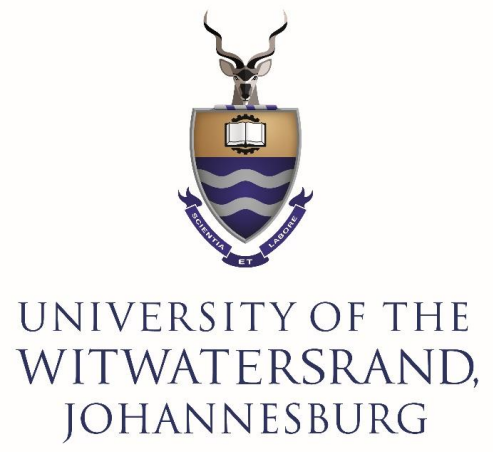
INCIDENCE OF INCOMPLETE EXCISION OF BASAL CELL CARCINOMA AND ASSOCIATED FACTORS AT TWO TERTIARY HOSPITALS



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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of **Master of Medicine in Plastic Surgery**

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DECLARATION

I, Dr Charles A Hoogendyk, declare that this Research Report is my own work. It is being submitted for the Degree of MMed in Plastic Surgery at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Sign: 

Date: 30/10/2023

DEDICATION

This project is dedicated to the patients attending the Department of Plastic Surgery at Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Academic Hospital.

ABSTRACT

Introduction

Basal Cell Carcinomas (BCC) account for the majority of skin cancers in South Africa. They have low mortality but can cause significant morbidity primarily through local destruction, therefore recurrence should be mitigated. Surgery is the preferred treatment for BCC. The excision margin is determined firstly by oncological safety and then preservation of normal tissues. Therefore, a wider or narrower margin increase the risk for aesthetic complications and recurrence, respectively. However, the optimal surgical excision margin size remains unclear and guidelines established based on lesion size and histological aggression are inconsistent. This may be because incomplete excision has a more complex relation with other associated factors.

Aim

The aim of this study was to examine the rate of incomplete excision (involved margin) of BCC at tertiary Hospitals in South Africa, and to assess the influence from associated factors, such as age, sex, histological type, size, site, and lesion occurrence (primary; re-excision; recurrence).

Method

This was a retrospective quantitative observational study with chart reviews, performed at the Plastic Surgery Department at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH). Patients who underwent BCC excision from January 2016 to December 2020 were screened and biopsies were collected. The normality of continuous data (age and biopsy size) was tested with Shapiro-Wilks test. The standard descriptive statistics and interquartile ranges (IQR) were reported. Involved excisional margins associations with continuous and categorical variables were tested using the Mann-Whitney U test, and Chi-squared test, respectively.

Results

The cohort consisted of 226 patients who underwent a total of 461 biopsies. The median age was 65.3 years, there were predominantly male (56.0%) patients, from CHBAH (81.0%). Baseline associated factors of largest biopsies (n=226) and smallest (n=91) biopsies of the cohort were examined overall. Margin was involved at excision on 16.8% (38/226) of largest samples and 23.1% (21/91) of smallest biopsies. The commonest site was the Head and Neck

region, with 146 (64.6%) in the largest biopsies and 61 (67.0%) amongst smallest biopsies. The commonest subtype was nodular which was 38.9% (88/262) and 40.6% (37/91) amongst the largest and smallest, respectively. On assessment of the diameter and the involved excisional margin, there was a significant association for smallest biopsy ($p<0.001$). On cross-tabulation, involved excisional margin for larger biopsies was significantly associated with head and neck biopsies ($p<0.001$) and aggressive lesions ($p=0.004$). In smallest biopsies lesions, involved excisional margin was also associated with head and neck sites ($p=0.009$) and primary occurrence ($p<0.001$), and smallest biopsies in the head and neck region was associated with aggressive type lesions ($p=0.003$). In the latter group, indolent type lesions were associated with primary biopsies ($p=0.001$).

Conclusion

In this population the associated factors for margin involvement on excision are head and neck site, aggressive type, and non-primary lesions. For best patient outcomes, and the prevention of BCC recurrence, we recommend that these factors are considered when deciding on excision margin size.

Key words: basal cell carcinoma, margin involvement, excision

Word count: 490

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LIST OF ABBREVIATIONS

BCC	Basal cell carcinoma
CEO	Chief Executive Officer
CHBAH	Chris Hani Baragwanath Academic Hospital
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
GCP	Good Clinical Practice
HREC	Human Research Ethics Committee
IFN Alpha	Interferon alpha
IQR	Interquartile range
mm	Millimeters
NHLS	National Health Laboratory Services
NMSC	Non-melanoma skin cancer
PMC	PubMed Central
UV	Ultraviolet

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1. INTRODUCTION

1.1 LITERATURE REVIEW

Basal cell carcinoma (BCC) is a type of skin cancer that involves the basal cells that form the bottom of the epidermis, above the dermis. BCC is the most common cutaneous malignancy in humans **(McDaniel et al 2022, Dourmishev et al 2013)** and is an important malignancy in sub-Saharan Africa, accounting for the majority of skin cancers in South Africa. However, there is still a paucity of data regarding BCC in South Africa **(Gallo *et al* 2022)**. South Africa has a multiracial population. The latest available statistics from the SA National Cancer Registry are from 2020, reporting the incidence of Basal Cell Carcinoma for South Africa to be 14.15% of all cancers **(The-National-Pathology-Cancer-Incidence-Report-2020)**.

1.1.1 HOST and ENVIRONMENT

Most BCCs are very slow-growing and seldom metastasize to other parts of the body. Lesions often start as an insidious, small, red, shiny spot or nodule, that may occasionally bleed. BCCs have low mortality but can cause significant morbidity primarily through destruction of local tissues **(McDaniel et al 2022, Dourmishev *et al* 2013)**. The occurrence of BCC is a complex relationship of host factors and environmental factors.

