gender, location of the SGT, and histological diagnosis. Data underwent descriptive statistical analysis with IBM SPSS Statistics for Windows version 26.0 (IBM Corp). Non-parametric data were represented with mean and interquartile ranges (IQR). Total salivary gland pathology statistics (n = 825) included benign salivary gland pathology, which was removed for analysis of SGTs (n = 569).

Results

A total of 825 patients were diagnosed with salivary gland pathology over the 10-year period at Waikato Hospital. Among them, 65% (540/825) had benign pathology, which was non-neoplastic in 47% (256/540) and benign neoplastic in 53% (284/540). Pleomorphic adenoma was the most common benign neoplastic (71%, 203/284) and overall SGT (36%, 203/569). For benign neoplastic tumours following pleomorphic adenoma, Warthin tumour (23%, 66/284) and oncocytoma (4%, 10/284) were the most common. Fifty per cent (285/569) of tumours were malignant, and of them 41% (118/285) were primary malignant and 51% (146/285) metastatic. Seven per cent (21/285) were lymphomas. MEC (25%, 29/118) and AdCC (21%, 25/118) were the most common primary malignant tumours and SCC (73%, 106/146) was the most common metastatic malignant tumour. Data pertaining to the distribution of tumours is presented in Table 1.

The age of the patients ranged from 3–102 years, with an overall mean (IQR) age of 58 (55–62) years. The mean (IQR) age of patients was 36 (32–38), 63 (61–65), 65 (62–68), and 75 (73–78) years for non-neoplastic, benign neoplastic, primary malignant, and metastatic tumours, respectively. The mean (IQR) age of patients with lymphoma was 75 (72–78) years. Overall 58% (476/825) of patients were male and 42% (349/825) female, giving a male:female ratio of 1.36:1. Gender differences were also seen for non-neoplastic pathology (M:F ratio 1.28:1), primary malignant (M:F ratio 1.2:1), metastatic (M:F ratio 3.6:1) SGTs, and lymphoma (M:F ratio 1.6:1). No gender difference was seen in neoplastic benign tumours. For ethnicity, 73% (417/569) of patients with SGTs were NZ European and 15% (83/569) Māori. For patients with non-neoplastic salivary gland pathology 46% (119/256) were NZ European and 38% (88/256) Māori. Data pertaining to age, sex, and ethnicity is presented in Table 1.

Eighty-two per cent (468/569) of SGTs occurred in the parotid gland, 9% (51/569) in the minor salivary glands, 8% (47/569) in the submandibular gland, and less than 1% (3/569) in the sublingual gland. Data related to SGT distribution are shown in Table 2.

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Table 1
Distribution and epidemiological data on salivary gland pathology. Data are number.

	Total	Age	Sex		New Zealand European	Maori	Pacific peoples	Other
			Male	Female				
Total	825	58	476 (58)	349 (42)	536 (65)	181 (22)	26 (3)	82 (10)
Non-neoplastic:	256	36	142 (55)	114 (45)	119 (46)	98 (38)	16 (6)	23 (9)
Mucocele	145	27	79 (54)	66 (46)	59 (41)	58 (40)	12 (8)	16 (11)
Sialadenitis	64	51	40	24	42	15	3	4
Ranula	32	34	17	15	7	23	1	1
Other	15	32	6	9	11	2	0	2
Neoplastic:	569	68	334 (59)	235 (41)	417 (73)	83 (15)	10 (2)	59 (10)
Benign:	284	63	142 (50)	142 (50)	194 (68)	48 (17)	6 (2)	36 (13)
Pleomorphic adenoma	203	60	98 (48)	105 (52)	132 (65)	36 (18)	6 (3)	29 (14)
Warthin tumour	66	70	36	30	50	11	0	5
Oncocytoma	10	74	6	4	9	0	0	1
Other	5	60	2	3	3	1	0	1
Primary malignancy:	118	65	65 (55)	53 (45)	76 (64)	27 (23)	4(3)	11 (9)
Mucoepidermoid carcinoma	29	63	16	13	16	10	0	3
Adenoid cystic carcinoma	25	67	15	10	20	2	0	3
Polymorphous aenocarcinoma	13	68	5	8	9	2	0	2
Myoepithelial carcinoma	11	66	5	6	7	3	1	0
Salivary duct carcinoma	11	71	6	5	5	3	1	2
Adenocarcinoma NOS	8	67	5	3	4	4	0	0
Carcinoma ex pleomorphic adenoma	5	64	2	3	4	1	0	0
Secretory carcinoma	5	60	5	0	4	0	0	1
Acinic cell carcinoma	4	52	2	2	3	1	0	0
Other	7	67	4	3	4	1	2	0
Metastatic:	146	75	114 (78)	32 (22)	132 (90)	5 (3)	0	9 (6)
Squamous cell carcinoma	106	80	87 (82)	19 (18)	97 (92)	3 (3)	0	6 (6)
Melanoma	27	77	20	7	25	1	0	1
Merkel cell carcinoma	6	86	5	1	6	0	0	0
Other	7	67	2	5	4	1	0	2
Lymphoma	21	75	13	8	15	3	0	3

