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Submandibular gland tumours: A clinicopathological review at the Chris Hani Baragwanath and Charlotte Maxeke Johannesburg academic hospital

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Submandibular Gland Tumours: A Clinicopathological review at the Chris Hani Baragwanath and Charlotte Maxeke Johannesburg Academic Hospital

Dr Yahya Atiya

A Research Report (Neus7009) submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirement for the degree of Master of Medicine in Otorhinolaryngology (MFOSENTS60)

Johannesburg 2014

Dedication

To my beautiful wife Ayesha Bibi,

for her undying love, support, patience,

understanding and exceptional encouragement

My parents, Goolam and Fatima

for their encouragement and support.

Without your sacrifice, none of this would ever have been possible.

And my Grandparents

Gone, but never forgotten.

Declaration

Candidate

This dissertation is my original work and has not been presented for a degree, or other academic award, in any other University or institution of higher learning.

Signed _____

Dr Yahya Atiya 12 May 2014

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This dissertation is submitted as a final copy with my approval as the University's Academic and Clinical Supervisor.

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- Professor MJ Hale, Academic Head of the Department of Anatomical Pathology, for allowing me access to the NHLS database.
- The numerous colleagues and peers who proof-read the manuscript and for providing constructive criticism.
- Last, but never least, to my family, for their endearing love, and their unwavering support and encouragement.

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List of Abbreviations

CEO – Chief Executive Officer

CHBAH – Chris Hani Baragwanath Academic Hospital

CMJAH – Charlotte Maxeke Johannesburg Academic Hospital

CT – Computerised Tomography

FNAB – Fine Needle Aspiration Biopsy

HIV – Human Immuno-deficiency Virus

HREC – Human Rights & Ethics Committee

MALT – Mucosa Associated Lymphoid Tissue

MRI – Magnetic Resonance Imaging

NHLS – National Health Laboratory Services

PET – Positron Emission Tomography

SD – Standard Deviation

WHO – World Health Organisation

WRT – with regards to

Abstract

Background: Reports relating to Submandibular gland tumours are sparsely reported in the literature. There are some reports of different patterns of tumour types in black/negroid patients, as compared to Caucasian patients[1,2,11].

Aim: To provide an audit of the histopathological types and the clinical presentations of submandibular gland tumours at our two academic hospitals.

Method: An analytical cross sectional study using retrospective clinical data from in-patient ward registers, patient's hospital records, operating room/theatre registers and the NHLS databases. The study was conducted in the ENT units at the Chris Hani Baragwanath Academic Hospital and the Charlotte Maxeke Johannesburg Academic Hospital, over a chosen period of 7 years from January 2005 to December 2011.

All patients who had a submandibular gland excision by members of the ENT department at the two hospitals were included. A total of 61 patient records were examined, of which 26 met the inclusion criteria. Data collected included age, gender, race and histological diagnosis.

Data was analysed using standard statistical methods.

Results: Twenty six patients were included in this study, comprising 46% females and 54% males. The ages ranged from 22 to 65 years, with a mean of 42.5 years – the majority being in the 22-40 years age group. There was no statistical difference in the age of males and females (p=0.29), nor in black vs. white patients (p=0.29).

Benign disease was found in 65.4% of patients, while 34.6% had malignancy. Black patients had a higher ratio of benign disease than white patients, and black males were more likely to have benign disease (83.33%) than black females (50%). However, there was no statistical difference in the ratio of benign to malignant tumours between blacks and whites.

Histopathologically, pleomorphic adenoma was the most common benign tumour (82%), while adenoid cystic carcinoma was the most common epithelial malignancy (22%). There was a high incidence of lymphoma (56% of patients) in the malignant group.

Local pain (p=0.03) and peripheral neurological deficit (p=0.05) was found to be significantly associated with malignancy.

CONCLUSION: The rate of malignancy in Black patients was found to be lower than that reported in the Western literature, which is in keeping with other studies in non-Caucasian (Black, Asian and Hispanic) populations[1,2,9,11]. Additionally, Black patients presented at a younger age. Pain and local/peripheral neurological involvement were clinical indicators of malignant disease.

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Chapter 1 - Introduction

Clinical studies relating to the submandibular salivary gland are less common compared to that of the parotid gland. The latter receives more attention due to the fact that Parotid gland lesions are far more common, and that surgery of the gland is technically more challenging due to the presence of the facial nerve within the gland substance, generating more technical interest and study[1].

In Africa, only 3 studies have been done exclusively on submandibular gland pathology, and only one of those is from South Africa[1,2], describing the spectrum of disease found in the submandibular glands.

1.1 Gross Anatomy

The human aero-digestive tract comprises 6 major and between 500 to 1000 minor salivary glands, scattered throughout the aero-digestive tract. The submandibular salivary gland is the second largest salivary gland after the parotid gland, situated in the submandibular triangles of the neck. It is bordered by the anterior and posterior bellies of the digastric muscle inferiorly and infero-laterally, and the mandible superiorly. The submandibular salivary glands are paired structures, approximately 20 grams each in weight, and each consisting of a superficial or lateral part, and a deep part or lobe, which is in anatomical relation to the mylohyoid muscle. Each gland has a large single duct, approximately 5cm long, which courses along the floor of the mouth to open anteriorly on either side of the lingual frenulum.

Its arterial supply is from the Lingual branch of the lingual-facial trunk – often the 3rd branch of the external carotid artery. Similarly named veins accompany the artery.

Secretomotor nerve fibres are conveyed from the facial nerve via the chorda tympani nerve, along with the somatic sensory lingual nerve, and synapsing in the submandibular ganglion, from which afferent parasympathetic fibres run to the gland with the lingual vasculature. Sympathetic fibres accompany the arteries, arising from the superior cervical ganglion. Lymphatic drainage is to the upper deep cervical nodes, particularly levels I, II and III[3,4].

A number of important peripheral neural structures are noted to lie in close proximity to the gland. Of particular importance are the Submandibular Ganglion, the somatic sensory lingual nerve, the motor Hypoglossal Nerve and the motor Marginal Mandibular Marginal Mandibular Nerve – the second lowest branch of the peripheral facial nerve.

1.2 Micro Anatomy (Histology)

Salivary glands consist of acini, which are composed of two types of cells: serous or mucous. This basic anatomical structure is known as the Salivary Gland Unit (figure 1). The ratio of these cells differs in each gland; the submandibular gland comprises almost equal proportions of each. The ducts consist of cuboidal to columnar epithelial cells. Both of these structures are supported by myoepithelial cells, which are the innervated contractile structures. The submandibular gland has no intraglandular lymph nodes, but lymph nodes are present in the fibrofatty tissue over its capsule[3].