The main aetiological factor responsible for BCC is chronic ultraviolet (UV) exposure. UV exposure activates proto-oncogenes and inactivates tumor suppressive genes in keratinocytes. Other, less responsible, causes of BCC include exogenous carcinogens and immune suppression **(Quazi *et al* 2020)**. While there is much literature on the primary occurrence of BCC, another extensively researched topic is the re-occurrence of BCC **(van Loo *et al* 2020, Kavoussi *et al* 2020, Gallo *et al* 2022, Quazi *et al* 2020).**

1.1.2 EXCISION MARGIN and RECURRENCE

Although superficial BCC may be managed with non-operative treatments, surgery is the preferred treatment for most BCCs. The margin of tissue excised is determined by oncological safety first and preservation of normal tissues second. A 4-5 mm peripheral margin has a clearance rate of approximately 95%, the remaining 5% of small BCCs extend over this margin **(Miszczyk *et al* 2017).** However, for small, well-circumscribed BCC's, only 7% infiltrate beyond 1 mm of the clinical margins **(Quazi *et al* 2020)**. Therefore excising all BCC with a 4-

5 mm margin is not indicated, especially for lesions in cosmetic and functional sensitive areas like the face **(Quazi *et al* 2020)**. The dilemma occurs when trying to preserve aesthetic features but also securing a reasonable margin that reduces the likelihood of recurrence. In a study utilizing natural language processing, a form of artificial intelligence, the overall incomplete excision rate in a cohort of 34 955 lesions in 15 657 patients, was 5.5% **(Ali et al, 2023)**. Meanwhile, other conventional studies showed the incomplete excision rate to be 20% **(Nahidi, *et al,* 2021).** The recurrence rate for completely excised BCC is 3-6% **(Work Group 2018)**. Meanwhile, the recurrence rate for incompletely excised BCC was as high as 46%. (**Miszczyk et al 2017)**. For this reason, complete excision is of utmost importance to minimize the risk of recurrence.

The discrepancy is that the involved margin rate is much higher than expected with standard excision margins (4-5 mm) yet only 7% of small lesions extend more than 1 mm beyond their clinical margin **(Quazi *et al* 2020)**. The reasons for this discrepancy are the factors associated with increased risk of incomplete excision. These factors include age, sex, histological type, size, site, lesion occurrence (primary; re-excision; recurrence). These factors can be assessed preoperatively on history and clinical examination and lesions at risk of incomplete excision with standard excision margin can be identified **(Codazzi *et al* 2014)**. The margin most commonly involved varies; some studies found the lateral margin **(Miszczyk *et al,* 2017)** and others found that the deep margin to be more involved **(Nahidi, *et al,* 2021)**.

1.1.3 ASSOCIATED FACTORS

Age and sex

Increased age is an associated factor in many studies **(Quazi *et al* 2020, van Loo *et al* 2020)**. The median age for BCC diagnosis in South Africa was reported to be 70 years of age **(Gallo *et al* 2022)** and males were more affected than females. Older patients have a higher risk for BCC recurrence than younger patients **(Miszczyk *et al* 2017).**

Histological type

BCC can be divided into two groups, indolent and aggressive, according to histological type. Aggressive types include subtypes morpheaform, metatypical, infiltrative and micronodular.

The aggressive types extend more sub-clinically than the indolent types and therefore require excision with a wider margin. Indolent types include nodular and superficial subtypes **(Fidelis et al 2020, Kavoussi et al 2020, Miszczyk et al 2017, Quazi et al 2020)**. Notably, incompletely excised lesions recur as more aggressive types **(Miszczyk *et al* 2017, Fidelis *et al* 2020),** and cause a greater rate of local invasion and destruction **(Fidelis *et al* 2020).** The most aggressive types can infiltrate tissues at a width of 7mm beyond macroscopic borders of a lesion **(Miszczyk *et al* 2017)**.

Size

Larger tumours have wider subclinical extension **(Quazi *et al* 2020, Fidelis *et al* 2020)**. It has been observed that there is a significant relationship between incomplete excision and a tumor size larger than 2 cm **(Nahidi, *et al* 2021*;* Kavoussi *et al* 2020).**

Site

The sun-exposed areas of the head and neck are the commonly affected sites for BCC, **(Quazi *et al* 2020, Dourmishev *et al* 2013, Miszczyk et al 2017, Fidelis et al 2020, Nahidi, et al, 2021)** accounting for over 80% in some studies (**Miszczyk et al 2017).** Reports of a positive margin ranges from 14% to 40% in the nasal region and from 11% to 85% in the periocular region (**Fidelis et al 2020)**. This is attributed to the minute tissue in the face between closely positioned vital structures, therefore preserving cosmesis when taking wide margins is very difficult **(Quazi *et al* 2020)**.

Lesion occurrence

Lesion occurrence refers to whether a lesion is a primary lesion, a re-excision of an incompletely excised lesion or a recurrent lesion. Incomplete excision rates are related to lesion occurrence. Incomplete excisions rate was three times higher for recurrent lesion vs primary lesion excisions (**Work Group 2018).**

1.2 IMPLICATION and AIM OF THE STUDY

1.2.1 IMPLICATIONS OF THE STUDY

The implications of the study include the incidence of involved surgical margin in excised BCC in a third-world setting which, through the identification of associated risk factors that can be

assessed on history and clinical examination, could potentially alert the surgeon to the higher risk of involved surgical margin with standard excision margins. This may lower the rate of involved surgical margin.

1.2.2 AIM OF THE STUDY

The aim of the study was to examine the rate of incomplete excision (involved margin) of BCC at tertiary Hospitals in South Africa, and to assess the influence from associated factors, such as age, sex, histological type, size, site and lesion occurrence (primary; re-excision; recurrence).

1.3 SPECIFIC OBJECTIVES

- To determine the incidence of involved excisional margin in surgically treated BCCs in two high volume, multi-disciplinary surgical centres in Johannesburg, South Africa.
- To analyse the association between involved excisional margin in surgically treated BCC and: Age, sex, histological type, size, site, lesion occurrence (primary; re-excision; recurrence).

