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The rate of submandibular gland involvement in patients who underwent neck dissections for oral cavity squamous cell carcinoma at Chris Hani Baragwanath Academic Hospital.

DR MOHAMMED NATHIE

A research report (NUES7009) submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirement for the degree of Masters of Medicine in Otorhinolaryngology (MFOSENTS60)

Johannesburg 2022

Dedication

To my beautiful wife Maryam,

For her unconditional love, patience, support, understanding and continuous encouragement

To my parents Goolam Hossein and Sayeda,

For their support, prayers and encouragement.

To my daughter Saarah and our new born son Mohammed Isa

For their inspiration.

Declaration

I, Mohammed Nathie, declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine in the branch of Otorhinolaryngology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.



(signed by candidate)

08/11/2022 – JOHANNESBURG

(date, place)

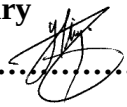
Co-Author Declaration

Declaration: students contribution to the article(s) and agreement of co-author(s):

I, Mohammed Nathie, student number 0703120A, declare that this Research Report is my own work and that I contributed adequately towards research findings published in the article(s) stated below which are included in my Research Report.

Signature of student……  **…….Date……01/08/2022…….**

Name of Primary Supervisor: Dr Yahya Atiya…….

Signature of Primary Supervisor……  **……Date…01/08/2022…….……..**

Agreement by co-authors: By signing this declaration, the co-author(s) listed below agree to the use of the article by the student as part of his/her Thesis/Dissertation/Research Repot. In cases where the student is not the 1st author of the published article, the primary supervisor must explain (under comments) why the student is entitled to use the paper for his/her degree purposes.

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Letter of Contribution

To whom it may concern

The MMED titled 'The rate of submandibular gland involvement in patients who underwent neck dissections for oral cavity squamous cell carcinoma at Chris Hani Baragwanath Academic Hospital', in submissible format (for the Wits Journal of Clinical Medicine) is primarily my work.

I, Dr M Nathie, student number 0703120A, conceived the idea for this study, wrote the protocol, collected all the data personally without any assistance, calculated the statistics with some assistance from a statistician in the protocol phase and assistance from my supervisor, and I wrote the final paper.

Dr Y Atiya assisted in a supervisory role with my work. He reviewed the protocol and the manuscript at each stage and provided guidance and the fine tuning and perfecting of the work being submitted. He also helped correct my statistics where needed.

Yours Sincerely,



Mohammed Nathie
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- Last, but not least, to my wife and family, for their love, support and encouragement.

List of abbreviations

CHBAH – Chris Hani Baragwanath Academic Hospital

ENT – Ear, nose and throat

SCC – Squamous cell carcinoma

HNC – Head and neck cancer

OSCC – Oral Squamous cell carcinoma

HIV – Human immunodeficiency virus

HPV – Human papilloma virus

TABLE OF CONTENTS

Dedication……..II
Declaration……...III
Co-Author Declaration……IV
Letter of Contribution……..VI
Acknowledgements……VII
List of Abbreviations……VIII
Abstract……..2
Article for Submission……3
Introduction……3
Epidemiology……3
Submandibular Gland Involvement in OSCC……4
Clinical Evaluation……5
Classification……..6
Management……...6
Neck Dissection……..7
Materials and Methods……...8
Results……9
Demographics……9
Pathological Results……10
Primary Tumour Location……10
Pathological T Stage……10
Pathological N Stage……10
Level 1B Involvement……10
Rate of Submandibular Gland Involvement……10
Discussion……12
Conclusion……14
References……15
Tables and Figures
Table 1: Changes in American Joint Cancer Committee staging in lip and oral cavity and nasopharynx……17
Table 2: Age and Gender……..17
Figure 1: Primary Tumour Location……18
Figure 2: Pathological T – Stage……..18
Figure 3: Pathological N classification for the patients in this study……...19
Table 3: Level 1B involvement……19
Table 4: Cross tabulation by Level 1 B node involvement……..20
Table 5: Submandibular Gland Involvement and Level 1 B Lymph node..21
Table 6: Gender differentials among patients……..22
Appendix A – Approved Protocol……23
Appendix B – Ethics Clearance……24
Appendix C – Change of Title Approval……25
Appendix D – Chris Hani Baragwanath Hospital Otorhinolaryngology HOD Approval Letter……...26
Appendix E – NHLS Letter……27
Appendix F – Medical Advisory Committee CHBAH Letter……28
Appendix G – Authorship Guidelines for the WITS Journal of Clinical Medicine……...29
Appendix H – Turnitin Report……...30

Abstract

Background Head and neck cancer (HNC) in Africa is increasing in incidence. The most frequent site of HNC is the oral cavity, with the most common histological type being squamous cell carcinoma (SCC). The submandibular gland may be involved by either direct spread (of a primary ipsilateral oral cavity tumour or locally involved lymph node) or from distant primaries outside the head and neck.

Objectives To determine the rate of involvement of the submandibular gland in neck dissections for oral cavity squamous cell carcinoma at Chris Hani Baragwanath Academic Hospital.

Methods A retrospective audit of the Chris Hani Baragwanath Academic Hospital Department of Otorhinolaryngology theatre register for patients who underwent primary tumour resection and neck dissection for OSCC, between November 2012 and December 2018. Tumour location, clinical and pathological T and N stages were investigated for their relevance to submandibular gland involvement.

Results 24 patients were identified, 58.3% male (n=14) and 41.7% female (n=10). The mean age was 57.9 years old. The submandibular gland was involved in one patient (rate=4.2%) and the method of involvement was by means of intraglandular metastasis. Nodal staging, tumour location and the presence of level 1b nodes did not increase risk for submandibular gland involvement. However an advanced T stage was a proven risk factor.

Conclusion There is a low rate of submandibular gland (4.2%) involvement in neck dissections for OSCC at Chris Hani Baragwanath Academic Hospital. Oncologically, the sparing of the submandibular gland is safe and sound provided the gland is not suspicious for involvement either radiologically, clinically or at the time of surgery.

Article for Submission

The rate of submandibular gland involvement in patients who underwent neck dissections for oral cavity squamous cell carcinoma at Chris Hani Baragwanath Academic Hospital.

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Introduction

Head and neck cancer (HNC) in Africa is increasing in incidence. This is attributed to the rise in smoking habits (and use of other tobacco products), alcohol usage, lifestyle and diet westernization, human papilloma virus (HPV), human immunodeficiency virus (HIV), and unfavourable health policies. [1] The most frequent site of HNC is the oral cavity, with the most common histological type being squamous cell carcinoma (SCC).[2] It is estimated that at least 90% of oral cavity cancers are squamous cell carcinoma.[2, 3]

Epidemiology

Globally, oral squamous cell carcinoma (OSCC) is the sixth most common cancer, while in developing countries it ranks third.[1] Internationally, the continent of Asia is most commonly affected by OSCC with a reported incidence of 3.8 per 100 000, while in the African continent and South Africa, the incidence rate per 100 000 is estimated at 2.6 and 4 respectively.[4] OSCC affects the middle-age to elderly population and occurs more commonly in men than women.[3]

Risk factors identified are tobacco smoking and alcohol, which have a synergistic effect in the aetiology of OSCC.[2, 3] Contributory host factors are described such as compromised immune systems in HIV-infected and transplant patients.[3] Viral causes such as HPV have been described, however there is disparity in the literature regarding its role in the pathogenesis of OSCC.[1, 3] Additionally, genetic predisposition in conditions such as Fanconi's anaemia, xeroderma

pigmentosum and ataxia telangiectasia are linked to the development of head and neck cancers.[3]

Submandibular gland involvement in OSCC

OSCC rarely metastasizes to the submandibular gland.[5] They are more commonly involved by either direct spread (of a primary ipsilateral oral cavity tumour or locally involved lymph node) or from distant primaries outside the head and neck, via haematogenous spread; such as the lung, breast and the urogenital system.[5-7] It is well described that primary OSCC do not metastasize to the submandibular gland via haematogenous spread.[6]

The submandibular gland does not contain intraglandular lymph nodes or lympho-vascular structures.[6, 8] The lymph node groups surrounding the submandibular gland are sublocations of sub level 1B and are identified as preglandular, postglandular, prevascular and postvascular.[7] This is in contrast to the parotid gland which contains intraparenchymal lymph nodes. The significance of this is that the parotid gland is a site for intraglandular lymph node metastases for other HNC, which is not the case for the submandibular gland.[8] This has implications for the surgical strategy adopted towards the submandibular gland in OSCC.