Fig. 1 shows the study search and selection criteria for the review. One per cent (18/1671) of studies met the inclusion criteria. Four originated from China, two each from Brazil and Poland, and one each from Iceland, Taiwan, Nigeria, Japan, Thailand, Chile, the United Kingdom, Iran, Croatia, and Mexico. Collectively they included 33,933 patients. The mean duration of research was 19 years. The gender distribution was 1:1 male:female (M:F 17,065:16,868). Seventy-one per cent (24,013/33,933) of patients had benign neoplastic tumours, and 29% (9920/33,933) had malignant tumours. Non-neoplastic lesions were reported in only one study by Liao et al,[15] who reported 19 cases of sialadenitis. Sixty-three per cent (21,471/33, 914) of SGTs occurred in the parotid, 24% (8167/33,914) in minor salivary glands, 11% (3840/33,914) in the submandibular gland, and 1% (427/33,914) in the sublingual gland. Sixty-eight per cent (16,404/23,994) of benign SGTs were pleomorphic adenoma, 19% (4799/23,994) were Warthin tumour, and less than 1% (133/23,994) oncocytoma. Twenty-eight per cent (2,826/9920) of malignant SGTs were MEC carcinoma, 28% (2794/9920) were AdCC, and 7% (2794/9920) adenocarcinoma not otherwise specified (NOS). SGTs in 22% (4619/21,471) of parotid, 33% (1268/3,859) of submandibular, 55% (4529/8167) of minor salivary, and 89% (381/427) of sublingual glands, were malignant. Data related to the literature review are presented in Table 3.

Discussion

Epidemiological studies of SGTs demonstrate variations related to patient demographics, tumour prevalence, and location. Over the 10-year period at Waikato Hospital 569 patients were diagnosed with SGTs and 256 were diagnosed with non-neoplastic salivary gland pathology. SGTs occurred most commonly in the sixth decade, in males, in NZ Europeans, and in the parotid gland. Patients with benign neoplastic SGTs were younger (mean 63 years, IQR 61–65) than those with primary malignant (65 years IQR 62–68) or metastatic (75 years, IQR 73–78 years) disease, as found previously.[16–18] Previous literature has indicated a female predominance for SGTs, but we found that for metastatic SGTs, males were 3.6 times more likely to be affected, and there was also a slight male predominance for primary malignant disease.[7,11,18,19] Gender-based differences were also found for individual tumours within this study as shown in Table 1.

The majority of tumours had a male predominance, excluding pleomorphic adenoma, carcinoma ex-pleomorphic adenoma, and polymorphous adenocarcinoma, which were more common in females, although these primary malignant tumours were rare overall. Benign neoplastic, primary malignant, and metastatic SGTs occurred most commonly in the parotid gland, and were uncommon in

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Table 2
Distribution of salivary gland pathology in major and minor salivary glands. Data are number.

	Total	Parotid	Submandibular	Sublingual	Minor salivary
Total	825	484 (59)	100 (12)	38 (5)	203 (25)
Non-neoplastic:	256	16 (6)	53 (21)	35 (14)	152 (59)
Mucocele	145	0	0	0	145
Sialadenitis	64	8	52	3	1
Ranula	32	0	0	32	0
Other	15	8	1	0	6
Neoplastic:	569	468 (82)	47 (8)	3 (< 1)	51 (9)
Benign:	284	257 (90)	13 (5)	0	14 (5)
Pleomorphic adenoma	203	180 (89)	13 (6)	0	10 (5)
Warthin tumour	66	66	0	0	0
Oncocytoma	10	10	0	0	0
Other	5	1	0	0	4
Primary malignancy:	118	64 (54)	16 (14)	2 (2)	36 (31)
Mucoepidermoid carcinoma	29	16	3	1	9
Adenoid cystic carcinoma	25	8	6	1	10
Polymorphous adenocarcinoma	13	2	0	0	11
Myoepithelial carcinoma	11	9	1	0	1
Salivary duct carcinoma	11	8	3	0	0
Adenocarcinoma NOS	8	4	1	0	3
Carcinoma ex pleomorphic adenoma	5	4	1	0	0
Secretory carcinoma	5	4	1	0	0
Acinic cell carcinoma	4	4	0	0	0
Other	7	5	0	0	2
Metastatic:	146	135 (92)	10 (7)	0	1 (< 1)
Squamous cell carcinoma	106	100 (94)	6 (6)	0	0
Melanoma	27	25	2	0	0
Merkel cell carcinoma	6	6	0	0	0
Other	7	4	2	0	1
Lymphoma	21	12	8	1	0