2. MATERIALS and METHODS

2.1 STUDY SITE

The study setting was the Plastic Surgery Department at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH). First patient contact was at the outpatient plastic surgery clinics, where patients were assessed by Consultant Plastic Surgeons. Medical officers and registrars perform excisions of BCC at these hospitals.

2.2 STUDY DESIGN

This was a retrospective quantitative observational study with chart reviews. Patients who underwent BCC excision during the 5-year period (January 2016 to December 2020) at CMJAH and CHBAH were screened for inclusion and exclusion criteria.

2.3 STUDY POPULATION

CMJAH is a public hospital situated in Parktown, Johannesburg, and serves a population of approximately 2 million South Africans of mixed socio-economic circumstances. CHBAH is a public hospital situated in Soweto, Johannesburg, and serves a mostly African, lower income population of at least 3 million South Africans. BCC excision procedures were performed free-of-charge at CMJAH and CHBAH. In this study all patients who had BCC excision procedures performed at CMJAH and CHBAH from January 2016 to December 2020 were included.

Inclusion criteria:

- All patients with cutaneous BCC lesions (primary, re-excision or recurrence lesions) who underwent excision biopsies during the study period.
- Patient who had surgical specimens submitted for pathological review.

2.4 DATA COLLECTION. MATERIALS and PATHOLOGICAL ASSESSMENT (refer to Appendix B)

Patients who underwent BCC excision procedures during the study period were identified from theatre booking lists. The histopathology reports for surgical specimens from these procedures were obtained. This information was recorded on a data collection sheet **(Appendix B)**, and included the following parameters: margin (complete/margin not involved, incomplete/margin involved; demographic data, including age, sex, study site; location and size (site, subsite, largest and smallest diameter (mm)); occurrence (primary, re-excision, recurrent); depth of

lesion (peripheral/deep); and histological type of BCC as either indolent (subtypes: nodular and superficial) or aggressive (subtypes: morpheaform, metatypical, infiltrative, and micronodular). Race and Albinism was not recorded because race was not reported on histology reports and Albinism was inconsistently reported. The use of frozen section as an associated factor for complete excision, was not assessed in this paper.

2.5 SAMPLE SIZE, STATISTICAL METHODS AND DATA ANALYSIS

A sample size between 200 to 300 patients fitting the defined criteria was expected for the study period, and 226 patients were included. The data collection sheet was to capture data **(Appendix B)**. A study number was assigned to each participant ensuring anonymity. Raw data was captured in an Excel spreadsheet and imported into STATA version 16 for statistical analysis. The Shapiro-Wilks test was applied to determine the normality of continuous data, such as age and lesion size. Statistical tests included standard descriptive statistics and means and standard deviations (SDs) or medians and interquartile ranges (IQRs) were reported, as appropriate, for continuous variables. Categorical variables were described using frequencies and proportions. Associations between involved excisional margins and continuous variables were tested using the T-test or Mann-Whitney U test, as appropriate, whereas associations with categorical variables were determined by the Chi-squared test and/or Fisher's exact test. A p-value of ≤ 0.05 were considered statistically significant.

2.6 ETHICAL CONSIDERATIONS

The Protocol was approved by the University of Witwatersrand Faculty of Health Sciences **(See Appendix A)**. Ethics approval from the Wits Human Research Ethics Committee (HREC) was contingent on approval from CHBAH Clinical Director, CMJAH Clinical Director and Chief Executive Officer (CEO), Head of Department of Plastic and Reconstructive surgery and National Health Laboratory Services (NHLS). The Ethics clearance reference number is M210838 **(See Appendix C).** A study number was assigned to each participant ensuring anonymity. All data will be stored per good clinical practice (GCP) regulations.

3. RESULTS

3.1 BASELINE ASSESSMENT OF PATIENTS

The cohort consisted of 226 patients who underwent a total of 461 biopsies, mostly males and the majority from CHBAH (Table 1). The median (IQR) age was 65.3 (56.0 - 74.8) years. Of the 226 patients, 135 (59.7%) had one biopsy only, 41 (18.1%) had two biopsies, 22 (9.7%) had three biopsies and the remaining 28 patients had between four and 18 biopsies each.

Table 1. Patient demographics and number of biopsies

Parameter	All patients, n=226
Age, years (median, IQR)	65.3 (56.0 – 74.8)
Sex, n (%)	
Male	128 (56.6)
Female	98 (43.4)
Facility, n (%)	
CHBAH	183 (81.0)
CMJAH	43 (19.0)
Total number of biopsies, n (%)	
1	135 (59.7)
2	41 (18.1)
3	22 (9.7)
4	8 (3.5)
5	9 (4)
6	4 (1.8)
7-10	4 (1.8)
11-18	3 (1.3)

Abbreviations: IQR, interquartile range

The smallest and largest biopsies were examined for each patient and grouped as “Smallest” and “Largest”, respectively. For the 135 patients who had only one biopsy, the biopsy was classified under “Largest” (Table 2). Altogether, there were 226 largest biopsies and 91 smallest biopsies. Table 2 describes the biopsies with regard to the lesion diameter, involvement of margin, depth of the lesion, location, occurrence and histological type according to the largest and smallest categories. The margin was involved in 38 (16.8%) of the largest biopsies and in 21 (23.1%) of the smallest biopsies. Biopsies were done for mainly primary lesions and at mainly head and neck locations for both the largest and the smallest.