Excision of the submandibular gland as part of a level 1B dissection of the neck is common practice in some centres, due to the common belief that this will facilitate complete removal of lymph nodes in the region of the gland.[8] Dhiwakar et al[9] showed that the submandibular gland can be safely preserved whilst still achieving complete removal of all lymph nodes in sub level 1B in neck dissections.

Submandibular gland resection is associated with several complications that impact anatomically, physiologically and functionally. The anatomical structure affected most commonly is the marginal mandibular nerve (a branch of the facial nerve), which runs

under the surface of the platysma muscle in the region of the submandibular gland.[10] In 2017, Hishamuddin et al[11] reported nerve complications in 23.3% of the neck dissections cases done in their centre, with the marginal mandibular nerve as the most commonly injured nerve in 13.1% of all neck dissection cases.[11]

In view of the physiological role of the submandibular gland in saliva production, removal of the gland decreases unstimulated saliva production and results in dryness of the mouth (xerostomia).[6] Xerostomia impairs chewing which affects nutritional intake of patients post submandibular gland resection. It also causes a chronic burning sensation within the oral cavity which impacts on patients' quality of life. The chronic mucosal dryness may result in fissuring of the tongue and lips, loss of appetite and weight, dental caries, oropharyngeal candidiasis and angular cheilitis.[9]

Functionally, marginal mandibular nerve injury may cause dysfunctional depression of the anguli oris muscle, resulting in drooping of the angle of the mouth which impairs feeding and alters cosmesis.[11]
In view of these complications, resection of the submandibular gland is not without risks, and preservation should be considered to reduce complication rates and improve patient outcomes.[5, 7, 9, 12]

Clinical evaluation

Due to the non-specific presenting complaints, patients with OSCC often present at an advanced stage of the disease process.[3] The spectrum of presentation includes: pain, oral mucosal changes, oral cavity and/or neck swelling, unexplained loosening of teeth in the absence of periodontal disease, odynophagia, dysphagia, persistent foreign body sensation, reduced tongue mobility and altered sensation of the oral cavity.[2]

A detailed history and comprehensive clinical examination of the ear, nose and throat, including endoscopy must be performed to ensure that the primary tumour is identified while not missing a second primary or synchronous metastases.[2]

The initial diagnostic workup requires a biopsy. In the outpatient clinic, lesions which are easily accessible may be biopsied using a punch forceps, core needle or fine needle aspiration techniques.[3] Lesions which are not easily accessed require a visit to the operating theatre to obtain an adequate sample for histological analysis.

A variety of imaging studies have value in confirming the diagnosis of OSCC such as: dental radiographs, magnetic-resonance imaging, ultrasonography, computed tomography and photon-emission tomography.[13] Each of these modalities has advantages and limitations which is beyond the scope of this text.
Lymph node identification is difficult to achieve both clinically and radiologically.[14]

Classification

Management is guided by tumour histopathological classification. The tumour, nodal, metastases (TNM) classification system is universally adopted as the classification of choice for malignant tumours.[15] The T category is defined by tumour size and depth of invasion, while the N category is defined by regional nodal involvement, and the M category is defined by distant metastases. Table 1 illustrates the TNM classification of OSCC according to the most recent release of the American Joint Committee on Cancer.[15]

Management

Various treatment modalities for OSCC are available such as radiation, chemotherapy and surgical resection.[16] The management requires a multidisciplinary team approach including representatives from oncology, otorhinolaryngology (ENT), oro-maxillo-facial,

radiotherapy, speech therapy and radiology, individualised to each patient's biopsychosocial context, while maximizing oncological control and minimizing alteration of the patient's form and function.[2] [3]

Multiple factors guide treatment options such as the nature of the tumour and surgical resectability, the balance between risk and benefit of treatment related complications on the patients' age, comorbid diseases, socioeconomic status and quality of life thereafter.[2, 3]

Many centres advise surgical resection as, it provides histopathological information on tumour stage, grade and spread, which is essential information to guide further management.[3]

Neck dissection

The surgical approach adopted is individualised to the patient's clinical and histopathological diagnosis.[17] Elective neck dissection (END) is recommended for any tumour where the risk of occult nodal metastasis is greater than 20%.[2] It is estimated that 60% of patients with early stage OSCC will present with a clinically negative neck (cN0).[3] In the oral cavity, the majority of tumours will require END, regardless of T status, with the exception of cancer of the hard palate and upper alveolar ridge.[2] This is in contrast to OSCC floor of the mouth and oral tongue which are more likely to metastasise to the neck; these patients should be offered END even if they are early stage tumours (if the depth of invasion exceeds 4mm).[3]

The goal of this surgical approach is to achieve loco-regional control and thus, enhance the cure rate of OSCC.[3] A significant clinical prognosticator of survival is the finding of metastases to the neck.[18] Neck Dissection (ND) includes the following types: extended radical ND, radical ND, modified radical ND, modified ND and selective ND.[11] In all forms of ND used to treat OSCC the submandibular gland is routinely removed.[6]

Neck dissection is a vital part of the surgical treatment for OSCC.[6] When indicated, neck dissection with adjuvant radiotherapy and chemoradiotherapy are the standard of care in OSCC.[6] Submandibular gland resection is a routine step in neck dissection, even though the rate of submandibular gland involvement is very low.[19] Preservation of the submandibular gland has been shown to improve patients' quality of life.[5]

The surgical treatment of choice is resection of the primary tumour, with appropriate neck dissection to ensure appropriate clearance of metastases.[16] In view of this, the author evaluated the rate of submandibular gland involvement in patients who underwent ND for OSCC at Chris Hani Baragwaneth Academic Hospital (CHBAH), in order to determine the feasibility of sparing the gland.

Materials and Methods

After obtaining ethics approval from the University of the Witwatersrand Human Research Ethics Committee (protocol number M190959), the author reviewed the CHBAH Department of Otorhinolaryngology theatre register for patients who underwent primary tumour resection and neck dissection (including level 1 dissection) for OSCC, between November 2012 and December 2018. Routine excision of the submandibular gland with accompanied level 1 B nodes was done on all participants, regardless of whether or not unilateral or bilateral neck dissection was carried out.

Once the patients' details were obtained, the histopathological results were reviewed using the reports available on the National Health Laboratory Services (NHLS) database, with documented permission of the head of anatomical pathology at the NHLS. The exclusion criteria were patients with any of the following: a tumour histology other than SCC, a previous history of head and neck radiotherapy, cancer occurring in sites other than the oral cavity and factors that make the patient a non-surgical candidate in the study

setting (i.e. stage T4b tumours, patients with distant metastasis). In total 24 patients met the criteria, and their results were reviewed and analysed. Clinical and Pathological Tumour-Node (T and N) staging of the patients was performed based on the American Joint Committee on Cancer (AJCC) staging eighth edition; all histopathological records collected were converted to this most updated version of the *AJCC Cancer staging manual*.[20]

Tumour location, clinical and pathological T and N stages were investigated for their relevance to level 1 metastases and submandibular gland involvement. Data was analysed in STATA version 14 software, at 95% Confidence interval and significance interpreted at 5% level. Fisher's exact test and Pearson chi-square test were carried out to identify potential risk factors associated with level I metastasis and submandibular gland involvement. A p-value of less than 0.05 was accepted as statistically significant.

Results

Demographics

The results were categorised according to demographics, pathological and clinical results (primary tumour location, prevalence and type of submandibular gland involvement, pathological T and N categories, prevalence & number of lymph nodes involved).

This study consisted of 24 participants where 58.3% were male (n=14) and 41.7% were female (n=10). The mean age of the participants was 57.9 years old (with a range of 34 – 74 years). There were 54.2% (n=13) participants between 41 and 60 years, while 37.5% (n=9) were more than 60 years and 8.33% (n=2) were aged 21 to 40 years. There were no patients aged less than 20.

Table 2 indicates that participants were more likely to be males aged 41-60 years (64.3% vs 40%), with no differences in proportions of those aged 60+ years in terms of gender. However, 20% of female

patients presented in the age group of 21-40 years old; there were no males in this age group. Thus, overall, female patients presented earlier than males.