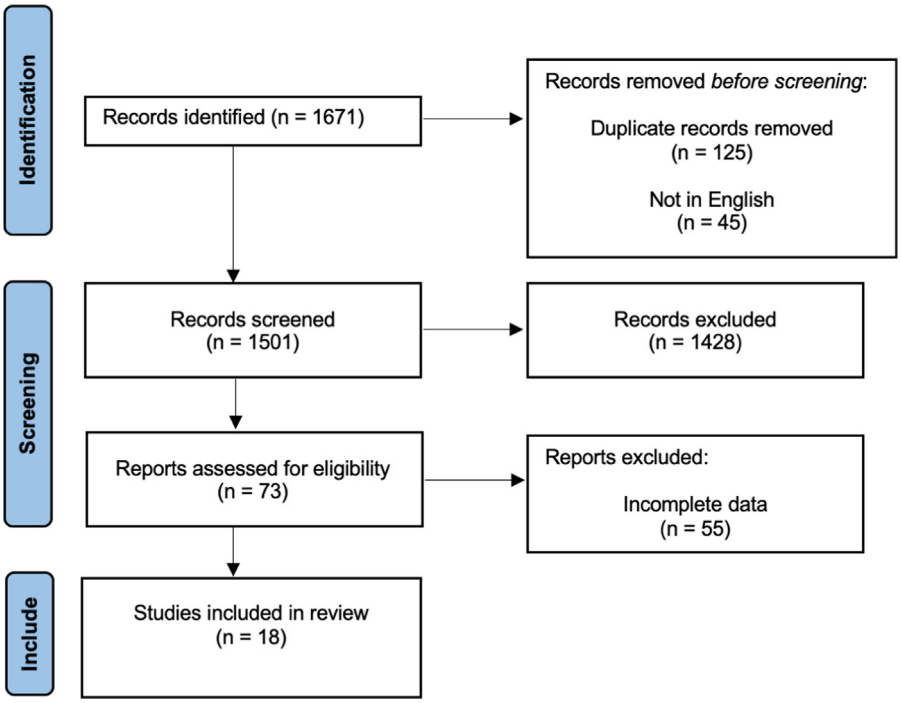

Fig. 1. Study inclusion flowchart.

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Table 3
Epidemiological, histological, and distribution literature review data

	No. (%)
Patients	33933
Gender	
Male	17065 (50)
Female	16868 (50)
Non-neoplastic	19 (<1)
Benign neoplastic	23994 (71)
Malignant	9621 (28)
Metastatic	299 (1)
Benign	
Pleomorphic adenoma	16404 (48)
Warthin tumour	4799 (14)
Oncocytoma	133 (<1)
Malignant	
Mucoepidermoid carcinoma	2826 (8)
Adenoid cystic carcinoma	2794 (8)
Polymorphous adenocarcinoma	442 (1)
Myoepithelial carcinoma	216 (<1)
Salivary duct carcinoma	142 (<1)
Adenocarcinoma NOS	787 (2)
Carcinoma ex pleomorphic adenoma	723 (2)
Secretory carcinoma	8 (<1)
Acinic cell carcinoma	675 (2)
Metastatic	
Squamous cell carcinoma	184 (<1)
Melanoma	0
Merkel cell carcinoma	0
Lymphoma	115
Distribution	
Parotid	21471 (63)
Submandibular	3859 (11)
Sublingual	427 (1)
Minor	8167 (24)
Malignancy	
Parotid	4619 (22)
Submandibular	1268 (33)
Sublingual	381 (89)
Minor	4529 (55)

the sublingual gland in accordance with previous authors.[7,11,15,18] Neoplastic tumours were less common in the submandibular and minor salivary glands, but AdCC and polymorphous adenocarcinoma were found predominantly in the minor salivary glands.