Table 2: Description of associated factors of largest (n=226) and smallest (n=91) biopsies

Parameter	Largest (n=226)	Smallest (n=91)
Diameter, mm (median, IQR)	35 (26 - 51)	20 (15 – 32)
Margin involved, n (%)	38 (16.8)	21 (23.1)
Depth of lesion, n (%)		
Peripheral	15 (6.6)	12 (13.2)
Deep	14 (6.2)	2 (2.2)
Both	9 (4.0)	7 (7.7)
None	188 (83.2)	70 (76.9)
Location, n (%)		
Head & Neck	146 (64.6)	61 (67.0)
Limbs	48 (21.2)	15 (16.5)
Trunk	30 (13.3)	2 (2.2)
Other	2 (0.9)	13 (14.3)
Occurrence, n (%)		
Primary	204 (90.3)	80 (87.9)
Re-excision	9 (4.0)	2 (2.2)
Recurrent	13 (5.6)	9 (9.9)
Histological type, n (%)		
Indolent	116 (51.3)	52 (57.1)
Superficial	17 (7.5)	8 (8.8)
Nodular	88 (38.9)	37 (40.6)
Non-specific	11 (4.9)	7 (7.7)
Aggressive	110 (48.7)	39 (42.9)
Morpheaform	26 (11.2)	9(9.9)
Infiltrative	25 (11.1)	8 (8.8)
Metatypical	25 (11.1)	5 (5.5)
Micronodular	34 (15.3)	17 (18.7)

3.2 FACTORS ASSOCIATED WITH INVOLVED EXCISIONAL MARGIN

Table 3 shows the relationship between involved excisional margins and age, lesion diameter, location, occurrence and histological type. On assessment of the age and the involved excisional margin, there was no significant association for both the largest and smallest biopsies. On assessment of the diameter in mm and the involved excisional margin, there was no significant association for the largest biopsies but for the smallest biopsies those with involved margins were significantly smaller than complete excisions ($p<0.001$). Excision margins from head and neck lesions from both largest and smallest lesion groups had significantly more involvement (90%) than non-head and neck BCCs, with 89.5% involved

margins for largest biopsies (p<0.001) and 90.5% involved margins for smallest biopsies (p=0.009). Differences in occurrence: primary, re-excision and recurrence of BCCs with significantly more involved margins was seen in the smallest lesion category. There was a significant association between biopsy occurrence and involved excisional margin in the smallest biopsies only: 95.7% of completely excised biopsies were in primary lesions and 4.3% were recurrent lesions, compared to 61.9% primary lesions and 28.6% recurrent lesions in those with involved margins (p=0.001). Finally, the aggressive histological type with involved margins was noted in largest (71%; p=0.004), not the smallest lesions (42.9%; p<0.142; Tabel 3).

Table 4 shows the relationship between histological type with location and occurrence for the largest and smallest biopsies. No differences between the indolent and aggressive histological BCC types were apparent with respect BCC location or occurrence in the largest lesion group. There was a significant association between head and neck biopsies and aggressive histological type for smallest biopsies (p=0.003), but not for the largest biopsies. There was a significant association between histological type and biopsy occurrence in the smallest biopsies only: 98.1% indolent type lesions were primary lesions and only1.9% were recurrent, compared to 74.4% of aggressive type lesions being primary and 20.5% recurrent (p=0.001; Table 4).

Table 3. Factors associated with involved excisional margin

	Largest (n=226)			Smallest (n=91)		
Parameter	**Involved margin (n=38)**	**Complete excision (n=188)**	**P-value**	**Involved margin (n=21)**	**Complete excision (n=70)**	**P-value**
Age, years (median, IQR)	59.7 (51.8-72.2)	66.0 (56.7-75.3)	0.127	68.4 (56.7-78.8)	61.6 (51.7-74.8)	0.141
Diameter, mm (median, IQR)	35.0 (25.0-45.0)	35.0 (27.0-51.5)	0.393	14.0 (10.0-18.0)	25.0 (18.0-35.0)	**<0.001**
Location, n (%)						
Head & Neck	34 (89.5)	112 (59.6)	**<0.001**	19 (90.5)	42 (60.0)	**0.009**
Non-Head & Neck	4 (10.5)	76 (40.4)		2 (9.5)	28 (40.0)	
Occurrence, n (%)						
Primary	32 (84.2)	172 (91.5)		13 (61.9)	67 (95.7)	
Re-excision	1 (2.6)	8 (4.3)	0.117	2 (9.5)	0 (0.0)	**0.001**
Recurrent	5 (13.6)	8 (4.3)		6 (28.6)	3 (4.3)	
Histological type, n (%)						
Indolent	11 (29.0)	105 (55.9)	**0.004**	12 (57.1)	27 (38.6)	0.142
Aggressive	27 (71.0)	83 (44.2)		9 (42.9)	43 (61.4)	

Table 4. Factors associated with histological type of BCC

	Largest (n=226)			Smallest (n=91)		
Parameter	**Indolent (n=116)**	**Aggressive (n=110)**	**P-value**	**Indolent (n=52)**	**Aggressive (n=39)**	**P-value**
Location, n (%)						
Head & Neck	70 (60.3)	76 (69.1)	0.210	28 (53.9)	33 (84.6)	**0.003**
Non-Head & Neck	46 (39.7)	34 (30.9)		24 (46.1)	6 (15.4)	
Occurrence, n (%)						
Primary	107 (92.2)	97 (88.2)		51 (98.1)	29 (74.4)	
Re-excision	5 (4.3)	4 (3.6)	0.334	0 (0.0)	2 (5.1)	**0.001**
Recurrent	4 (3.5)	9 (8.2)		1 (1.9)	8 (20.5)	

4. DISCUSSION

Arthur Jacob, an Irish ophthalmologist, first described BCC in 1827, calling it a "rodent ulcer" in his article **(Kasper *et al* 2012)**. The rodent ulcer was later named BCC because it histologically resembled the basal cells of the epidermis. The aetiology lies in the pluripotential stem cells, which have a high potential to convert to BCC when exposed to excessive sunlight or have p53 gene mutations **(Kasper *et al* 2012)**.

In this study, the incidence of incomplete excision of BCC and associated factors was examined. There were 463 BCC biopsy samples collected from 226 patients at CMJAH and CHBAH over a five-year study period. In this study, the margin was involved in 38 (16.8%) of the largest biopsies and in 21 (23.1%) of the smallest biopsies.