Pathological Results

Primary tumour location

With regards to location of the primary tumour, the most frequent subsite was the floor of the mouth 33.3%(n=8), the lip 29.2% (n=7) and the tongue 25% (n=6). Other tumour location sites were: the lower gingiva 4.2%(n=1), hard palate 4.2% (n=1), and buccal mucosa 4.2% (n=1). There were no tumours of the upper gingiva and retromolar trigone present in the study. (See figure 1)

Pathological T- Stage

Figure 2 shows pathological T- Stage for the patients in this study. Most patients were pathologically staged T2 tumours (37.5%), followed by T1 tumours (29.2%), T3 tumours (20.8%) and lastly T4A tumours (12.5%), indicating that patients present with a smaller rather than larger primary.

Pathological N Stage

The most common Nodal staging (N) was N0 (54.2%), followed by N2B (20.8%), then N2C (12.5%) lymph node category/stage. Other nodal stagings were N1 (8.3%) and N2A (4.2%). (See Figure 3)

Level 1 B involvement

Three quarters of the participants were reported to have no level 1B lymph nodes (75%), while a quarter (n=6) did have nodes present in level 1B. (See Table 3)

Rate of sub mandibular gland involvement

Submandibular gland involvement was observed in only one case (4.2% rate) out of the 24, and the method of sub mandibular gland

involvement was an intra-glandular metastasis. The remainder of the 23 patients did not have the submandibular gland involved by either intra-glandular metastasis, direct tumour invasion or invasion by adjacent level 1B or other nodes.

Table 4 indicates that there was no statistically significant association between level 1B involvement and gender of participants (Fisher's exact test, p =1.000). Age of participants was also not statistically significant in association with level 1 B involvement (Fisher's exact test, p =0.678). However, a difference can be noted between those aged 21-40 years, who were more likely to have Level 1B lymph nodes i.e. 50% or 1 out of 2 patients in this age group. Tumour location was not significantly associated with level IB lymph nodes (Fisher's exact p= 0.632). Noteworthy results suggest that those with lip tumour were three times more likely to have level 1B lymph nodes (57.1% vs 17.6%) and those with tongue tumour were two times less likely to level IB lymph nodes. However, a noteworthy finding is that the only patient to exhibit submandibular gland involvement had a primary lip tumour with no lymph node involvement.
The pathological Tumour (T) staging was not associated with lymph nodes in this study (Fisher's exact =0.924). Although the results are not significant they provide an insight that those with T2 tumours (41.2% vs 28.6%) were less likely to have level 1B lymph nodes and those with T3 tumours were more likely to have level 1B lymph nodes (17.6% vs 28.6%).

Table 5 indicates there was no association between SMG involvement and level 1b lymph nodes. Out of the 24 patients studied only one patient had involvement of the submandibular gland, and this was by metastasis to the gland i.e. no direct infiltration from primary tumour nor from level 1b nodes. However, the table does indicate that from the 24 patients studied, 6 had level 1b nodes present, which could potentially be a source of submandibular gland involvement by direct

spread from the nodes, however this was not shown in the data reviewed.

There was no statistically significant association between number of lymph nodes (level 1B) and SMG involvement. There were no significant associations between clinical and pathological tumour–node (N) and SMG and level 1B lymph nodes (Fisher's exact test, p=0.719).

Table 6 indicates that male patients were twice as likely to have tumours on the floor of the mouth compared to females (42.9% vs 20%). There were no significant differences between male and female in terms of lip and tongue tumours. There seem to be slight differences in early-stage cancer (T2) between males (28.6%) and females (50%) whilst no differences are observed in late-stage cancer (T3 and T4). Males (28.6%) and females (30%) had equal chances of level 1b involvement with no significant differences (Fishers exact=0.548). The only patient to have submandibular gland involvement was a male patient. Differences are noted between males (14.3%) and females (30%) in terms of level 1B lymph nodes.

The results suggest that females were twice as likely to develop level 1B lymphadenopathy compared to males. Significant results indicate that there were differences in pathological N category cancer among the patients (Fisher's exact=0.05). Male patients were more likely to be at risk of higher staged N category cancer (N2B and N2C), compared to females who were more at risk of early cancer (N0 and N1). Lastly, males were more at risk of having 1 or more lymph nodes, compared to females (53.8% vs 25%).

Discussion

Several authors have described the rate of submandibular gland involvement in OSCC. According to Malgonde et al[21] the submandibular gland was involved in 3.06% of OSCC cases, where

metastasis was due to direct invasion of a tumour in close proximity to the gland. Yang et al[19] identified involvement of the submandibular glands in 52 out of 2 126 patients who underwent neck dissections for OSCC. Similarly, Cetin et al[6] found involvement of the submandibular gland via direct invasion was evident in 2 out of 155 patients, and the floor of mouth location was the only risk factor for submandibular gland involvement. In view of this, submandibular gland preservation should be considered on a case-by-case basis.
The limited data from South Africa describes the distribution of head and neck primary cancer and metastases. A study conducted at the University Of The Witwatersrand oral health centre reported the incidence of OSCC at 19.8% and identified the oral cavity as the most common site of HNC (16.4%).[22] The author identified one South African based retrospective study by Loock et al[23] which identified the oral cavity (14%) as the commonest site for primary HNC, with merely one patient (of the 107 cases) with submandibular gland involvement.

The primary objective of this retrospective audit was to ascertain the rate of submandibular gland involvement in neck dissections for OSCC at CBHAH. A summary of the above results shows that 1 patient (out of the 24 that met the inclusion criteria) had submandibular gland involvement – a rate 4.2%. The patient was a male, aged >60 years old, with a primary tumour of the lip, pathological TNM stage of T4a N0 M0, indicating no neck nodes were involved. The method of involvement was by means of an intraglandular metastasis, which is rare. The notable risk factors for malignancy in this patient were age (>60) and gender (male). The notable risk for submandibular gland involvement was a large primary tumour; however the primary site being lip, N0 neck or absent nodes in level 1b are all factors that usually are not associated with submandibular gland involvement. In the majority of series, the submandibular gland was involved by direct invasion from floor of mouth tumours or the involved mandible.[6]

According to the literature, the presence of level 1B nodes increases the risk of submandibular gland involvement (by direct spread of a locally involved node). This was not shown in our study. Another compelling fact is that advanced nodal status in our study did not increase the risk of submandibular gland involvement. It is particularly interesting that the method of submandibular gland involvement was by means of intraglandular metastasis, as this is a rare occurrence in the literature.[6]

The surgical technique of sparing the submandibular gland has already been established by a number of previous studies.[21] The benefit in sparing the gland in patients who don't receive radiation is that a large reservoir for saliva is maintained. This provides predominantly mucinous basal salivary flow, responsible for mucosal lubrication, minimizing the risk of xerostomia and the complications thereof. It may also improve the response of sialagogues both during and after radiotherapy.[9] The possible pitfalls of sparing the gland, is that some otorhinolaryngology surgeons are of the opinion that the spared gland can lead to the perception of a persistent palpable mass at the site of the previous lymphadenectomy, which could potentially scar and cause concern for follow-up.[21]

Conclusion

Overall, there is a low rate of submandibular gland (4.2%) involvement in neck dissections for OSCC at Chris Hani Baragwanath Academic Hospital. Oncologically, the sparing of the submandibular gland is safe and sound provided the gland is not suspicious for involvement either radiologically, clinically or at the time of surgery.