It is well established that pleomorphic adenoma is the most common SGT, and this has been further shown in our research and literature review in which it constituted 36% (203/569) and 48% (16404/33914) of tumours, respectively.[11,18,20,21] Within our study, patients with pleomorphic adenoma had a mean age of 60 years and it mainly affected the parotid gland. However, in contrast to previous literature, we found no female predominance.[4,11,13,14] Following pleomorphic adenoma, the most common benign SGT was Warthin tumour, which had a predilection for males and NZ Europeans, and was found in patients with a mean age of 60 years, consistent with previous NZ and international literature.[7,11,18,22] Other benign neoplastic SGTs were uncommon, collectively comprising 5% of all those that were benign (15/284). For malignant SGTs we found that MEC was the most common tumour, followed by AdCC, which is consistent with previous literature.[8,11,23,24] However, in comparison to our literature review, within the Waikato Hospital population we found a low incidence of primary epithelial SGT, including AdCC, adenocarcinoma NOS, carcinoma ex pleomorphic adenoma, and acinic cell carcinoma.

Within our study population we found a high prevalence of malignancy, in particular metastatic SCC related to a high incidence of skin cancer metastasising to the parotid.[5,7,11,18] New Zealand has one of the highest rates of melanoma and non-melanoma skin cancer (NMSC) in the world, with an increasing prevalence with age in men, Caucasians, and people with high rates of cumulative sun exposure.[25,26] Forty-five per cent of all NMSCs occur in the head and neck, with 1%–3% metastasising to the parotid gland due to the parotid lymphatic group providing first echelon drainage for skin regions of high sun exposure, including the forehead, scalp, and midface.[26,27] Our research showed high rates of parotid SCC and melanoma occurring most frequently in patients in the seventh to eighth decades, with a male and NZ European predominance, consistent with NZ's melanoma and NMSC epidemiology. Our findings are also emulated in Australia, where there are high rates of melanoma and NMSC of the parotid gland (23%–32% of all tumours), with an increased incidence in Caucasian males.[28–30] The conclusion reached by Subramaniam et al[30] that 80% of parotid gland tumours are benign, may not apply in Australian tertiary referral settings, which demonstrate high rates of cutaneous malignant disease. We also found this in NZ.[17,31] This is significant for patient prognosis, as patients with metastatic parotid SCC have a five-year survival of 32.6%, and require parotidectomy and neck dissection with or without adjuvant therapy.[12,32]

Epidemiological studies of non-neoplastic salivary gland pathology are limited, with only one author presenting the epidemiology of sialadenitis in our literature review.[15] Defining the epidemiology of non-neoplastic salivary gland pathology is difficult, as entities such as mucoceles, sialadenitis and ranulas may be managed conservatively with no histological data collected, or may be managed outside specialist centres,[33] which would lead to the under-reporting of non-neoplastic salivary gland pathology. Previously, mucoceles were found to the be the most common non-neoplastic salivary gland pathology, followed by sialadenitis and ranulas, as demonstrated by our research.[14,16,34] We found few non-neoplastic lesions in the parotid gland, with a higher incidence in the minor salivary and submandibular glands. While the majority of sublingual pathologies were non-neoplastic in origin, mucoceles and ranulas occurred primarily in the third to fourth decade, with a slight male predominance, and were over-represented in the Māori population. Previous literature within NZ, has identified a high prevalence of ranulas in male and Māori/Pacific Island patients, potentially related to an increased incidence of Boutonnière deformity.[35–37] Sialadenitis occurred primarily in males, in the submandibular gland, and in NZ Europeans in their fifth decade of life, which is consistent with previous authors.[38,39]

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Conclusion

To our knowledge, our body of literature provides the first epidemiological study of salivary gland pathology in NZ, and an up-to-date review of the epidemiology of SGTs internationally over the last 10 years. Our results support previous findings that SGTs most commonly affect the parotid gland in the sixth decade of life, with pleomorphic adenoma being the most common type. We have provided one of few studies to present data on non-neoplastic salivary gland pathology, in which we identified high numbers of mucoceles and a predisposition for ranulas in Māori people. Consistent with pre-existing literature, MEC and AdCC were the most common malignant SGTs. However, in comparison to pre-existing literature we found high rates of metastatic SGTs in males and in the parotid gland, related to high rates of NMSC and melanoma skin cancer metastasising to the salivary glands. This research provides a greater understanding of differences in the global distribution of SGTs, and an updated review of recent research into their epidemiology.

Conflict of interest

The authors declare no competing interests.

Ethics statement/confirmation of patients permission

Ethics approval was obtained from the New Zealand Heath and Disability, Waikato District Health Board and Māori Research Committees. Patients' permission NA.

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