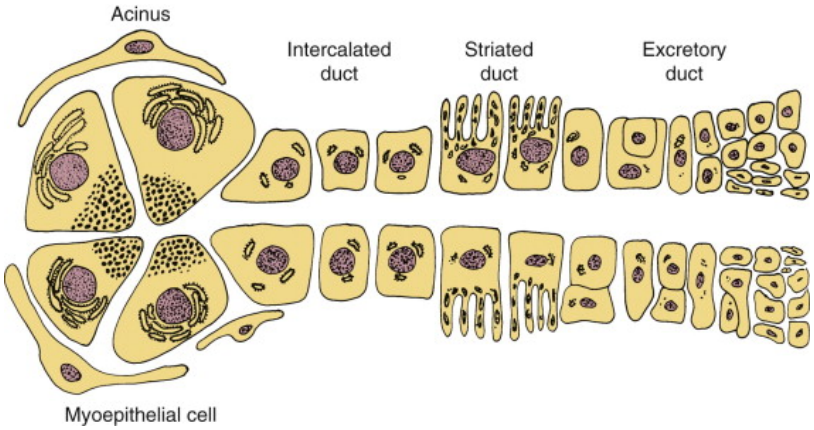

Figure 1 The Salivary Gland Unit (Reproduced with permission from Elluru RG, Lacey J, Rogers J et al. Salivary Glands. In: Flint P, Haughey B, Lund V et al, editors. Cummings Otolaryngology Head & Neck Surgery. Fifth ed. Philadelphia: Mosby; 2010. p. 1133-1199)

Chapter 2 - Literature Review

2.1 Epidemiology

The majority of swellings in the submandibular gland are due to mechanical obstructions of the duct with consequent inflammation[6]. Worldwide, salivary gland neoplasms are rare, accounting for less than 3% of head and neck neoplasms[1,2,5-7]. The parotid gland is affected most frequently, accounting for 64-80% of cases, followed by the submandibular gland, accounting for 7-15% of cases[5,7,8]. Tumours of the submandibular salivary gland account for less than 1% of all head and neck neoplasms[6]. Males and females are equally affected by submandibular gland neoplasms, with the peak incidence in the fifth to sixth decades of life[6].

2.2 Clinico-pathology

Historically, it is believed that the majority (up to 80%) of neoplasms arising in the submandibular gland are malignant[6-8]. However, this figure is based on reports in the Western literature. The rates from around the world seem to vary. In Asian and Black populations, the incidence of malignancy is as low as 10%[2,8,9].

Spiro reported the largest case series of salivary gland tumours in 1986, at Memorial Sloane Kettering Cancer Centre, New York. He reviewed 2807 patients, of which 235 had neoplasia in the submandibular gland. In his series, 43% of these tumours were malignant. Further, most neoplasia occurred in the parotid gland (70%), and only 8% in the submandibular gland[10].

In a Ugandan series, Vuhahula (2004) reported a 33% incidence of neoplasia in the submandibular gland, and only 22% of those were malignant[11]. In the only published

South African study, Schoeman and Clifford (2007) confirm this low incidence in Black patients, with a malignancy rate of 10%[2]. They analysed 127 patients who had resection of salivary gland tumours, of whom 126 were black patients. Of these, 30 tumours were in the submandibular gland, and only three were malignant. There were no white patients with submandibular tumours. Further, similar findings were published in Mexican subjects, with 14% malignancy[8]. A Nigerian study is at odds with these findings, and cites a malignancy rate of 52.8%[1].

To date, no reason has been proposed for this heterogeneity in tumour distribution, nor for the apparent racial differences[6]. Further, there is no study on African Americans, reflecting whether the incidence is equally low in that population.

The commonest benign tumour of the submandibular gland is the Pleomorphic Adenoma. Other rare benign tumours include Warthin's Tumour, oncocytoma and lymphoepithelial lesions[1,8,10-13]. Amongst malignancies, adenoid cystic carcinoma is the most commonly reported[1,8,11-13]. Other histologic types include mucoepidermoid, squamous cell carcinoma and carcinoma ex-pleomorphic adenoma.

The lymphoid tissue of the submandibular gland is considered to be part of Mucosa-Associated Lymphoid Tissue (MALT), and as such may give rise to lymphoma.[1,6,11]. Further, lymph nodes in the submandibular triangle may be enlarged due to lymphoma, without the gland being affected[1].

2.3 Classification

Salivary gland tumours are classified according to the World Health Organization Histological Classification of Salivary Gland Tumours, first published in 1972, and revised in 1992 and again in 2005. This allows uniformity, and easy comparison of

diagnoses. This classification divides neoplasms into four broad categories, with distinct entities in each[3,12,14,15] (Table 1). The incidence of particular types depends on the site. Polymorphous low-grade adenocarcinoma, for example, almost never affects the major glands[3].

Malignant epithelial tumours	Benign epithelial tumours
Acinic cell carcinoma	Pleomorphic adenoma
Mucoepidermoid carcinoma	Myoepithelioma
Adenoid cystic carcinoma	Basal cell adenoma
Polymorphous low-grade adenocarcinoma	Warthin's tumour
Epithelial–myoepithelial carcinoma	Oncocytoma
Clear cell carcinoma, not otherwise specified	Canalicular adenoma
Basal cell adenocarcinoma	Sebaceous adenoma
Sebaceous carcinoma	Lymphadenoma
Sebaceous lymphadenocarcinoma	Sebaceous
Cystadenocarcinoma	Non-sebaceous
Low-grade cribriform cystadenocarcinoma	Ductal papillomas
Mucinous adenocarcinoma	Inverted ductal papilloma
Oncocytic carcinoma	Intra-ductal papilloma
Salivary duct carcinoma	Sialadenoma papilliferum
Adenocarcinoma, not otherwise specified	Cystadenoma
Myoepithelial carcinoma	**Soft tissue tumours**
Carcinoma ex pleomorphic adenoma	Haemangioma
Carcinosarcoma	**Hematolymphoid tumours**
Metastasizing pleomorphic adenoma	Hodgkin's lymphoma
Squamous cell carcinoma	Diffuse large B-cell lymphoma
Small cell carcinoma	Extranodal marginal zone B-cell lymphoma
Large cell carcinoma	**Secondary tumours**
Lymphoepithelial carcinoma	
Sialoblastoma	

Table 1 Histological Classification of Tumours of the Salivary Glands. Reproduced with permission from Eveson, J.W. 2011, "Salivary tumours", *Periodontology 2000*, vol. 57, no. 1, pp. 150-159.

2.4 Clinical Evaluation

Submandibular tumours most commonly present as a painless mass below the mandible, regardless of whether they are benign or malignant[1,10,11,13]. Pain is a late symptom, but should alert to possible malignancy, since it very rarely occurs in benign tumours[1,5,6,9-11]. Patients presenting with advanced disease may present with pain, ulceration of the floor of the mouth, regional lymph node enlargement or palsies of

the major nerves in the region, namely the marginal mandibular branch of the facial nerve, lingual nerve and hypoglossal nerve[1,10,11]. Tethering of the overlying skin or to the mandible is also an indicator of malignancy[3].

History and clinical examination are supplemented by imaging studies, including computerised (CT) and magnetic resonance (MRI) tomography. However, radiology fails to distinguish between benign and malignant neoplasms, unless there is invasion of the surrounding tissues[6]. Further, there are few studies which evaluate the usefulness of CT in submandibular disease[9]. PET scans are not widely applied to salivary tumours, as they are expensive, and do not provide the anatomical detail that CT or MRI do[3].