Conflict of Interests: None

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Table 1: Changes in American Joint Cancer Committee staging in lip and oral cavity and nasopharynx

	Seventh edition	Eight edition
Lip and oral cavity		
T1	Tumor <2 cm	Tumor ≤2 cm, ≤5 mm depth of invasion
T2	Tumor 2–4 cm	Tumor ≤2 cm, >5 mm, and ≥10 mm depth of invasion or tumor >2 cm but ≤4 cm and depth of invasion ≤10 mm
T3	Tumor >4 cm	Tumor >4 cm or depth of invasion >10 mm , but ≤20 mm
T4a	Moderately advanced local disease: (Lip) tumor invades through cortical bone or involves inferior alveolar nerve, floor of mouth, or skin of face (oral cavity) tumor involves adjacent structures such as cortical bone of maxilla or mandible, maxillary sinus or skin of face, or extrinsic muscles of tongue	Extrinsic muscles of tongue removed, Included extensive tumors with bilatarel tongue involvement and / or DOI >20 mm
T4b	Very advanced local disease; tumor invades masticator space, pterygoid plates, skull base, and/or encases the internal carotid artery	No change
N1	Metastases to single lymph node, 3 cm or less in greatest diameter	Same, except node must be extranodal extension negative
N2a	Metastases to single ipsilateral node >3 cm but not >6 cm	Same, except node must be extranodal extension negative or single ipsilateral or node 3 cm or smaller with extranodal extension
N2b	Metastases to multiple ipsilateral nodes >3 cm but not >6 cm	Same, except nodes must be extranodal extension negative
N2c	Metastases to bilateral nodes or contralateral nodes none >6 cm	Same, except nodes must be extranodal extension negative
N3	Metastases to nodes >6 cm	Subdivided into 3a: Same as N3 before, but extranodal extension negative 3b: Single ipsilateral node >3 cm in greatest dimension with extranodal extension Or multiple ipsilateral, contralateral, or bilateral nodes, any with extranodal extension Or single contralateral node 3 cm or smaller and with extranodal extension

Table 2: Age and gender

Age group	Male		Female		Total
	Freq	Perc	Freq	Perc	Freq
21-40 years	0	0	2	20.00	2
41-60 years	9	64.29	4	40.00	13
60+ years	5	35.71	4	40.00	9
Total	**14**	**100**	**10**	**100.00**	**24**

Figure 1: Primary tumour location

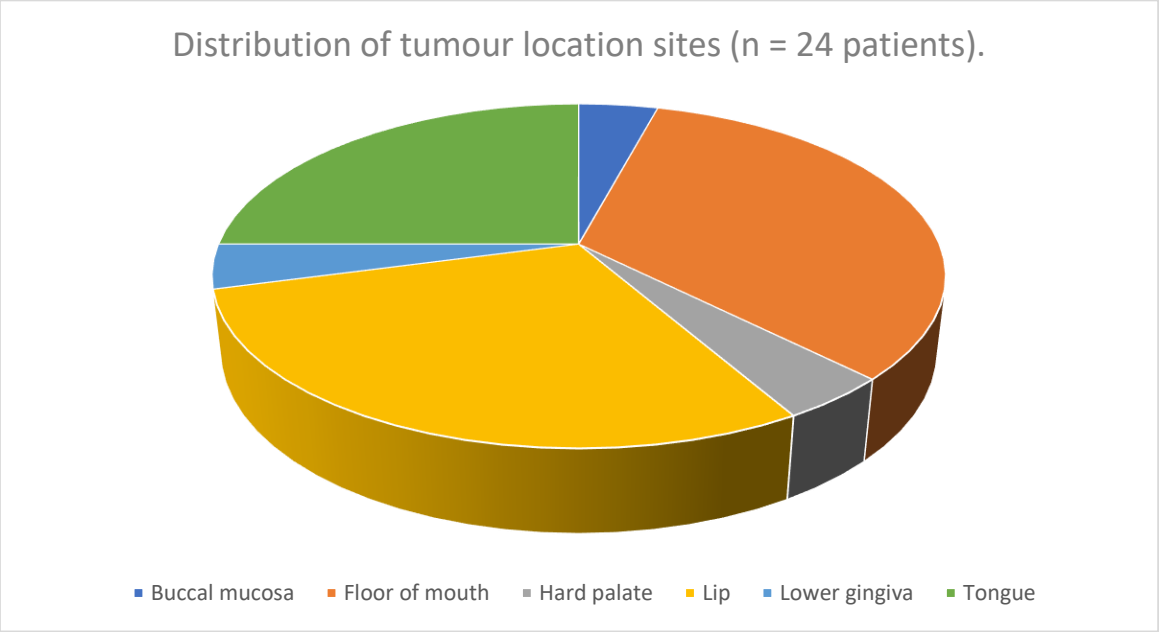


Figure 2 Pathological T- Stage

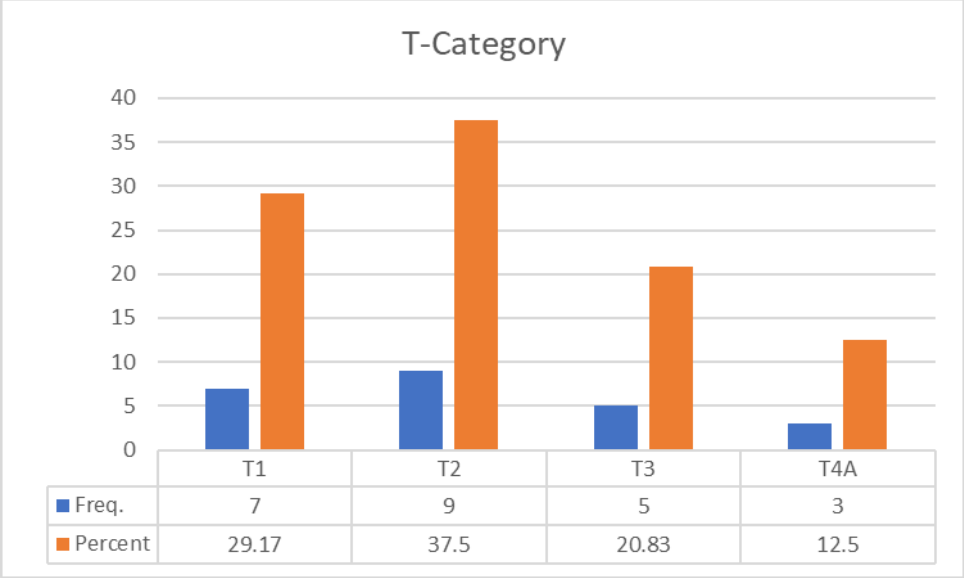


Figure 3: pathological N classification for the patients in this study.

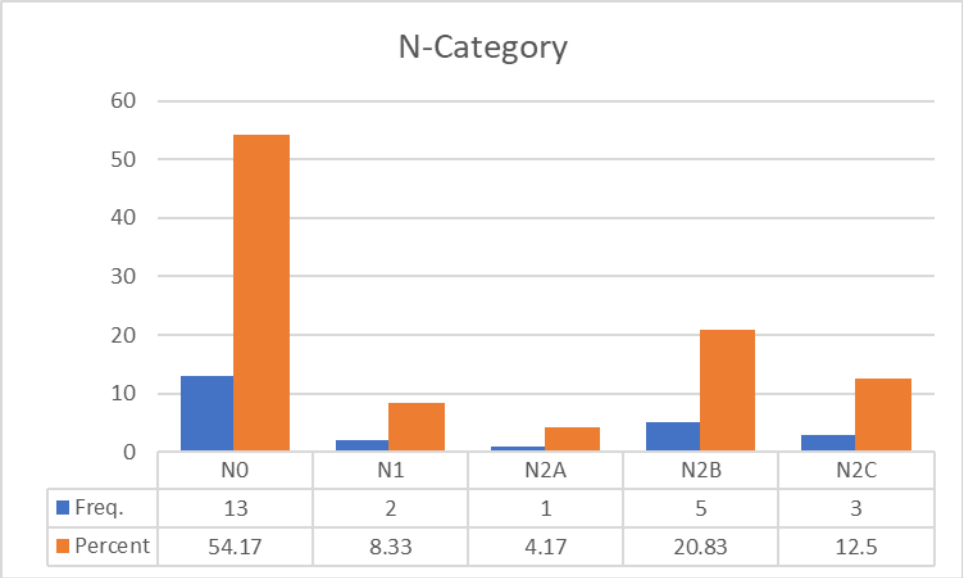


Table 3: Level 1 B involvement

Variable	Category	Freq.	Percent
Level 1B lymph nodes	**No**	**18**	**75**
	Yes	**6**	**25**
	Total	**24**	**100**

