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PERINEURAL INFILTRATION OF THE INFERIOR ALVEOLAR NERVE IN MANDIBULAR AMELOBLASTOMAS

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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 Dentistry

in the branch of Maxillofacial and Oral Surgery

Johannesburg, 2012

DECLARATION

I, Hanlie Engelbrecht declare that this research report is my own work. It is being submitted for the Degree of Master of Dentistry in the branch of Maxillofacial and Oral Surgery to the University of the Witwatersrand, Johannesburg. It has not been submitted before for any other degree or examination at this or any other University.

_____

Hanlie Engelbrecht

31st day of August 2012

I dedicate this work to my parents Lieb and Laetitia van Jaarsveld,

my loving husband Riaan Engelbrecht and my son Steph

for all their love and support in the realisation of my degree.

"If I have seen further it is by standing on the shoulders of giants"

Sir Isaac Newton

PRESENTATIONS ARISING FROM THIS STUDY

Engelbrecht H, Meer S, Kourie JF. Perineural infiltration of the inferior alveolar nerve in mandibular ameloblastomas. Oral presentation. *SASMFOS Congress*, Centurion, South Africa. September 2011.

ABSTRACT

Introduction: Ameloblastomas are locally aggressive with a high recurrence rate, warranting continuity jaw resection. The preservation of the inferior alveolar nerve during ablative surgery in the treatment of ameloblastoma is contentious. Studies have suggested salvaging the nerve by pulling it out of the tumour prior to resection. There are presently no studies that have explored the surgical merit of nerve preservation in the treatment of ameloblastomas.

Aim: To determine the histological association of mandibular solid and multicystic ameloblastoma to the inferior alveolar nerve, in situ and in separately removed segments of the nerve in order to determine the feasibility of preserving the nerve during ablative surgery for mandibular ameloblastomas.

Materials and Methods: 13 resected hemimandibulectomy specimens were histologically examined with respect to the course and association of the inferior alveolar canal/nerve and the ameloblastoma. In group 1 (8 patients) this association was examined with the nerve within the mandibular segment following resection whilst in group 2 (5 patients) the nerve was explanted from the resected tumour and examined separately. In group 1 the closest histologic distance between tumour cells and the inferior alveolar canal was measured.

Results: Perineural and intraneural ameloblastoma involvement of the inferior alveolar nerve was confirmed in 62.5% and 40% of cases in groups 1 and 2 respectively. Tumour cells were noted abutting directly onto the nerve in Group 1. Tumour cells were removed together with the pulled out nerve in Group 2. There was no correlation between the histological variants of ameloblastoma and the presence of tumour either in situ or within the pulled-out nerve bundle.

Conclusion: Both peri- and intraneural involvement of the inferior alveolar nerve was histologically confirmed in solid and multicystic hemimandibular specimens both in situ within the tumour as well as in separately removed segments of the nerve. Preservation of the inferior alveolar nerve during ablative surgery for mandibular ameloblastomas cannot be advocated.

ACKNOWLEDGEMENTS

This research project was made possible by the unwavering support of my family, supervisors and colleagues.

To the Department of Maxillofacial and Oral Surgery and the Department of Oral Pathology at the University of the Witwatersrand, I would like to extend my gratitude for their support and motivation.

I wish to thank my supervisors; Prof Shabnum Meer and Dr Jeff Kourie, for theirs are the giant shoulders that I am standing on. It is with the deepest respect and admiration that I thank you for your guidance.

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PREFACE

The ameloblastoma is the most commonly treated benign odontogenic tumour. The treatment and subsequent reconstruction of the defect has been extensively researched and debated, with several treatment modalities available to the surgeon.

Of late, several authorities have suggested that the inferior alveolar nerve be spared during ablative surgery, by pulling the nerve out from the tumour and anastomosing the cut ends, a procedure which results in a high rate of sensory recovery. There have been no studies, however, commenting on the recurrence rate of the tumour in patients having had such surgery in comparison to patients where the nerve had been sacrificed.

There have been no studies examining the inferior alveolar nerve histologically when the nerve has been spared by pulling it out from the tumour or when the nerve has been removed together with the tumour in order to determine the viability of the different techniques. This study is thus highly relevant as the anticipated findings will aid the surgeon in treatment planning for mandibular ameloblastomas.