Fine-Needle Aspiration Biopsy (FNAB) is recognised as an accurate technique in the diagnosis of salivary gland neoplasms. Sensitivity ranges from 85.5% to 99%, while specificity is reported at 96.3% to 100%. However, these ranges are highly operator dependant. The most important factor is adequate sampling; this may be improved by using ultrasound guidance[4,12]. Inadequate sampling can result in false-negative rates as high as 48%[12].

FNAB is safe and simple to perform[4,12]. However, its use has been contested, particularly whether it would change the management of the patient. In one study, FNAB changed the clinical approach in 35% of patients. These changes included avoiding surgery for lymphoma, and adopting a more conservative approach for benign masses or for high-risk patients. The risk of tumour seeding has been shown to be negligible[3]. The general consensus is that FNAB should be used as an adjunct to clinical assessment, but the decision for surgery should be made holistically[3,9,12].

2.5 Treatment

Benign tumours are generally treated by surgical excision of the submandibular gland. Care should be taken particularly in patients with pleomorphic adenoma, as capsule rupture could result in recurrence of the tumour[12]. Malignant tumours may be treated by excision of the gland in early disease. Depending on expertise available, some centres undertake excision in regionally advanced disease as well[6].

The decision to do a neck dissection depends on the lymph node status. An in-depth discussion on treatment modalities for metastatic disease is beyond the scope of this dissertation.

Chapter 3 – Materials & Methods

3.1 Hypothesis

The rate of submandibular gland malignancy amongst patients at Chris Hani Baragwanath and Charlotte Maxeke Johannesburg Academic Hospitals is not as high as reported in the Western Literature, in keeping with other studies in Black patients[1,2,11].

3.2 Aims and Objectives

- To audit the histopathology of submandibular gland tumours seen in the Department of Otorhinolaryngology at Chris Hani Baragwanath and Charlotte Maxeke Johannesburg Academic Hospitals.
- To describe the clinical presentations of submandibular gland tumours at Chris Hani Baragwanath and Charlotte Maxeke Johannesburg Academic Hospitals.

3.3 Study Design

This study is a retrospective clinical audit.

3.4 Study Location

The study was conducted in the clinical units of Otorhinolaryngology at the Chris Hani Baragwanath Academic Hospital in Soweto, Johannesburg, and at the Charlotte Maxeke Johannesburg Academic Hospital, South Africa. Both hospitals are tertiary level teaching hospitals affiliated to the University of the Witwatersrand.

3.5 Study Period

The study extended from 1 January 2005 up to 31 December 2011 (7 years).

3.6 Study Population

The study included all patients who had submandibular gland surgery with subsequent histological analysis.

3.6.1 Inclusion Criteria

- All patients with submandibular gland neoplasms, who had been treated surgically, and for whom histopathological results were available on the NHLS database.
- Any patient who had only an open biopsy of the submandibular gland performed in theatre.
- Patients must have been attended to by members of the Department of Otorhinolaryngology.
- Patients over 18 years.

3.6.2 Exclusion Criteria

- Patients under 18 years of age. The spectrum of salivary gland disease is markedly different in children and young adults, in whom inflammatory disorders predominate[3]. They were thus excluded to avoid a selection bias.
- Patients with non-neoplastic disease. These patients formed part of the initial data collection, but were excluded if the histology report showed non-neoplastic disease.

- Patients who had submandibular masses excised that were not part of the submandibular gland, and thus did not have a submandibular gland excision.
- Patients who had needle biopsies performed in the out-patient clinic (difficult to trace patient data).
- Patients who had submandibular resection as part of a neck dissection for other Head and Neck malignancies.
- Patients who had surgery performed by other clinical departments.

3.7 Data Collection

Patients were identified from two sources:

- ENT Operating Theatre register
- ENT Ward Admissions register

The operating theatre register was used as a primary reference to identify eligible patients.

The ward admission register was used as a secondary reference to identify patients whose theatre record was unclear or lacking detail (eg incorrectly spelt names, missing or partial hospital numbers).

All patients who were clearly identified from the theatre register were recorded as part of the initial sample population. This information was then used to interrogate the database of the National Health Laboratory Services (NHLS), and all findings were recorded into one of the following categories:

- Histology report, in which a histological analysis was performed on the specimen.

- No result, in which no result was found on the database.
- Incomplete or incorrect information, in which insufficient information was available to perform the interrogation.

Patients identified exclusively from the secondary reference were cross checked against their recorded laboratory findings and were included in the study population. If these patients lacked sufficient information, they were not included in the study sample.

The following data was recorded for each patient (Appendix A):

- Hospital registration number
- Age
- Sex
- Race
- Presenting complaint
- Clinical findings
- Date of surgery
- Histological result

All data was recorded electronically using Microsoft Access and Microsoft Excel.

3.8 Data Analysis and Presentation

The following software was used for data manipulation, analysis and presentation:

- Microsoft Access 2013 for data storage, retrieval and selection.
- Microsoft Excel 2013 for descriptive analysis, summary statistics and comparison of sample means.

- Standard statistical methods were used. Student's *t* test was used to analyse continuous data and the Chi Square (X^2) test for ordinal data. Fischer's Exact Test was used for ordinal data where actual counts were less than five. A probability (p) value of less than (or equal to) 0.05 was regarded as significant.
- Microsoft Word 2013 for final documentation and presentation.

3.9 Ethics Committee Approval

As this is a retrospective clinical audit, no patient consent was required. The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (Clearance Number M120286 – Appendix B).

Signed written approvals were obtained from the CEO's of the respective hospitals, as well as the Head of the Department of Anatomical Pathology, to access histology results (Appendix C).

All data was confidential and stored on a password-protected database, to which the principle researcher alone had access.

3.10 Funding

No funding was required for this study. The minimal costs incurred were covered by the University of the Witwatersrand's Department of Otorhinolaryngology study budget, or personally financed.

3.11 Potential Limitations

- Cross-sectional study
- Inadequate records
- Inadequate patient numbers
- Not all patients with submandibular disease will be accounted for, since not all have excision as part of their management. Also, not all patients are attended to by members of the Department of Otorhinolaryngology (some are seen by members of General Surgery, for example). This could cause a selection bias.

Chapter 4 – Results

4.1 Study Sample

A total of 61 patients were identified who had had submandibular gland excision. Of these, 29 patients were excluded because they had non-neoplastic disease, three patients were excluded because they were younger than 18 years of age, and 3 were excluded because there were no histological results available. Thus, a total of 26 patients were included in the study sample

4.2 Demographic data

4.2.1 Age

The age ranged from 22 to 65 years, with a mean age (SD) at surgery of 42.5 years (14.5). The majority (53.85%, n=14) of patients were aged 21-40 years. Of these, 30.8% (n=8) were male and 23.1%% (n=6) were female. Although the average male age was 45.3 and females were 39.2, a t-test revealed no significant difference in the age of males and females (p=0.29). Furthermore, the mean age of black patients (40.78 year) was not significantly different from that of white patients (51.75 years), p=0.29. Additionally, there was no significant difference between the mean age of patients with benign (40.29 years) versus malignant disease (46.56 years), p=0.29.