4.1 DEMOGRAPHICS

This study demonstrated that the median age of the cohort was 65.3 years, and there were predominantly male patients (56.0%), consistent with local studies reporting a median age of 70 years and male predominance (**Gallo et al 2022**). Likewise, international studies show similar findings with the median age of diagnosis of BCC being in the seventh decade and occurring more frequently in males **(McDaniel *et al* 2022, Kasper *et al* 2012**, **Miszczyk *et al* 2017, Dourmishev *et al* 2013, Quazi *et al* 2020).**

4.2 SITE AND INCOMPLETE EXCISION

The commonest site for BCC in this study population was the head and neck region for both the largest and smallest BCCs. Of the 461 biopsies sampled in the 226 patients, 60.5% occurred in the head and neck region. This is however, lower to other literature where the head and neck region maintained approximately 80% prevalence **(McDaniel et al 2022, Kasper et al 2012, Miszczyk et al 2017, , Quazi et al 2020, Kavoussi et al 2020, van Loo et al 2020, Codazzi et al 2014, Nahidi, et al, 2021),** with half of those in the aesthetic area of the cheek and nose (**Dourmishev et al 2013)**. On assessment of associations, our findings are aligned with the literature in that significantly more patients with BCCs in the head and neck region also had involved margins when compared to the non-head and neck regions in both the largest and smallest biopsy groups.

4.3 HISTOLOGICAL TYPE

BCC is classified into two main histological groups: indolent and aggressive. Aggressive types include morpheaform, metatypical, infiltrative and micronodular. Indolent types include nodular and superficial. In this study the commonest histological type was the indolent, nodular subtype, in line with previous studies **(Fidelis *et al* 2020, Dourmishev *et al* 2013, Quazi *et al* 2020)**. Complete excisions of the largest lesions were significantly more likely for indolent tumours compared to aggressive BCCs. Head and neck tumours were more aggressive compared to non-head and neck sites, although this association was only statistically significant in the smallest biopsy group. Current literature demonstrates that BCC lesions on the head and neck region are most common and most consistent with aggressive lesions **(Kappelin *et al* 2020**). Studies also show that the head and neck area has smaller and more multiple lesions owing to the anatomy of the local structures **(McDaniel *et al* 2022)**.

It is established that BCC aggressiveness is related to more subclinical extension and therefore need to be excised with a wider margin **(Fidelis et al 2020).** This explains why in our study, recurrence or re-excisions were more frequent for aggressive BCCs compared to indolent lesions. Studies show that the morpheaform subtype had the highest relative risk of recurrence and was determined to be the most aggressive **(Miszczyk et al 2017**). In our study for both smallest and largest biopsies, the micronodular was the commonest aggressive biopsy, followed by the morpheaform.

4.4 THE OPTIMAL MARGIN SIZES

Key factors determining the relationship between the excision margin size and BCC recurrence, include the size of the primary BCC, the histological type, the degree of sun-exposure of the location of the BCC **(van Loo *et al* 2020, Quazi *et al* 2020).** The updated Dutch BCC guideline from 2015, recommended surgical margins of 3-4mm in low risk small (≤10 mm) primary BCC, and 5 mm in large (>20 mm and H zone), high-risk (aggressive histological subtype) or recurrent BCC **(van Loo *et al* 2020)**. It is a consistent finding in our study that both larger and smaller biopsies have an association with margin involvement when the associated factors are present, which include location on head and neck, aggressive type and non-primary lesions.

Studies have demonstrated that the highest recurrence is noted in lesions from sun-exposed locations and those having compromised margins on excision **(Fidelis *et al* 2020).** In this study incomplete excision was statistically significant with sun exposed regions and excision of non-

primary BCCs. Incomplete excision of larger lesions was strongly associated with the histological aggression of the lesion. This underpins the implications of the tumour aggression and the subclinical extension associated with aggressive types.

Recurrence of lesions is thought to be related to incomplete excision, however the consensus on the correct margin size has not been reached because the relationship is much more complex than margin size alone **(van Loo *et al* 2020, Fidelis *et al* 2020, Quazi *et al* 2020, Miszczyk *et al* 2017, Nahidi, et al, 2021, Kavoussi *et al* 2020)**.

In this study, margin was involved at excision on 16.8% of largest biopsies and 23.1% of smallest biopsies. The margin was not involved with primary lesions for the majority of smallest biopsies; margin involvement is a feature of non-primary lesions which were re-excision and recurrence lesions in our study.

This study conducted in South Africa has identified that the sun-exposed regional distribution, non-primary lesions, and aggressive histological types are the factors associated with the incomplete excision of a BCC. The concern with an incompletely excised BCC arises from the documented risk for recurrences. From the literature, the recurrence rate for completely excised BCC is 3-6% **(Codazzi et al 2014, Bozan et al 2015).** Meanwhile, the recurrence rate for incompletely excised BCC was 46% (**Miszczyk et al 2017)**. For this reason, complete excision is chiefly important to minimize the risk of recurrence. The overall incomplete excision rate in this cohort was 16.8% of the largest biopsies and in 23.1% of the smallest biopsies.

BCC accounts for the majority of skin cancers in South Africa **(Gallo *et al* 2022)** and 14.15% of all cancers **(The-National-Pathology-Cancer-Incidence-Report-2020)**. Given that the recurrence is a consequence of incomplete excision as well as other associated factors, the best clinical decision for the patient, is to have careful follow-up post excision. This may increase the detection rate of BCC recurrence and reserved the option for further intervention, such as re-excision, if needed **(Miszczyk *et al* 2017, Lara *et al* 2015, Fidelis *et al* 2020)**. This is certainly the practice in our study as noted in the number of serial biopsies undergone by patients. In some cases, staged excision after four years of follow-up was considered curative **(Kavoussi *et al* 2020).** Overall, follow up also allows for the detection of other complications such as bleeding and infections, and is not limited to BCC recurrence only. A great benefit for regular follow-up is the overall preservation of healthy tissue in anatomic constraint lesions to avoid the need for complex reconstructive procedures **(Quazi *et al* 2020).**

LIMITATIONS

The study is retrospective in nature; thus, it relies on the accuracy of hospital records for the study patients. Important information might have been omitted in these records.

5. CONCLUSIONS

In our study, margin was involved in 16.8% of the 226 largest biopsies and in 23.1% of the 91 smallest biopsies. The associated factors for margin involvement on excision are head and neck site, aggressive type, and non-primary lesions. For best patient outcomes, and the prevention of BCC recurrence, we recommend that the location, tumour size, histological type and non-primary lesions, need to be considered when deciding on excision margin size.