Table 4: Cross tabulation by Level 1 B node involvement

		Level 1 B node involvement					
Variable	**Category**	**No**		**Yes**		**Total**	**Fisher's exact**
		Freq	**Perc**	**Freq**	**Perc**	**Freq**	
Gender	**Male**	**10**	**58.824**	**4**	**57.143**	**14**	**1.000**
	Female	**7**	**41.176**	**3**	**42.857**	**10**	
Age group	**21-40 years**	**1**	**5.8824**	**1**	**14.286**	**2**	**0.678**
	41-60 years	**10**	**58.824**	**3**	**42.857**	**13**	
	60+ years	**6**	**35.294**	**3**	**42.857**	**9**	
Site of primary tumour	**Buccal mucosa**	**1**	**5.8824**	**0**	**0**	**1**	**0.632**
	Floor of mouth	**6**	**35.294**	**2**	**28.571**	**8**	
	Hard palate	**1**	**5.8824**	**0**	**0**	**1**	
	Lip	**3**	**17.647**	**4**	**57.143**	**7**	
	Lower gingiva	**1**	**5.8824**	**0**	**0**	**1**	
	Tongue	**5**	**29.412**	**1**	**14.286**	**6**	
T-category	**T1**	**5**	**29.412**	**2**	**28.571**	**7**	**0.924**
	T2	**7**	**41.176**	**2**	**28.571**	**9**	
	T3	**3**	**17.647**	**2**	**28.571**	**5**	
	T4A	**2**	**11.765**	**1**	**14.286**	**3**	
	Total	**17**	**100**	**7**	**100**	**24**	

Table 5: Sub mandibular gland involvement and level IB Lymph node

		Sub mandibular gland involvement and level IB Lymph node					
Variable	**Category**	**No**		**Yes**		**Total**	**Fisher's exact**
		Freq	**Perc**	**Freq**	**Perc**	**Freq**	
Number of lymph nodes: Level 1B	**0**	**17**	**100**	**1**	**14.286**	**18**	**0**
	1	**0**	**0**	**5**	**71.429**	**5**	
	2	**0**	**0**	**1**	**14.286**	**1**	
N Category	**N0**	**12**	**70.59**	**1**	**14.286**	**13**	**0.7197**
	N1	**0**	**0**	**2**	**28.571**	**2**	
	N2A	**0**	**0**	**1**	**14.286**	**1**	
	N2B	**4**	**23.53**	**1**	**14.286**	**5**	
	N2C	**1**	**5.88**	**2**	**28.571**	**3**	
	Missing	**1**	**6.25**	**2**	**28.571**	**3**	**0.05**
Number of lymph nodes involved	**None**	**11**	**64.706**	**1**	**14.286**	**12**	
	More than 1	**3**	**17.647**	**4**	**57.143**	**7**	
	One	**2**	**11.765**	**0**	**0**	**2**	

Table 6: Gender differentials among the patients

Variable	Category	Male		Female		Yes	
		Freq	Perc	Freq	Perc	Freq	Fisher's exact
Site of primary tumour	Buccal mucosa	0	-	1	10.00	1	0.562
	Floor of mouth	6	42.86	2	20.00	8	
	Hard palate	1	7.14	0	-	1	
	Lip	4	28.57	3	30.00	7	
	Lower gingiva	0	-	1	10.00	1	
	Tongue	3	21.43	3	30.00	6	
T Category	T1	4	28.57	3	30.00	7	0.548
	T2	4	28.57	5	50.00	9	
	T3	3	21.43	2	20.00	5	
	T4A	3	21.43	0	-	3	
Level 1B	0	11	78.57	7	70.00	18	0.777
	1	2	14.29	3	30.00	5	
	2	1	7.14	0	-	1	
N Category	N0	6	42.86	7	70.00	13	0.05
	N1	0	-	2	20.00	2	
	N2A	1	7.14	0	-	1	
	N2B	5	35.71	0	-	5	
	N2C	2	14.29	1	10.00	3	
Number of lymph nodes involved	None	6	46.15	6	75.00	12	0.53
	More than 1	5	38.46	2	25.00	7	
	One	2	15.38	0	-	2	

Appendix A – Approved Protocol

A protocol in planning for a Research Report (NEUS7009) in part fulfilment towards the degree of Master of Medicine in Otorhinolaryngology, university code MFOSENTS60.

Candidate: **Dr Mohammed Nathie**

Student number: **0703120A**

Supervisor: **Dr Yahya Atiya**

Division:
OTORHINOLARYNGOLOGY-HEAD NECK SURGERY

Department: Neurosciences
School of Clinical Medicine
Faculty of Health Sciences
University of the Witwatersrand. Johannesburg

Proposed title: The rate of submandibular gland involvement in patients undergoing elective Neck Dissection for Oral Cavity Squamous cell carcinoma at Chris Hani Baragwanath Academic Hospital.

Declaration

I, Mohammed Nathie, declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine in the branch of Otorhinolaryngology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.



(signed by candidate)

13/02/2019 – JOHANNESBURG

(date, place)

List of abbreviations

CHBAH – Chris Hani Baragwanath Academic Hospital

ENT – Ear, nose and throat

SCC – Squamous cell carcinoma

HNC – Head and neck cancer

OSCC – Oral Squamous cell carcinoma

HIV – Human immunodeficiency virus

HPV – Human papilloma virus

Table of contents:

Declaration i
1. Introduction 1

1.1. Background 1

1.2. Statement of the problem 1

1.3. Justification for the research 2

2. Literature review 2

3. Research question 9

4. Aim 9

5. Methodology 9

5.1. Research design 9

5.2. Study population 9

5.2.1. Inclusion and exclusion criteria 9

5.3. Study period 10

5.4. Study location 10

5.5. Data collection 10

5.6. Data analysis 11
5.7. Significance of this study 12
6. Limitations 12
7. Ethical considerations 12
8. Timing 13

1. Introduction

1.1. Background

Head and neck cancer (HNC) in Africa is increasing in incidence. This is attributed to the rise of smoking habits (and use of other tobacco products), lifestyle and diet westernization, increase use of alcohol, human papilloma virus (HPV), human immunodeficiency virus (HIV), and health policies which are unfavourable. [1]

The most frequent site of HNC is the oral cavity and squamous cell carcinoma (SCC) is the commonest histological type. It is estimated that at least 90% of oral cavity cancers are squamous cell carcinoma.[2, 3]

Neck dissection is a vital part of the surgical treatment; which together with adjuvant radiotherapy and chemoradiotherapy, when indicated, are the treatment for oral SCC(OSCC). [4] Submandibular gland resection is a routine step in neck dissection, even though the rate of submandibular gland involvement is very low.[5] Preservation of the submandibular gland has been shown to have better outcomes in patients' quality of life.[6]

1.2. Statement of the problem

Globally, oral cavity SCC is the sixth most common cancer, while in developing countries it ranks third[1] The surgical treatment of choice is resection of the primary tumour with appropriate neck dissection to ensure no metastases are missed.[7] Although tumour metastasis to the submandibular gland is uncommon, it has been routinely resected resulting in significant alterations in the oral health, hygiene, nutrition and quality of life of patients post-surgical resection.[4] There is literature to support the lack of involvement of submandibular glands as a site of metastases in primary OSCC[5]. This has not been investigated in our setting at Chris Hani Baragwanath Academic Hospital (CHBAH).

1.3. Justification for the research

The routine resection of the submandibular gland has a negative impact on the patients' long term oral health and quality of life. Therefore, this retrospective audit aims to describe whether or not involvement of the submandibular glands exists in neck dissections of patients who underwent excision of OSCC at CHBAH.

2. Literature review

2.1. Epidemiology

Internationally the continent of Asia is most commonly affected by OSCC with a reported incidence of 3.8 per 100 000, while in the African continent and South Africa, the incidence rate per 100 000 is estimated at 2.6 and 4 respectively.[8] OSCC affects the middle-age to elderly population and occurs more commonly in men than women.[3]

Risk factors identified are tobacco smoking and alcohol which have a synergistic effect in the aetiology of OSCC.[2, 3] Contributory host factors are described such as compromised immune systems in HIV-infected as well as transplant patients.[3] Viral causes such as HPV have been described, however there is disparity in the literature regarding its role in the pathogenesis of OSCC.[1, 3] Additionally, genetic predisposition in conditions such as Fanconi's anaemia, xeroderma pigmentosum and ataxia telangiectasia are linked to the development of head and neck cancers.[3]

Presenting features are non-specific leading to missed diagnosis and more commonly presentation with advanced disease and thus, higher mortality.[3]

2.2. Oral cavity anatomy

The anatomy of the oral cavity is defined superiorly by the junction of the soft and hard palate and inferiorly from vermillion border of the lips to the circumvallate papillae of the tongue.[3] There are eight anatomical subsites of the oral cavity namely: hard palate, retromolar trigone, upper and lower gum, buccal mucosa, oral tongue, floor of mouth and lip.[3] The most common subsite of origin of OSCC is the anterior two-thirds of the tongue.[9]