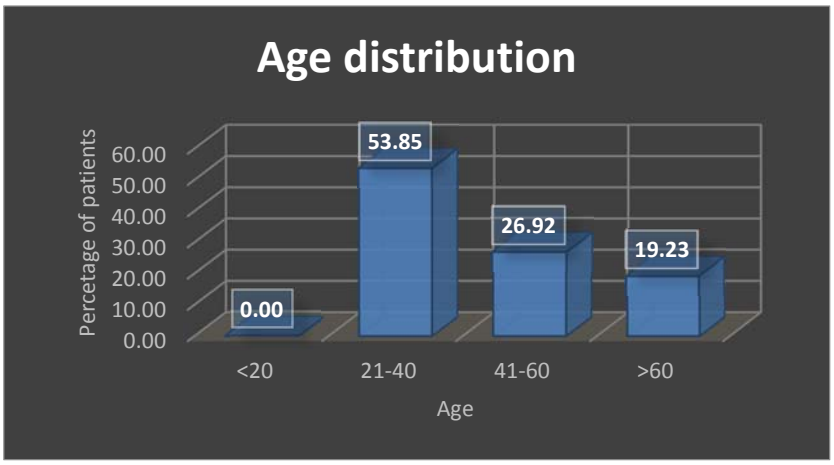

Figure 2 Age distribution

4.2.2 GENDER

Females represent 46% (n=12) and males 54% (n=14) of the sample. The male:female ratio is thus 1.17:1.

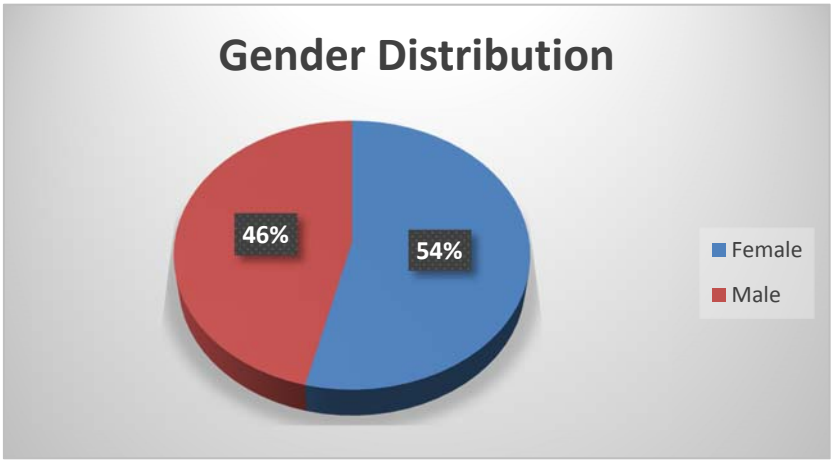

Figure 3 Gender distribution

4.2.3 Race

Twenty-two patients (84.6%) were black; the remainder (n=6) were white. No other racial denominations were represented. Of the black patients, 12 were male, representing 54.6%, and 10 were female (45.4%). Among white patients, 2 patients were male, and 2 female, representing 50% each.

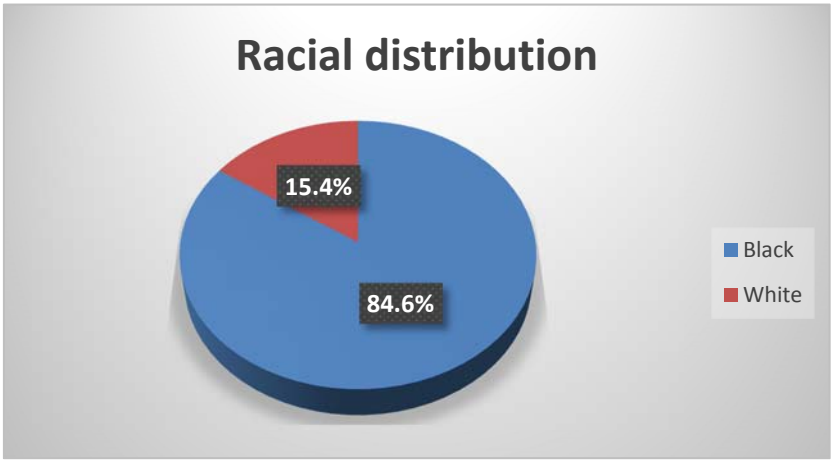

Figure 4 Racial distribution

4.2.4 Distribution across hospitals

Most patients were found at CMJAH, representing 62% (n=16). The remainder were at CHBH (38%, n=10).

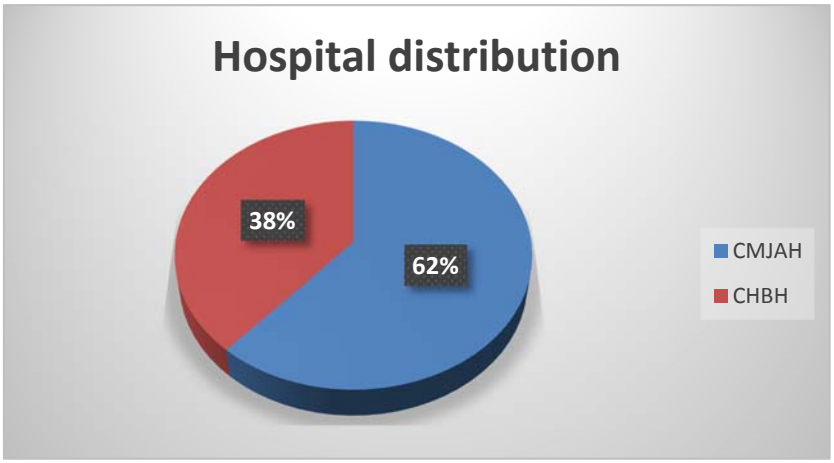

Figure 5 Distribution across hospitals

4.2.5 DISTRIBUTION OVER TIME

There was no significant difference in the number of patients presenting in different years. On average, 3.7 patients per year were operated on for neoplasia, ranging from 2 to 5 per year.