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APPENDICES

Appendix A - Approved Protocol

Appendix B - Data Collection sheet

Appendix C - Wits HREC approval (Ref M210838)

Appendix D - Turnitin Plagiarism Report

APPENDIX A – APPROVED PROTOCOL

(NOT TO BE EXAMINED)

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08 July 2021
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Dr CA Hoogendyk
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Dear Dr Charles Hoogendyk

Master of Medicine in Plastic and Reconstructive Surgery: Approval of Title

We have pleasure in advising that your proposal entitled *Incidence of incomplete excision of Basal Cell Carcinoma and Associated Factors* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

PROTOCOL

Title

Incidence of incomplete excision of Basal Cell Carcinoma and Associated Factors.

Name: Charles A Hoogendyk

Degree: MMed (Wits)

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Background

The most common malignancy in humans is Basal cell carcinoma.(Preston and Stern, 1992) (Telfer, Colver and Morton, 2008) Basal cell carcinoma incidence vary significantly and are affected by host and environmental factors of which UV irradiation plays an important role. UV exposure vary according to geographic location. Therefore the highest incidence rate is in Australia, 788/100,000 annually,(Staples, Marks and Giles, 1998) as compared to a much lower incidence in the United states, 146/100,000 annually.(Chuang *et al.*, 1990) In South Africa we have a multiracial population. The latest available statistics from the SA National Cancer Registry are from 2014, reporting the incidence of NMSC for South Africa to be 4.76/100,000 non-Whites and 19.2/100,000 Whites.(Norval, Kellett and Wright, 2014)

Although superficial BCC may be managed with non-operative treatments, surgery is the preferred treatment of choice for basal cell carcinoma. When deciding what margin of normal tissue should be excised, oncological safety comes first and second preservation of normal tissues. A 4-5mm peripheral margin has a clearance rate of approximately 95%, the remaining 5% of small BCCs extend over this margin. (Wolf and Zitelli, 1987) (Kimyai-Asadi *et al.*, 2005)

Epstein et al showed that for small well circumscribed BCC's, only seven percent infiltrate beyond 1mm of the clinical margins.(EPSTEIN, 1973) Therefore excising all BCC with a 4-5mm margin is not indicated, specially for lesions in cosmetic and functional sensitive areas like face.(David *et al.*, 1999) The recurrence rate for completely excised basal cell carcinoma is 3 to 6 percent.(Codazzi *et al.*, 2014) (Bozan *et al.*, 2015) For incompletely excised basal cell carcinoma, recurrence rate is 26 to 38 percent.(Codazzi *et al.*, 2014) (Bozan *et al.*, 2015) (Sussman and Liggins, 1996) (Richmond and Davie, 1987) For this reason complete excision is of utmost importance to minimize the risk of recurrence.

Retrospective studies have reported a incomplete excision rate for basal cell carcinoma ranging from 6.3 to 25 percent.(Sussman and Liggins, 1996) (Richmond and Davie, 1987) (Dieu and Macleod, 2002) (Griffiths, 1999) (Mak *et al.*, 1995) (Schreuder and Powell, 1999) (Rippey and Rippey, 1997) (Hauben *et al.*, 1982) (Hussain and Earley, 2003) (Bogdanov-Berezovsky *et al.*, 2001) However, Emmett and Broadbent, had a 0.7 percent incomplete excision rate.(Emmett and Broadbent, 1981) The reason for there exceptionally good result was two fold, they are two very experienced surgeons and there excision margins were wider than the standard practice (3 to 10mm). Prospective studies have reported a incomplete excision rate for basal cell carcinoma ranging 2 to 18.2 percent.(Thomas, King and Peat, 2003) (LAWRENCE, COMAISH and DAHL, 1986) (Bisson *et al.*, 2002) (Kumar *et al.*, 2002) (Hsuan *et al.*, 2004) The question then arise – why is the involved margin rate so much higher than expected with standard excision margins (4 – 5mm), if only 7% of small lesions extend more than 1mm beyond their clinical margin. The reason for this discrepancy lies in factors associated with increased risk of incomplete excision. These factors are: Age; sex; Histological type; Size; Site; Margin involved and Recurrent lesions. All previous studies on incomplete excision and associated factors were conducted in first world countries, no studies exist that specifically look at incomplete excision and associated factors in the South African setting.

Age and sex

In a retrospective audit by Kumar et al,(Kumar *et al.*, 2000) advanced age was associated with incomplete excision (mean age 73.7 in incomplete excision group vs. 68.6 in complete excision group). Other than Robins et al,(Robins and Albom, 1975) and Rakofsky,(Rakofsky, 1973) who reported a higher incidence in females, most other studies did not find sex to be a associated variable.

Histological type

BCC can be divided into two groups, indolent and aggressive according to histological type. The aggressive types extends more sublinicaly than the indolent types and therfore need to be excised with a wider margin. Aggressive types include morphoeic (sclerosing or fibrosing), metatypical, infiltrative and micronodular. Indolent types include nodular and superficial. (Crowson, 2006) This then also explain why the incomlete excion rate for morphoeic subtype is significantly higher than the other types.(Su *et al.*, 2007) (Kumar *et al.*, 2002) (Nagore *et al.*, 2003). Metatypical subtype is associated with incomplete excision.(Rakofsky, 1973) and has been shown to be more aggressive.(Goldberg, 1997) (Dellon, 1978) (De Faria, 1985) Mohs micrographic surgery is recommended for aggressive BCC subtypes. This technique involves intraoperative histological evaluation of the entire surgical margin, which enables complete tumour excision and decrease false clear margin rates, which in return decreases recurrence rates.(Kimyai-Asadi *et al.*, 2005) Recurrence risk with Mohs micrographic surgery has been reported as 3.3 percent. (Kuiper *et al.*, 2018) Due to cost we don't have access to Mohs micrographic surgery.