2.3. Submandibular gland and physiology

The submandibular glands are paired major salivary glands located beneath the floor of the mouth and contributes to both basal unstimulated and stimulated saliva production.[10] Saliva, which moistens the oral cavity, contains mucous, amylase, bicarbonate, lactoferrin and immunoglobulins.[11] Amylase enables the digestion of starch, while mucous assists the lubrication of food and eases swallowing.[11] Bicarbonate alkalinises the saliva enabling the buffering of acidic bacterial enzymes and preserving the mineral integrity of teeth. Lactoferrin and immunoglobulins assists in immune function and maintenance of oral hygiene.[11] In view of these crucial functions, the absence of the submandibular gland has implications for lack of oral hygiene, teeth integrity, nutrition and quality of life of the affected individual.[4]

2.4. Submandibular gland involvement in OSCC

OSCC rarely metastasizes to the submandibular gland.[6] They are more commonly involved by either direct spread (of a primary ipsilateral oral cavity tumour or locally involved lymph node) or from distant primaries outside the head and neck, via haematogenous spread; such as the lung, breast and the urogenital system.[4, 6, 12] It is well described that primary OSCC do not metastasize to the submandibular gland via haematogenous spread.[4]

The submandibular gland does not contain intraglandular lymph nodes or lympho-vascular structures.[4, 10] The lymph node groups surrounding the submandibular gland are sublocations of sub level 1B and are identified as preglandular, postglandular, prevascular and postvascular.[12] This is in contrast to the parotid gland which contains intraparenchymal lymph nodes. The significance of this is that the parotid gland is a site for intraglandular lymph node metastases for other HNC, which is not the case for the submandibular gland.[10] This has implications for the surgical strategy adopted towards the submandibular gland in OSCC.

Excision of the submandibular gland as part of a level 1B dissection of the neck is routine practice, due to the common belief that this will facilitate complete removal of lymph nodes in the region of the gland.[10] Dhiwakar et al[13] showed that the submandibular gland can be safely preserved whilst still achieving complete removal of all lymph nodes in sub level 1B in neck dissections.

Submandibular gland resection is associated with several complications that impact anatomically, physiologically and functionally. The anatomical structure affected most commonly is the marginal mandibular nerve which is a branch of the facial nerve (VII) which runs under the surface of the platysma muscle in the region of the submandibular gland.[14] In 2017, Hishamuddin et al[15] reported nerve complications in 23.3% of the neck dissections cases done in their centre. This study further identified, the marginal mandibular nerve as the most commonly injured nerve in neck dissections with a 13.1% rate of occurrence in all neck dissection cases.[15]

In view of the physiological role of the submandibular gland in saliva production, removal of the gland decreases unstimulated saliva production and results in dryness of the mouth (xerostomia).[4]

Xerostomia impairs chewing which affects nutritional intake of patients post submandibular gland resection. It also causes a chronic burning sensation within the oral cavity which impacts on patients' quality of life. The chronic mucosal dryness may result in fissuring of the tongue and lips, loss of appetite and weight, dental caries, oropharyngeal candidiasis and angular cheilitis.[13]

Functionally, marginal mandibular nerve injury may cause dysfunctional depression of the anguli oris muscle, resulting in drooping of the angle of the mouth which impairs feeding and alters cosmesis.[15]

In view of these complications, resection of the submandibular gland is not a benign procedure and preservation should be considered to reduce complication rates and improve patient outcomes.[6, 12, 13, 16]

Several authors have described the rate of submandibular gland involvement in OSCC. According to Malgonde et al[11] the submandibular gland was involved in 3.06% of OSCC cases, where metastasis was due to direct invasion of a tumour in close proximity to the gland. Yang et al[5] identified involvement of the submandibular glands in 52 out of 2 126 patients who underwent neck dissections for OSCC. Similarly, Cetin et al[4] found involvement of the submandibular gland via direct invasion was evident in 2 out of 155 patients, and the floor of mouth location was the only risk factor for submandibular gland involvement. In view of this, submandibular gland preservation should be considered on a case by case basis.

The author did not identify literature on the rate of submandibular gland involvement in OSCC in South Africa and Africa as a whole. According to the literature, this is attributed to the lack of quality data management in resource constraint settings.[8] The limited data from South Africa does not describe the rate of submandibular gland

involvement, but rather describes the distribution of head and neck primary cancer and metastases. A study conducted at the University Of The Witwatersrand oral health centre reported the incidence of OSCC at 19.8% and identified the oral cavity as the most common site of HNC (16.4%).[17] A SA based retrospective study by Loock et al [18] similarly identified the oral cavity (14%) as the commonest site for primary HNC, with merely one patient (of the 107 cases) with submandibular gland involvement.

2.5. Classification

The tumour, nodal, metastases (TNM) classification system is universally adopted as the classification of choice for malignant tumours.[9] The T category is defined by tumour size and depth of invasion, while the N category is defined by regional nodal involvement, and the M category is defined by distant metastases. Table 1[9] illustrates the TNM classification of OSCC according to the most recent release of the American Joint Committee on Cancer.[9]

Table 1: Changes in American Joint Cancer Committee staging in lip and oral cavity and nasopharynx

	Seventh edition	Eight edition
Lip and oral cavity		
T1	Tumor <2 cm	Tumor ≤2 cm, ≤5 mm depth of invasion
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T3	Tumor >4 cm	Tumor >4 cm or depth of invasion >10 mm , but ≤20 mm
T4a	Moderately advanced local disease: (Lip) tumor invades through cortical bone or involves inferior alveolar nerve, floor of mouth, or skin of face (oral cavity) tumor involves adjacent structures such as cortical bone of maxilla or mandible, maxillary sinus or skin of face, or extrinsic muscles of tongue	Extrinsic muscles of tongue removed, Included extensive tumors with bilatarel tongue involvement and / or DOI >20 mm
T4b	Very advanced local disease; tumor invades masticator space, pterygoid plates, skull base, and/or encases the internal carotid artery	No change
N1	Metastases to single lymph node, 3 cm or less in greatest diameter	Same, except node must be extranodal extension negative
N2a	Metastases to single ipsilateral node >3 cm but not >6 cm	Same, except node must be extranodal extension negative or single ipsilateral or node 3 cm or smaller with extranodal extension
N2b	Metastases to multiple ipsilateral nodes >3 cm but not >6 cm	Same, except nodes must be extranodal extension negative
N2c	Metastases to bilateral nodes or contralateral nodes none >6 cm	Same, except nodes must be extranodal extension negative
N3	Metastases to nodes >6 cm	Subdivided into 3a: Same as N3 before, but extranodal extension negative 3b: Single ipsilateral node >3 cm in greatest dimension with extranodal extension Or multiple ipsilateral, contralateral, or bilateral nodes, any with extranodal extension Or single contralateral node 3 cm or smaller and with extranodal extension

2.6. Clinical evaluation

Due to the non-specific presenting complaints, patients with OSCC often present late at an advanced stage of the disease process.[3] The spectrum of presentation includes: pain, oral mucosal changes, oral cavity and/or neck swelling, unexplained loosening of teeth in the absence of periodontal disease, odynophagia, dysphagia, persistent foreign body sensation, reduced tongue mobility, altered sensation of the oral cavity.[2]

A detailed history and comprehensive clinical examination of the ear, nose and throat, including endoscopy must be performed to ensure that the primary tumour is identified while not missing a second primary or synchronous metastases.[2]

The initial diagnostic workup requires a biopsy. In the outpatient clinic, lesions which are accessible, may be the biopsy sample site for adequate tissue diagnosis, using a punch forceps, core needle or fine needle aspiration.[3]

A variety of imaging studies have value in confirming the diagnosis of OSCC such as: dental radiographs, magnetic-resonance imaging, ultrasonography, computed tomography and photon-emission tomography.[19] Each of these modalities has advantages and limitations which is beyond the scope of this text.
Lymph node identification is difficult to achieve both clinically and radiologically.[20]

2.7. Management

Various treatment modalities for OSCC are available such as radiation, chemotherapy and surgical resection.[7] The management requires a multidisciplinary team approach including representatives from oncology, ENT, oromaxillofacial, radiotherapy and radiology, who individualise to each patients' biopsychosocial context, while

maximizing oncological control and minimizing alteration of the patient's form and function.[2] [3]