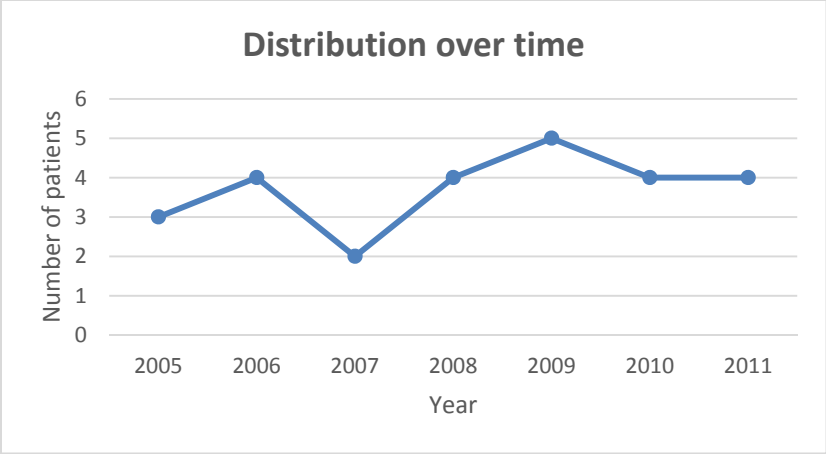

Figure 6 Distribution over time

Variables	Males	Females
Age Groups		
<20	0	0
20-40	8 (30.8%)	6 (23.1%)
41-60	2 (7.7%)	5 (19.2%)
>60	4 (15.4%)	1(3.8%)
Hospitals		
CMJAH	6 (23.1%)	10 (38.5%)
CHBH	8 (30.8%)	2 (7.7%)
Yearly Statistics		
2005	0	3 (25.0%)
2006	1 (7.1%)	3 (25.0%)
2007	2 (14.3%)	0
2008	1 (7.1%)	3 (25.0%)
2009	4 (28.6%)	1 (8.3%)
2010	4 (28.6%)	0
2011	2 (14.3%)	2 (16.7%)

Table 2 Summary - Demographics by gender

4.2.6 HISTOLOGIC CHARACTERISTICS

In total, 17 patients had benign disease, representing 65.4%, while the remaining 9 patients (34.6%) had malignant disease.

Out of the total of 17 patients with benign tumours, benign disease was present in 15 black patients (88.2%), and 2 white patients (11.8%). Proportionally, this represents 68.18% of black patients (n=15) and 50% of white patients (n=2). In black patients, 10 were male and 5 were female. White patients were represented equally across gender (1 male and 1 female). Thus, in total, 6 females (50% of total number of females) and 11 males (78.57% of total number of males) had benign disease.

In patients with malignant disease, 7 were black (77.8%), while 2 were white (22.2%). Proportionally, blacks with malignant disease account for 31.8% (n=7), and whites 50% (n=2). Of the 7 black patients, 2 were male and 5 were female. In white patients, again there was 1 male and 1 female. In total, 3 males (21.43% of total number of males) and 6 females (50% of total number of females) had malignant disease.

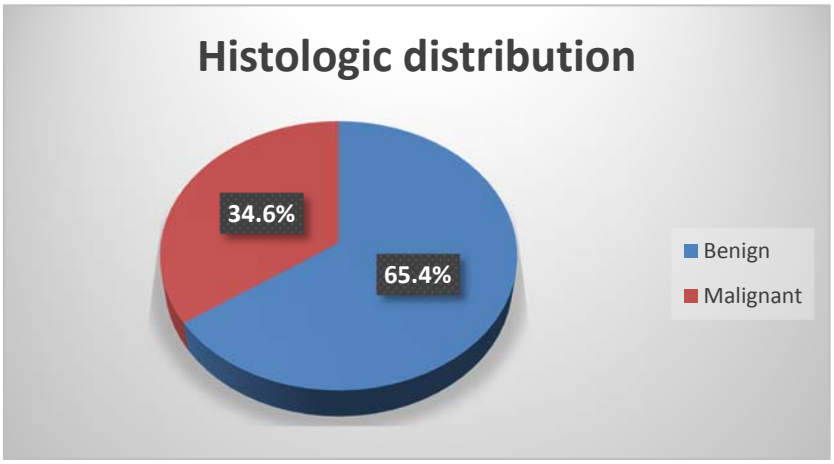

Figure 7 Histologic distribution

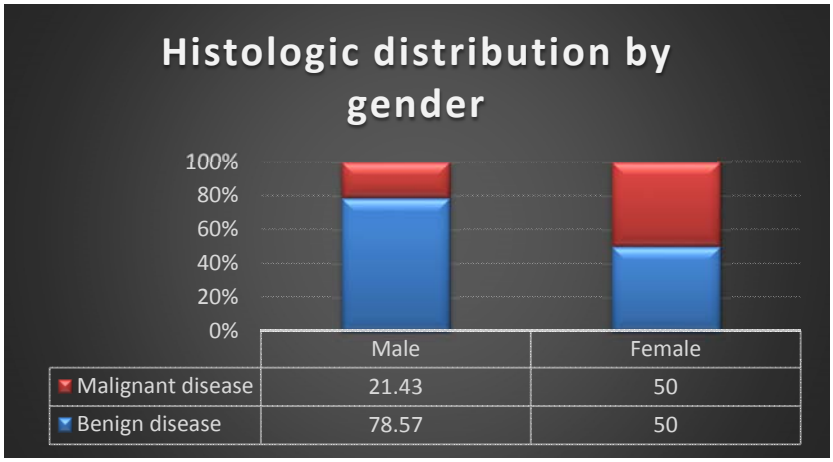

Figure 8 Histologic distribution by gender

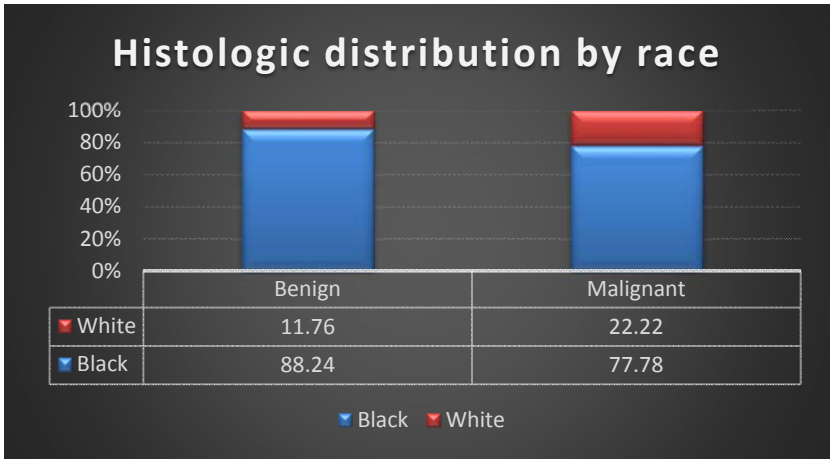

Figure 9 Histologic distribution by race

Comparing the ratio of benign to malignant tumours between blacks and whites, revealed no statistical significance when using Fisher's Exact test (p=0.59).

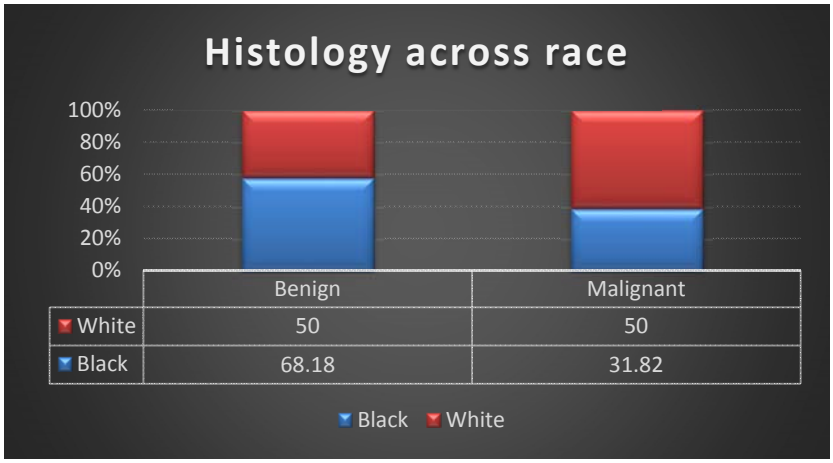

Figure 10 Proportional histology by race

4.2.6.1 Distribution of benign tumours

Of the total of 17 benign tumours, the majority (82.4%) were pleomorphic adenomas. The other 3 were lipomas. No other histological types were encountered.