Size

The lager the tumor the wider the subclinical extention.(Burg *et al.*, 1975) (EPSTEIN, 1973)This explains why BCC larger than 20mm have a 10 percent higher incomplete excision rate versus tumors smaller than 20mm (20.4% versus 10.8%),(Su *et al.*, 2007)

Site

The most prevalent site for BCC is the head and neck area 80 - 90%.(Griffiths, 1999) (Bogdanov-Berezovsky *et al.*, 2001) (Kumar *et al.*, 2002) Incomplete excision rate is also much higher in the head and neck as compared to other areas (14.5 vs 8 percent).(Su *et al.*,

2007) Many other publications have shown similar findings.(Griffiths, 1999) (Sussman and Liggins, 1996) (Kumar *et al.*, 2002) (Friedman *et al.*, 1997) (Richmond and Davie, 1987) Of all incomplete excisions, 86 percent of them occur in the head and neck area, in particular the central face zone and ears - 70% of incompletely excised lesions.(Griffiths, 1999) The reasons for this is because there is little tissue in the face between closely positioned vital structures, therefore preserving cosmesis when taking wide margins is very difficult.(Rakofsky, 1973) (Robins and Albom, 1975) (Koplin and Zarem, 1980) It is because of these reasons that surgeons underestimate excision margins for head and neck lesions and overestimate margins for lesions on the limbs.(Thomas, King and Peat, 2003)

Margin Involved

Margin most commonly involved is the lateral margin.(Park, Strick and Watson, 1994) (Richmond and Davie, 1987) (Griffiths, 1999) (Kumar *et al.*, 2000)

Recurrent lesions

Recurrent lesions have a much higher incomplete excision rate as compared to primary lesions 26.8 percent compared to 11.2 percent for primary lesions,(Su *et al.*, 2007) finding similar to other studies.(Richmond and Davie, 1987) (Rippey and Rippey, 1997) (Emmett and Broadbent, 1981) (Kumar *et al.*, 2002) (Codazzi *et al.*, 2014)

In conclusion, there are factors associated with increased risk of incomplete excision of basal cell carcinoma. These factors can be assessed preoperatively on history and clinical examination and lesions at risk of incomplete excision with standard excision margin can be identified.(Codazzi *et al.*, 2014) Excision margin for these lesions should be adapted accordingly and this may lower the rate of involved surgical margin.(Su *et al.*, 2007)

Study Aim

To analyse rate of incomplete excisions of BCC at a tertiary Hospital in South Africa, as well as how, Age; Sex; Histological type; Size; Site; Margin involved and Recurrent lesions, influences the risk of incomplete excision.

Study Objectives

- To measure the incidence of involved excisional margin in surgically treated Basal cell carcinomas in two high volume, multi-disciplinary surgical centres in Johannesburg, South Africa.
- To analyse the association between involved excisional margin in surgically treated basal cell carcinoma and: Age, sex, Histological type, size, site, margin involved and recurrent lesions.

Methods

Study Site

The study setting is that of the Plastic surgery Department at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH). First patient contact is at the outpatient plastic surgery clinics, where patients are assessed by Consultant Plastic Surgeons. Medical officers and registrars perform excisions of BCC at these hospitals.

Study Design

Patient records will be reviewed retrospectively. Patients that underwent BCC excision during the last 5 years (January 2016 – December 2020) at Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Academic Hospital.

Study population

Charlotte Maxeke Johannesburg Academic Hospital is a public hospital situated in Parktown, Johannesburg, and serves a population of approximatel 2 million South Africans of mixed socio-economic circumstances. Chris Hani Baragwanath Academic Hospital is a public hospital situated in Soweto, Johannesburg, and serves a mostly African, lower income, population of 3 million South Africans. Basal cell carcinoma excision procedures are performed free-of-charge at Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Academic Hospital. For this study purpose all patients who had basal cell carcinoma excision procedures performed at Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Academic Hospital during January 2016 – December 2020 will be included in this retrospective review.

Data Collection

Patients undergoing basal cell carcinoma excision procedures during this time period will be identified from theatre booking lists. The histopathology reports for surgical specimens from these procedures will be obtained. Information recorded will be patient demographics (age and sex). Pathological findings:

- Margin clear or involved
- For involved margin specimens: Type, size, site, margin involved, recurrent lesion.

This information will be recorded on a data collection sheet (see Appendix A).

Choice of material for study

Pathological examination of surgical specimens is the most definitive way to decide whether a patient has involved excisional margin of basal cell carcinoma. Therefore, histopathology reports will be used to determine which patients had involved excisional margin.

Pathological assessment

Pathologic findings will be categorized into two broad groups: Involved or clear excisional margin. For the involved margin group – histological type, size, site, margin involved and recurrent lesion, will be assessed.

Inclusion Criteria

- All cutaneous basal cell carcinoma lesions excised
- Surgical specimens submitted for pathological review

Sample Size

The aim is to sample between 200 to 300 patients. All patients records fitting the above inclusion criteria will be included in this study. This should include patient records from January 2016 to December 2020.

Data Analysis

The data collection sheet will be used to capture data (See Appendix A). A study number will be assigned to each participant ensuring anonymity. Raw data will be then captured in an Excel spreadsheet and imported into STATA version 16 for statistical analysis. The Shapiro-Wilks test will be applied to determine the normality of continuous data, such as age and lesion size. Statistical tests will include standard descriptive statistics and means and standard deviations (SD) or medians and interquartile ranges (IQR) will be reported, as appropriate, for continuous variables. Categorical variables will be described using frequencies and proportions. Associations between involved excisional margins and continuous variables will be tested using the T-test or Mann-Whitney U test, as appropriate, whereas associations with categorical

variables will be determined by the Chi-squared test and/or Fisher's exact test. A p-value of ≤0.05 will be considered statistically significant.

Study Implications

The implications of the study include incidence of involved surgical margin in excised BCC in a third-world setting. Through the identification of statistically significant associated risk factors, that can be assessed on history and clinical examination, they can alert the surgeon to the higher risk of involved surgical margin with standard excision margins. This may lower the rate of involved surgical margin.