Multiple factors guide treatment options such as the nature of the tumour and surgical resectability, the balance between risk and benefit of treatment related complications on the patients' age, comorbid diseases, socioeconomic status and quality of life thereafter. [2, 3]

Many centres advise surgical resection as, it provides histopathological information on tumour stage, grade and spread, which is essential information to guide further management.[3]

2.8. Neck dissection

The surgical approach adopted is individualised to the patients clinical and histopathological diagnosis.[21] Elective neck dissection (END) is recommended for any tumour where the risk of occult nodal metastasis is greater than 20%.[2] It is estimated that 60% of patients with early stage OSCC will present with a clinically negative neck (cN0).[3] In the oral cavity, the majority of tumours will require END, regardless of T status, with the exception of cancer of the hard palate and upper alveolar ridge.[2] This is in contrast to OSCC floor of the mouth and oral tongue which are more likely to metastasise to the neck; these patients should be offered END even if they are early stage tumours (if the thickness exceeds 4mm).[3]

The goal of this surgical approach is to achieve loco-regional control and thus, enhance the cure rate of OSCC.[3] A significant clinical prognosticator of survival is the finding of metastases to the neck.[22] ND include the following types: extended radical ND, radical ND, modified radical ND, modified ND and selective ND.[15] In all forms of ND used to treat OSCC the submandibular gland is routinely removed.[4]

2.9. Outcomes

It is estimated that one fifth of patients treated for oral cavity cancer experience local tumour recurrence of 76% within 2 years, therefore it is advised these patients receive long term follow up.[2]

3. Research question

What is the rate of submandibular gland involvement in patients who underwent neck dissection for oral cavity squamous cell carcinoma?

4. Aim

- To determine the rate of SMG involvement in neck dissection specimens of patients undergoing surgery for OSCC
- To determine the feasibility of SMG preservation at neck dissection.

5. Methodology

5.1. Research design

This will be a retrospective clinical audit.

5.2. Study population

The study will include all patients who had undergone elective neck dissection at CHBAH, as part of surgical treatment for OSCC. The expected number of records examined will be approximately 50 patients.

5.2.1. Inclusion and exclusion criteria

Inclusion criteria for this study will be:

- Histopathologically confirmed SCC of the oral cavity
- Surgery as the primary treatment modality

Exclusion criteria for this study will be:

- Tumour histology other than SCC
- Patients with a previous history of head and neck radiotherapy
- Patients with cancer occurring in sites other than the oral cavity.

5.3. Study period

The study will extend from 1st January 2014 to 31st December 2018.

5.4. Study location

The study will be conducted in the clinical unit of Otorhinolaryngology at the Chris Hani Baragwanath Hospital in Soweto, Johannesburg, South Africa. CHBAH is a tertiary level teaching hospital affiliated to the University of the Witwatersrand.

5.5. Data collection

Patients will be identified from two sources:

- ENT Operating Theatre register
- ENT Ward Admissions register

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

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

All patients who are clearly identified from the theatre register will be recorded as part of the initial sample population. This information will then be used to interrogate the database of the National Health Laboratory Services (NHLS), and all findings will be 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 will be cross checked against their recorded laboratory findings and will be included in the study population. If these patients lack sufficient information, they will not be included in the study sample.

The following data will be recorded for each patient:

- Hospital registration number
- Age
- Sex
- Presenting complaint
- Clinical findings
- Date of surgery
- Site of primary tumour
- Histological result

All data will be recorded electronically using Microsoft Access and Microsoft Excel.

5.6. Data analysis

- Microsoft Access 2010 for data storage, retrieval and selection.
- Microsoft Excel 2010 for descriptive analysis, summary statistics and comparison of sample means.
- Statistica (Statsoft GmBH) software for statistical analysis
- Standard statistical methods will be used. Student's *t* test will be used to analyse continuous data and the Chi Square (χ^2) test for ordinal data. A probability (p) value of less than (or equal to) 0.05 is regarded as significant. In the event that numbers are

too low to use the Chi square test, Fischer's exact test will be used.

- Microsoft Word 2010 for final documentation and presentation.

5.7. Significance of this study

- To identify the rate of involvement of the submandibular gland in patients with oral cavity SCC. The author's hypothesis is that in this audit the patients who underwent neck dissection for resection of OCSCC did not have metastatic spread to the submandibular glands and preservation should have been considered.
- Decrease surgical time during neck dissections
- Improve quality of life for the patient (oral hygiene, nutrition)
- Reduce surgical morbidity
- Reduce marginal mandibular nerve injury

5.8. Funding

No funding is required for this study. The minimal costs (approx. R500) associated with printing and binding will borne by the principle investigator.

6. Limitations

- Inadequate patient numbers
- Inadequate patient records
- Cross-sectional study

7. Ethical considerations

In view of this study being a retrospective audit, no patient consent is required. The study will commence after approval by the Human

Research Ethics Committee of the University of the Witwatersrand. All data will be confidential and stored on a password-protected database, to which the author alone will have access. Permission will be obtained from the clinical and academic HODs of ENT at CHBAH, as well as the CEO of CHBAH, and the HOD of the NHLS, to conduct the study and access records.

8. Timing

Activity	Feb 2019	March 2019	April 2019	June-Nov 2019	Dec 2019	Jan 2020	Feb 2020
Proposal preparation							
Literature review							
Proposal submission							
Ethics and postgrad approval							
Data collection							
Data analysis							
Write and submission							

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Appendix A: Data collection sheet

Study Number		
Age	**<20**	
	21-40	
	41-60	
	>60	
Gender	**Male**	
	Female	
Site of primary tumour	**Floor or mouth**	
	Tongue	
	Lip	
	Lower gingiva	
	Upper gingiva	
	Retromolar trigone	
	Hard palate	
	Buccal mucosa	
T category	**T1**	
	T2	
	T3	
	T4a	
	T4b	
Submandibular gland involvement	**Yes**	
	No	
Method of submandibular gland involvement	**Direct invasion from primary tumour**	
	Direct invasion from level 1B	
	Intraglandular metastasis	
Level 1B lymph nodes	Yes	
	No	
Number of lymph nodes involved		

Appendix B – Ethics Clearance

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Dr M Nathie
School of Clinical Medicine
Department of Medicine
Division of Otorhinolaryngology
Chris Hani Baragwanath Academic Hospital

E-mail: moh.nathie@gmail.com

CC: Supervisor: Dr Y Atiya <yatiya@gmail.com>
and <HREC-Medical.ResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2020/01/03

REF: *R14/49*

PROTOCOL NO: **M190959** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *The rate of submandibular gland involvement in patients undergoing elective neck dissection for oral cavity squamous cell carcinoma at Chris Hani Baragwanath Academic Hospital*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

Appendix C - Change of Title Approval

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

01 June 2022
Person No: 0703120A
TAA

Dr M Nathie
P O Box 149
Johannesburg
Crown Mines
2092
South Africa

Dear Dr Mohammed Nathie

Master of Medicine in Otorhinolaryngology: Change of title of research

I am pleased to inform you that the following change in the title of your Research Report for the degree of **Master of Medicine in Otorhinolaryngology** has been approved:

From:	**The rate of submandibular gland involvement in patients undergoing elective Neck Dissection for Oral Cavity Squamous cell carcinoma at Chris Hani Baragwanath Academic Hospital**
To:	**The rate of submandibular gland involvement in patients who underwent neck dissections for oral cavity squamous cell carcinoma at Chris Hani Baragwanath Academic Hospital**

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix D – Chris Hani Baragwanath Hospital Otorhinolaryngology HOD Approval letter

Dr MRI Ahmed

HOD

Dept of Otorhinolaryngology

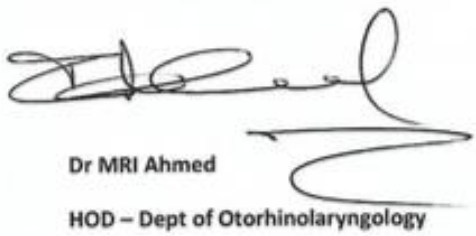
Chris Hani Baragwaneth Academic Hospital

To whom it may concern

Permission is hereby granted to Dr Mohammed Nathie to conduct a research study entitled "The rate of submandibular gland involvement in patients undergoing elective Neck Dissection for Oral Cavity Squamous cell carcinoma at Chris Hani Baragwaneth Academic Hospital" within the department of Otorhinolaryngology at Chris Hani Baragwaneth Academic Hospital.