CHAPTER 1

1.0 INTRODUCTION

The ameloblastoma is the most commonly occurring and treated benign tumour in the head and neck area. It may reach grotesque sizes, leading to debilitating deformity and loss of function. The treatment and subsequent reconstruction of the defect has been extensively researched, debated and published with several accepted treatment modalities available to the surgeon.[1-4] In certain types of ameloblastoma, complete excision with a 1cm safety margin is the accepted standard of care, with reconstruction of the bony framework and soft tissue aimed at restoring masticatory function, speech and appearance.[4]

With regard to the restoration of neurosensory function following ablative surgery, several authorities[5-7] have recently advocated the sparing of the inferior alveolar nerve by pulling the nerve out from the tumour. As the tumour is benign in nature, it is postulated that the inferior alveolar nerve bundle would be free of tumour if removed from the affected mandible, and thus should not increase the patient's chance of developing a recurrent tumour.[5]

Ameloblastomas are known to be locally aggressive and destructive, with a high rate of recurrence if not treated aggressively. To the best of our knowledge there are presently no studies that have assessed the recurrence rate of the tumour in patients who have had surgical removal of the tumour with preservation of the inferior alveolar nerve, in comparison to patients where the nerve was sacrificed with removal of the tumour.

Furthermore, no studies have examined the inferior alveolar nerve bundle histologically following either procedure. Thus the need for a histologic study in which the association of ameloblastoma in relation to the inferior alveolar nerve is assessed both when removed with the tumour and when removed separately. The findings of such an investigation will be useful in guiding the management of the inferior alveolar nerve during ablative surgery for mandibular ameloblastoma.

CHAPTER 2

2.0 LITERATURE REVIEW

2.1 The ameloblastoma

The most common benign tumour affecting the jaws is the ameloblastoma.[1-3] It is a tumour of odontogenic epithelial origin, that exhibits locally aggressive behaviour.[1-4] The mandible is involved 7 to 8 times more frequently than the maxilla.[1] The angle, ascending ramus and body are most commonly affected in the mandible.[1,2,8] Benign ameloblastomas are classified into 3 main groups, namely the solid and multicystic, unicystic and peripheral variants.[3] The distinction between the different clinicopathologic subtypes is important as the biological behaviour, treatment and prognosis may differ for each variant.[3,4,9-12]

Ameloblastomas can reach grotesque sizes, causing a substantial amount of local destruction and severe deformity (Figs. 2.1 and 2.2). In general though, they are not known to be infiltrative[11-14] and very seldom undergo malignant change or metastasize.[3,4]

Multiple histological subtypes of ameloblastoma have been described,[1-3] and some authors suggest that the histological subtype should guide the surgeon in treatment planning.[8,11] Their contention is that certain histological subtypes tend to exhibit less aggressive behaviour than others.[2,11] Other authors[1,2] have noted that larger ameloblastomas generally have a mixed histological pattern rendering the notion that histological subtype could guide treatment planning invalid.



Fig. 2.1 Patient exhibiting gross deformity caused by a mandibular solid and multicystic ameloblastoma