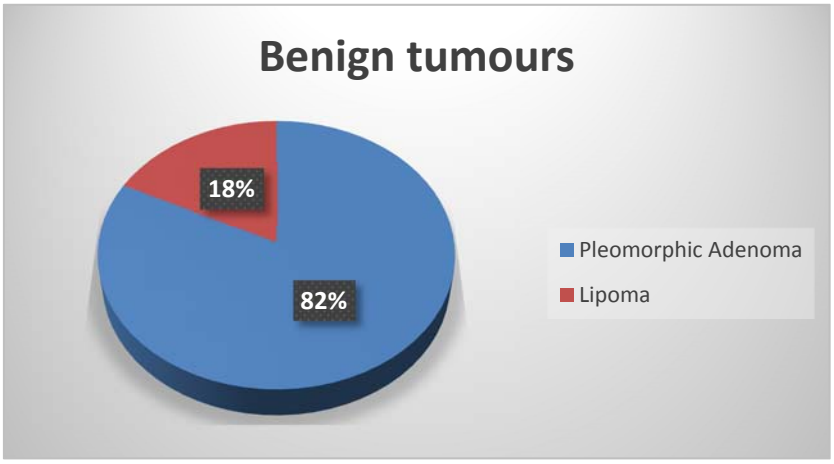

Figure 11 Benign tumours

4.2.6.2 Distribution of malignant tumours

Lymphomas were the most commonly found malignant tumours (55.6%). The most common epithelial tumour was Adenoid Cystic carcinoma (22.2%). There was one each of Squamous Cell carcinoma and Carcinoma ex Pleomorph. No other histological types were found.

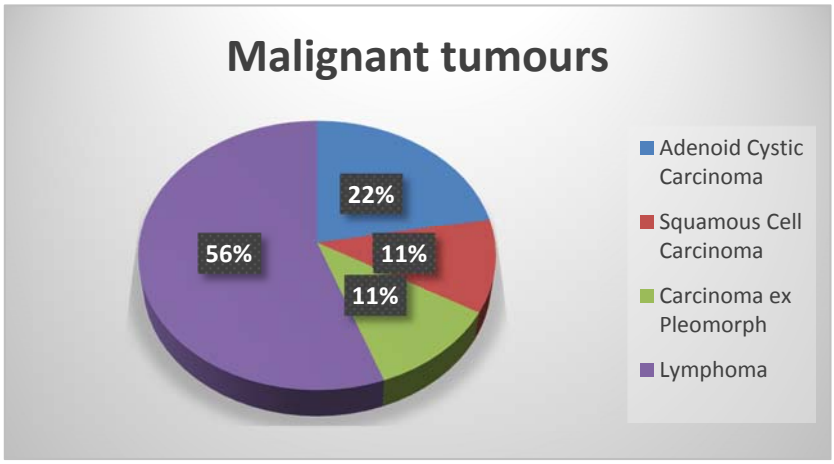

Figure 12 Malignant tumours

4.2.7 CLINICAL SIGNS AND SYMPTOMS

4.2.7.1 Pain

Pain was the presenting feature in 7 patients (27%). Of those, only 2 had benign disease; the remainder had malignancies. This difference was found to be statistically significant, using Fisher's exact test (p=0.03)

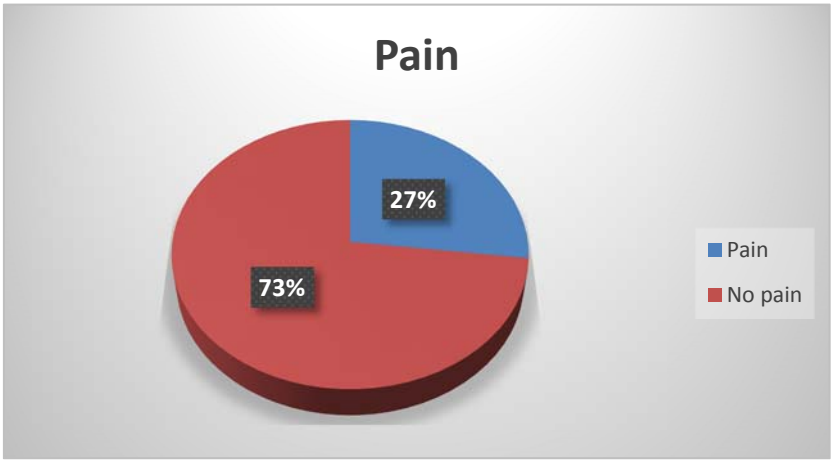

Figure 13 Pain as a presenting feature

4.2.7.2 Tenderness

Only 3 patients (12%) had tumours which were tender on palpation; 1 had benign disease and 2 had malignant disease. Tenderness was not found to be statistically associated with malignancy (p=0.27).

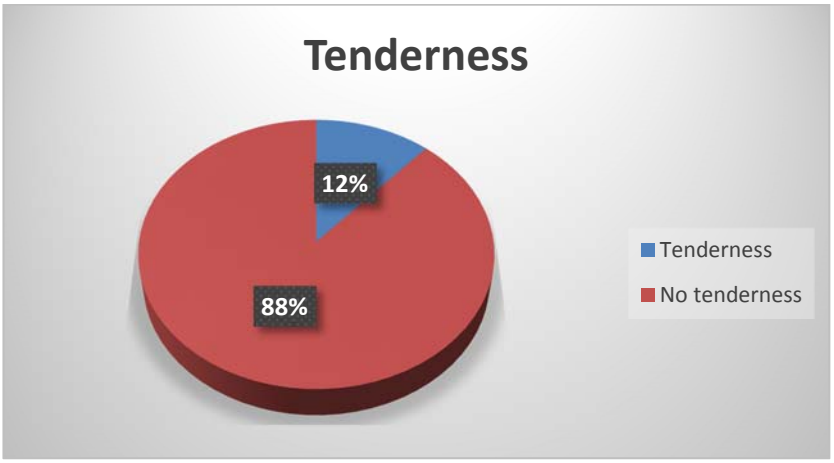

Figure 14 Incidence of tenderness

4.2.7.3 Marginal Mandibular Nerve weakness

Only 3 patients had clinically obvious marginal mandibular nerve weakness (evidenced by drooping of the corner of the mouth), but all had malignant disease. However, this was found to be statistically significant (p=0.05).