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

Yours Faithfully



Dr MRI Ahmed

HOD – Dept of Otorhinolaryngology

Chris Hani Baragwaneth Academic Hospital

Appendix E – NHLS letter

NATIONAL HEALTH LABORATORY SERVICE
UNIVERSITY OF THE WITWATERSRAND – JOHANNESBURG

SCHOOL OF PATHOLOGY
Division of Anatomical Pathology

NATIONAL HEALTH LABORATORY SERVICE

P.O. Box 1038, Johannesburg 2000
Tel : +27-11-489-8477
+27-11- 489-8479
Fax:+27-11-489-8512

Division of Anatomical Pathology
Faculty of Health Sciences
York Road
Parktown e-mail: yvonne.perner@nhls.ac.za

Dr Yvonne Perner
Head: Division of Anatomical Pathology.

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

March 6, 2019

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 Mohammed Nathie with his research entitled "The rate of submandibular gland involvement in patients undergoing elective neck dissection for oral cavity squamous cell carcinoma at Chris Hani Baragwanath Academic Hospital".

Publication of such work is encouraged and in the event that the information used comprises the diagnosis only then joint authorship from a member of staff in the Department of Anatomical Pathology would not be expected. However, should additional information be extracted from the report for purposes of further interpretation such as morphological details and immunohistochemical profiles, it would be expected that this would be done in conjunction with a member of staff in the Department of Anatomical Pathology and that joint authorship would follow in resulting publications. Dr Nathie will be in contact with the Department of Anatomical Pathology in respect of this.

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

With best wishes.

Yours sincerely,

Dr Yvonne Perner
Head: Department of Anatomical Pathology

Appendix F – Medical Advisory Committee CHBAH Letter

GAUTENG PROVINCE

REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 26th February 2019

TITLE OF PROJECT:

The rate of submandibular gland involvement in patients undergoing elective Neck Dissection for Oral Cavity Squamous cell carcinoma at Chris Hani Baragwanath Academic Hospital.

UNIVERSITY: Witswatersrand

Principal Investigator: Dr M Nathie

Department: ENT

Supervisor : Dr Y Atiya

Permission Head Department (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic 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: 26/02/2019

Approved/~~Not Approved~~
Hospital Management
Date: 28/02/2019

Appendix G – Authorship Guidelines for the WITS Journal of Clinical Medicine

WITS JOURNAL OF CLINICAL MEDICINE

Instructions for Authors

The Wits Journal of Clinical Medicine aims to provide peer-reviewed publication of original articles, reviews, opinion papers, case and meeting reports dealing with all facets of Clinical Medicine practice and research. All articles will be independently peer-reviewed. Material accepted for publication is done on the undertaking that it has not been submitted for publication anywhere else.

SUBMISSIONS

All submissions should follow the style of the Journal and be clear and concise. The word count, including references, should not exceed 5000 words. Email to: rita.kruger@wits.ac.za

ARTICLE STRUCTURE

All articles should have a title page and include the following: a short descriptive title, authors surname and first name, email address for each author, a full postal address, telephone number, fax and email address for the corresponding author. The corresponding author should be identified with an asterix. All contributors will require an ORCiD which should also be submitted as an alphanumeric string. Please register at www.orcid.org if you don't have one already. The Editors may at a later date request validation authorisation for this publication.

THE TEXT

Please submit all text in Times New Roman, 12 point with 1.5 spacing in English (UK or South African). Text must be submitted as a Word document.

Tables and figures placement must be indicated in the text as part of the sentence example, see Table 1, or in parentheses (see Table 1). All tables and figures must include a descriptive heading with appropriate attribution and permissions indicated. Figures and tables must be submitted separately from the Word document with the following file-naming convention (Lead author surname Fig.1.jpg) eg (Manga Fig. 2.jpg). Submit each figure electronically as a high resolution JPEG (at least 300 dpi). All tables and graphs (containing original data or which are not archival in nature) will be redrawn to suit the house style. Please ensure that all elements are included especially legends, scale indicators and all axes.

REFERENCES

References should be numbered in the order of appearance in the text (in parentheses after punctuation) and be presented according to Vancouver styling.

For articles:

Author A, Author B, Author XYZ. Title of article. Journal title abbreviated Year; volume: xx-zz.

Leurs R, Church MK, Taglialatela M. H_1-antihistamines: inverse agonism, anti-inflammatory actions and cardiac effects. Clin Exp Allergy. 2002; 32(4):489-498.

List first 5 authors. If more than 5 authors list the first three and add et al.

For chapters in edited books:

Author A, Author BC. Title of the book chapter. In: Editor E, Editor FG, ed. Title of the book, X edn. Location: Publisher, year: xxx-zzz.

Glennon RA, Dukat M. Serotonin receptors and drugs affecting serotonergic neurotransmission. In: Williams DA, Lemke TL, editors. Foye's principles of medicinal chemistry. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2002.

For authored books:

Author A, Author B, Author C. Title. Edition. Location: Publisher; Year.

Rang HP, Dale MM, Ritter JM, Moore PK. Pharmacology. 5th ed. Edinburgh: Churchill Livingstone; 2003.

For all other reference queries eg datasets, websites and social media please consult the Vancouver style guide. When submitting articles to the Journal please try to adhere to the conventions outlined above as closely as possible.

STRUCTURE

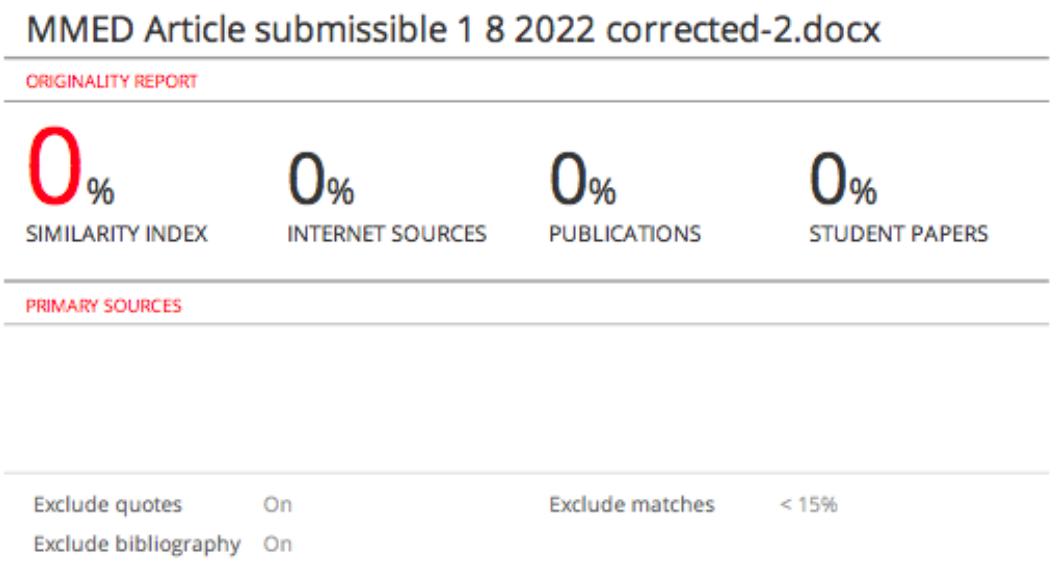
The **abstract** (250 words) should outline the main purpose of the study, the key methods, the main results and conclusion.

The **Introduction** provides a background to the study and should be sufficient to permit non-specialists to understand the framework of the work. Include a well-defined statement regarding the purpose of the study. The methods: provide a description of the study design, all procedures, techniques and statistical analyses. The results: stipulate the study findings and ensure to cross-reference figures and tables. The discussion should elicit an interpretation of the study set against the background of current knowledge of the field and provide definitive conclusions.

Reviews will comprise a title page as above; an abstract (250 words), providing the setting of the review, any key messages and conclusions drawn. The body should be presented with headings and subheadings and lead to summary with conclusions to end. A few (2-5) key statements could be itemised in separate box. Acknowledgements, references, tables and figures must be as detailed above.

WITS UNIVERSITY PRESS

Appendix H – Turnitin Report



MMED Article submissible 1 8 2022 corrected-2.docx

ORIGINALITY REPORT

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PRIMARY SOURCES

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