Study limitations

The study is retrospective in nature, thus it relies on the accuracy of hospital records for the patients included in it. Important information might have been omitted in these records.

Ethics

Ethics approval will be sought from the Wits Human Research Ethics Committee (HREC) during June 2021. A study number will be assigned to each participant ensuring anonymity.

Timing

	2021								
	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov
Literature review									
Preparing protocol									
Protocol assessment									
Ethics application									
Data collection									
Data analysis									
Writing up thesis									
Writing up paper									

Funding

The research will be relatively devoid of significant expense and will be borne by the researcher. Projected expenses include photocopying of R500 and transport costs to Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Academic Hospital of R1000.

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<u>Appendix A</u> – Data Collection Sheet

Study Number:	_____
Age:	_____
Female or Male:	_____
Hospital:	Charlotte Maxeke Johannesburg Academic Hospital or Chris Hani Baragwanath Academic Hospital

Surgery

Site:

Head & Neck:
Eyelids/eyebrows/nose/upper lip/lower lip/jaw angle/preauricular /postauricular/ears/temples/cheeks/forehead/chin/scalp/neck

Trunk:
Chest/abdomen/back/perineum/genitals

Limbs:
Upper/lower/hands/feet/pretibial

Occurrence:	Primary/Recurrent excision	
Pathology		
Lesion diameter(mm):	Largest	
	Smallest	
Margin:	Clear/Involved	
Involved margin:	Deep/Peripheral/Both	
Histological type:	Indolent:	Nodular Superficial
	Aggressive:	Morphoeic Metatypical Infiltrative Micronodular

APPENDIX B – Data Collection Sheet

Study Number: _____

Age: _____

Female or Male: _____

Hospital: Charlotte Maxeke Johannesburg Academic Hospital or

Chris Hani Baragwanath Academic Hospital

Surgery

Site: *Head & Neck:*
Eyelids/eyebrows/nose/upper lip/lower lip/Jaw angle/preauricular/ postauricular/ ears/temples/cheeks/forehead/chin/ scalp/neck

Trunk:
Chest/abdomen/back/perineum/genitals

Limbs:
Upper/lower/hands/feet/pretibial

Occurrence: Primary/Re-excision/Recurrent

Pathology

Lesion diameter (mm): Largest

Smallest

Margin: Clear/Involved

Involved margin: Deep/Peripheral/Both

Histological type:

Indolent:	Nodular Superficial)
Aggressive:	Morpheaform Metatypical Infiltrative Micronodular

APPENDIX C – WITS HREC APPROVAL

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO:	Dr CA Hoogendyk School of Clinical Medicine Department of Surgery Division of Plastic and Reconstructive Surgery Medical School University E-mail: gushoogendyk@hotmail.com
CC:	Supervisor: Dr C Sofianos and Professor D Kruger <sofianosc@gmail.com> and <HREC-Medical Research Office@wits.ac.za>
FROM:	Mr Iain Burns Human Research Ethics Committee (Medical) Tel: 011 717 1252 E-mail: Iain.Burns@wits.ac.za
DATE:	2022/05/24
REF:	R14/49
PROTOCOL NO:	**M210838** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)
PROJECT TITLE:	*Incidence of incomplete excision of Basal Cell Carcinoma and associated factors*

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 Government funding of the University.

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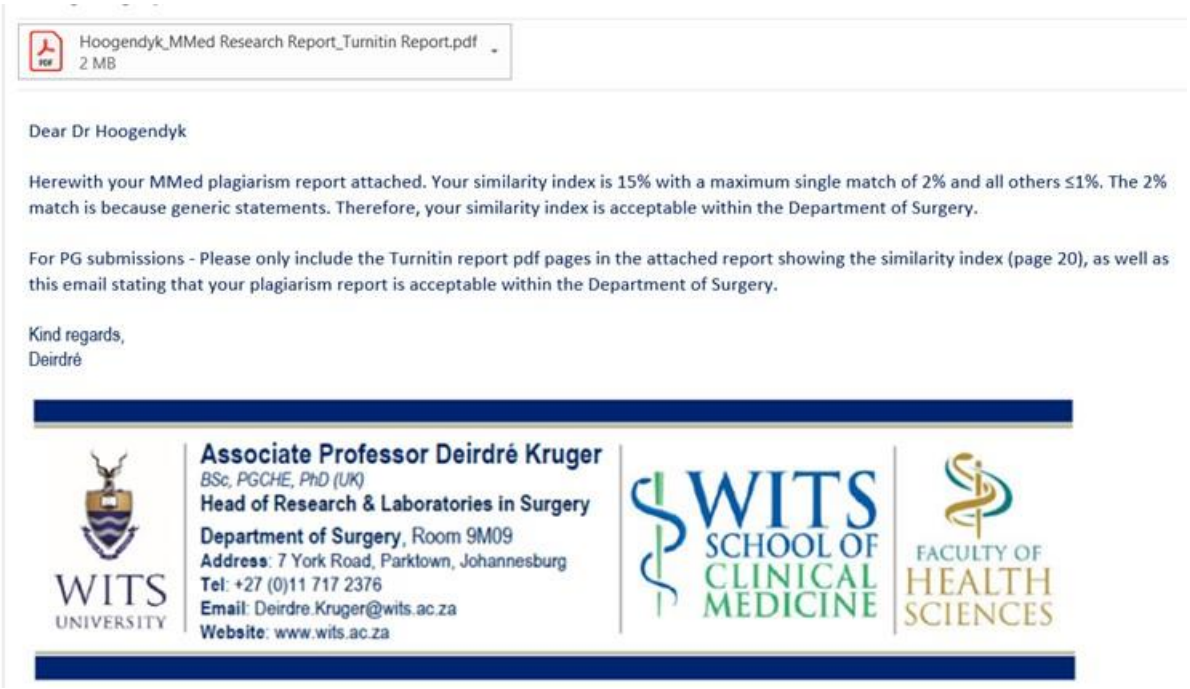
APPENDIX D – TURNITIN PLAGIARISM REPORT



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