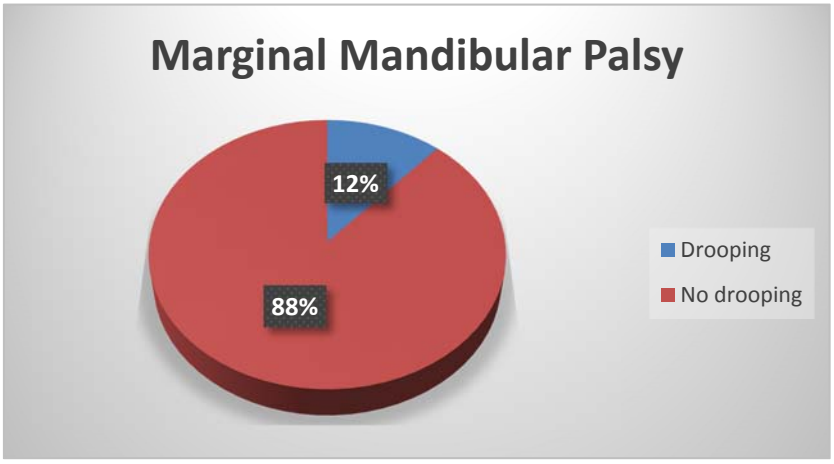

Figure 15 Marginal mandibular nerve palsy

4.2.7.4 Other clinical signs & symptoms

No patients had hypoglossal nerve palsies (indicated by weakness of the tongue), skin tethering, fixation to the mandible or ulceration of the skin.

Clinical signs	n	%
Pain		
Absent	19	73.1
Present	7	26.9
Tenderness		
Absent	23	88.5
Present	3	11.5
Marginal mandibular weakness		
Absent	23	88.5
Present	3	11.5

Table 3 Summary of clinical signs

Signs	Benign	Malignant	P value
No pain	15	4	**0.03**
Pain	2	5	
No facial weakness	17	6	**0.05**
Facial weakness	0	3	
No tenderness	16	7	**0.27**
Tenderness	1	2	

Table 4 Difference between benign & malignant tumours wrt clinical signs

Chapter 5 – Discussion

The aim of this project was two-fold:

1. To audit the clinicopathology of submandibular gland tumours
2. To assess whether the malignancy rate in a South Africa population is comparable to results elsewhere in Africa.

5.1 Limitations

It is of note that this is a retrospective data collection based on a defined set of criteria. The data was obtained from old – not so well kept – patient records, the consistency and quality of which varied considerably.

The study was conducted at two of the largest academic hospitals in South Africa, namely Chris Hani Baragwanath Hospital, and Charlotte Maxeke Johannesburg Academic Hospital. Patient numbers in these two hospitals are enormous, and accessing records proved challenging.

In addition, submandibular gland tumours are not common[6]. Thus, obtaining statistically significant patient numbers for study was challenging. Nonetheless, the data presented compares favourably with other studies in terms of sample size[1,5,6,8]. Due to this small sample size, however, conclusive analysis is not possible.

Another limitation in collection of data was that only records from the Department of Otorhinolaryngology were accessed. Submandibular tumours are, however, also attended to by other disciplines, most notably Maxillofacial and General Surgery. Additionally, not all patients with tumours have a surgical excision as treatment. Therefore, the true incidence may not be reflected in this study.

Lastly, this study was only conducted at two hospitals, serving a very similar population group. The results may not extend to other populations or regions.

5.2 Demographic Data

Although there were no statistical significance in the demographic data reviewed, it is worthwhile to compare our findings to those of other studies.

5.2.1 Age

The mean age of patients presenting with any submandibular tumour was 42.5 years. This compares well with other studies in Africa, which show a similar trend[1,2,11]. A study amongst Asian patients also showed similar findings[9]. However, in Western literature, the mean age is markedly higher[6-8,10].

Most tumours occurred in the age group 22 – 40 years. This contrasts markedly with the international literature which quotes a peak incidence at 40 – 60 years[10,12].

The data therefore suggests that submandibular tumours occur at younger ages in non-Caucasian races.

There was no difference in the mean ages of males vs. females, nor of patients with benign vs. malignant disease. Our findings concur with that of the Pretoria study[2].

5.2.2 Sex

Overall, males and females were almost equally represented, with a ratio of 1:1.17. This is in keeping with some studies, which show no difference in the ratio of males to females[1,2,6,12]. However, other studies have shown a higher incidence in females[8,11], as high as 3:1 in one study[5]. It should be noted that certain tumour types, particularly Warthin's Tumour, have a marked sex predilection, although none of our patients presented with this entity.

Analysis of the data gathered, especially with regards to the ratio of males to females and with regard to tumour behaviour i.e. benign vs. malignant in different race groups, revealed that, in black patients, males were more likely to have benign disease than females, with a ratio of 2:1. The incidence of malignant disease was higher in females in the ratio 2.5:1. These findings are comparable with other studies[5,8].

5.2.3 Race

There are no studies which specifically examine differences between races. In our study, the majority of patients were black patients. Due to the limited number of patients, no further statistical analysis was possible in terms of clinical presentation or tumour types. However, there was no statistical difference in the ages of black compared to white patients.

5.2.4 Presenting Hospital

Most patients presented at CMJAH. The reasons for this are not clear, but may include better primary facility referral, and patient education.

There was also no difference in the number of patients from year to year, over the time period under study.

5.3 Histologic characteristics

Of the total of 26 patients, 17 patients (65.4%) had benign tumours, and 9 (34.5%) had malignant tumours. Overall, this is a striking contrast to the commonly quoted rates of malignancy in the general literature, of up to 80%[1,6,10,12]. When account is taken of race, this increases to 68.2% of black patients having benign disease.

Interestingly, although there were only 4 white patients, the ratio follows that of Western literature (50% malignancy).

Other African studies have also found that the rate of malignancy is markedly lower in black patients[2,11].

The difference in malignancy rate between blacks and whites was not found to be statistically significant, however.

5.3.1 Benign tumours

The majority of benign tumours were pleomorphic adenomas. This is consistent with all studies, both African and western[1,2,5,8,11.] No other histological subtypes were found. This is probably due to the low number of patients in the study, but the rarity of Warthin's tumour in black patients has been noted previously[11].

Three patients had lipomas. Although primary lipoma of the submandibular gland has been described[16], it is exceedingly rare. It is more likely that these patients had a lipoma of the peri-glandular soft tissues, which is abundant in fat, which was excised together with the gland.

5.3.2 Malignant tumours

The dominant malignant disease / tumour – found mostly in females – was the Lymphoma. Lymphomas commonly occur in the lymphatic tissues surrounding the gland, but have also been described as primarily involving the submandibular gland[17].

The commonest epithelial malignancy encountered was adenoid cystic carcinoma. Several other studies have shown this trend[1,5,6,13]. However, Becerill-Ramírez et al reported adenocarcinoma and squamous cell carcinoma as the most common. They

do, however, acknowledge that a limitation of that study was very low patient numbers (22 patients over 10 years)[8]. Studies in Africa have shown a similar pattern[2,11].

5.4 Clinical signs and symptoms

5.4.1 Pain and tenderness

Most patients did not present complaining of pain. However, when pain was present, it was strongly associated with malignant tumours. Most studies confirm that the presence of pain is a sinister feature[1,10,12,13,18].

Tenderness was present in only 3 patients. We did not find a significant difference between benign and malignant tumours, although most reports indicate that tenderness is often associated with malignancy.

5.4.2 Neurological sequaelae

Weakness of the marginal mandibular nerve was present in 3 patients, all of whom had malignant disease. Thus, neurological involvement is a strong indicator of malignancy. This is in keeping with other studies[1,6,13].

Although none of our patients presented with it, weakness of the hypoglossal and lingual nerves has also been reported[6,12,13].

5.4.3 Other symptoms

Fixation to skin or the mandible, and ulceration of the skin has been reported as indicating malignancy[1]. No patients in our series had these features.

5.5 Summary

The data presented in this study confirms our hypothesis, that black patients have a lower rate of submandibular gland malignancy than is reported in the literature. This is in keeping with other studies in Africa.

Furthermore, tumours in black patients tend to occur in lower age groups. This is particularly true of malignant tumours.

Pleomorphic adenoma and adenoid cystic carcinoma were the commonest epithelial benign and malignant tumours, respectively.

Pain and neurological weakness were confirmed as being associated with malignant tumours

5.6 Suggested research & recommendations

We did not examine the HIV status of the patients involved in this report. The reason for this was that in most cases the data was not available, and patients could not be contacted to give informed consent for testing.

In view of the high number of lymphomas that were presented, it would make sense to test the association of submandibular malignancy with HIV, since the latter is known to cause lymphoma, and is potentially oncogenic.

Although the number of patients we examined was limited, in view of other studies of a similar nature, we would recommend a higher index of suspicion in young black patients presenting with submandibular masses.

Lastly, a prospective, multicentre study with larger samples should be conducted to confirm our and other studies' findings.

Chapter 6 - References

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Appendix A

Study Number	
Age	<20
	21-40
	41-60
	>60
Gender	Male
	Female
Race	Black
	White
Clinical signs and symptoms	Swelling
	Drooping of the mouth
	Tongue weakness
	Tenderness
	Pain
	Skin ulceration
	Tethering to mandible or skin
Histological type	
Benign	Pleomorphic adenoma
	Warthin's tumour
	Oncocytoma
	Myoepithelial adenoma
	Basal cell adenoma
	Other (Specify)
Malignant	Muco-epidermoid carcinoma
	Adenoid cystic carcinoma
	Adenocarcinoma
	Epidermoid carcinoma
	Myoepithelial carcinoma
	Squamous cell carcinoma
	Lymphoma
	Other (Specify)

APPENDIX B

Ethics clearance certificate



UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Yahya Atiya

CLEARANCE CERTIFICATE	**M120286**
PROJECT	Submandibular Gland Tumours: A Clinico-pathological Review at the CH Baragwanath and CM Johannesburg Academic Hospitals
INVESTIGATORS	Dr Yahya Atiya.
DEPARTMENT	Division of Otorhinolaryngology
DATE CONSIDERED	24/02/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 24/02/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof PC Modi

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

Appendix C

Letters of permission:

1. Head of Department – Charlotte Maxeke Johannesburg Academic Hospital
2. Head of Department – Chris Hani Baragwanath Academic Hospital
3. Office of the CEO – Charlotte Maxeke Johannesburg Academic Hospital
4. Medical Advisory Committee – Chris Hani Baragwanath Hospital
5. Head of Department of Anatomical Pathology – National Health Laboratory Service, University of the Witwatersrand

Professor PC Modi

Department of Otorhinolaryngology

Charlotte Maxeke Johannesburg Academic Hospital

24/01/12

To whom it may concern

Permission is hereby granted to Dr Yahya Atiya in the Department of Otorhinolaryngology to conduct a research study entitled "Submandibular Gland Tumours: A clinico-pathological review at the Chris Hani Baragwanath and Charlotte Maxeke Johannesburg Academic Hospital".

Permission is further granted to access patient records and any data deemed pertinent to the study.

Yours sincerely

Prof PC modi 25/1/2012

HOD – Dept of ORL

Dr MRI Ahmed
HOD
Dept of Otorhinolaryngology
Chris Hani Baragwanath Hospital

To whom it may concern

Permission is hereby granted to Dr Yahya Atiya to conduct a research study entitled "Submandibular Gland Tumours: A Clinicopathological review at the Chris Hani Baragwanath and Charlotte Maxeke Johannesburg Academic Hospital" within the Department of Otorhinolaryngology at Chris Hani Baragwanath Hospital.

Permission is also granted to access any patient records and other data that may be required to conduct the study.

Yours faithfully

Dr MRI Ahmed
HOD – Dept of Otothinolaryngology
Chris Hani Baragwanath Hospital

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Office of the CEO
Enquiries:
Ms. L. Mngomezulu
(011): 488-3793
(011) 488-3753
29th January 2013

Dr. Yahya Atiya
Division of Otorhinolaryngology
CMJAH

Dear Dr. Atiya

RE: "Submandibular gland tumours: A clinic-pathological review at the Charlotte Maxeke Johannesburg Academic Hospital"

Permission is granted for you to conduct the above research as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic hospital will not in anyway incur or inherit costs as a result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall be observed at all times.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the Head of Department and Unit Manager or Sister in Charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Yours sincerely

Dr. T.E. Selebano
Chief Executive Officer

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 26 January 2012

(Revised title – originally approved 2011)

TITLE OF PROJECT: Submandibular gland tumours: A clinicopathological review at Chris Hani Baragwanath and Charlotte Maxeke Johannesburg Academic Hospitals

UNIVERSITY: Witwatersrand:

Principal Investigator: Dr Y Atiya

Department: ENT

Supervisor (If relevant): Professor PC Modi and Dr M Torres-Holmes

Permission Head Department (where research conducted):

Date of start of proposed study:

Date of completion of data collection:

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO /management of Chris Hani Baragwanath Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- the Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- the MAC will be informed of any serious adverse events as soon as they occur
- permission is granted for the duration of the Ethics Committee approval.

.....

Recommended

(On behalf of the MAC)

Date: 26 January 2012

.....

Dr P. Lingham
Dep CEO

Approved/Not Approved

Hospital Management

Date: 30 Jan 2012

NATIONAL HEALTH LABORATORY SERVICE
UNIVERSITY OF THE WITWATERSRAND – JOHANNESBURG

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Professor & Head: Division of Anatomical Pathology,

Human Research Ethics Committee (Medical)
University of the Witwatersrand
Johannesburg
20000

February 2, 2012

Re: Consent for access to NHLS database

This letter serves to confirm that the Department of Anatomical Pathology at the University of the Witwatersrand and NHLS is happy to assist Dr Atiya with his study entitled "Submandibular gland tumours: a clinicopathological review at the Chris Hani Baragwanath and Charlotte Maxeke Johannesburg Academic Hospital".

Assuring you of the Department of Anatomical Pathology's co-operation in this and future research projects.

With best wishes.

Yours sincerely,

Professor MJ Hale
Head: Department of Anatomical Pathology

2nd February 2012.
Date