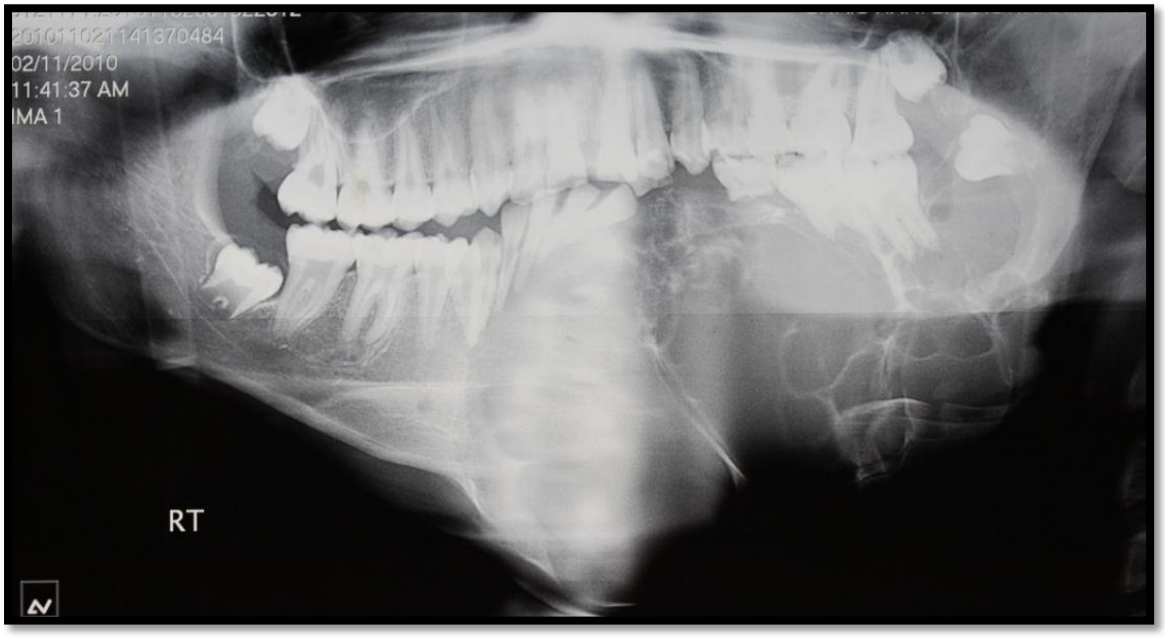


Fig. 2.2 Panoramic radiographic view of the patient above (Fig 2.1) demonstrating obliteration/loss of the course of the inferior alveolar canal on the left side

It is well known and widely published that ameloblastomas in spite of being benign in nature, have a high recurrence rate if appropriate primary treatment is not instituted timeously.[1,2,4] Recurrence rates of 1% to 15% have been recorded following radical treatment, especially following resection with a safety margin,[15] and up to 90% following conservative management such as enucleation and marsupialisation.[15,16]

Increased recurrence rates have been linked to specific histological subtypes of ameloblastomas, specifically the follicular, granular and acanthomatous types.[8] The desmoplastic type has been found to be less aggressive with a lower recurrence rate.[3]

2.2 Current treatment modalities

Various treatment modalities for ameloblastomas have been described and these range from conservative therapies such as decompression with marsupialisation and enucleation,[11] to the more radical approach which includes a large continuity resection.[1,2,4] Furthermore, the treatment options for each clinical variant of ameloblastoma differs; ranging from excision for the peripheral variant, enucleation with adjunctive therapy for luminal and intraluminal unicystic ameloblastomas and resection with clear margins for the mural unicystic and the solid and multicystic ameloblastomas.[1-4] The various recommendations on the extent of the resection[4,9-12] range from resection with a 1 to 2 cm margin in bone[4,17,18] to a more conservative en-bloc resection with preservation of the lower border of the mandible.[10]

In addition, different treatment protocols for each histological subtype have also been suggested, such as an aggressive resection for follicular subtypes and resection with a smaller margin for plexiform or desmoplastic variants.[3,11] However, the treatment protocol requires

correlation of the clinical and radiographic appearance, the operative findings and the histological subtype of the tumour.[1-4,9-12]

Recent consensus is that a more aggressive approach is warranted for the treatment of the solid and multicystic ameloblastoma due to the extremely high recurrence rate following conservative treatment.[3,4,8-10,13,19] Some authors believe that the only exception to such treatment would be in children, where a more conservative approach is advocated.[20]

Aggressive surgical removal of the tumour more often than not leads to ablative surgery resulting in continuity defects of the mandible. These defects may cause great functional, aesthetic and emotional debilitation. Following the impairment of the initial surgery, the reconstruction of the patient has been widely debated and published.[9-12,19] Surgeons concur that the patient be restored as closely as possible to pre-treatment function and aesthetics. Options for reconstruction of the patient after tumour resection include vascularised tissue transfer, most notably of the fibula;[19] free block grafts commonly taken from iliac crest;[3,7] particulate cortico-cancellous bone and marrow grafts also taken from iliac crest[3,4] and recently distraction osteogenesis.[21] These procedures aim to create a bony and soft tissue base upon which further dental rehabilitation can be done, by means of implant placement into the graft (either immediate or delayed) and placement of a fixed or removable prosthesis[19,22] as demonstrated in Fig. 2.3. The eventual outcome must be a patient that has been rehabilitated functionally and cosmetically.

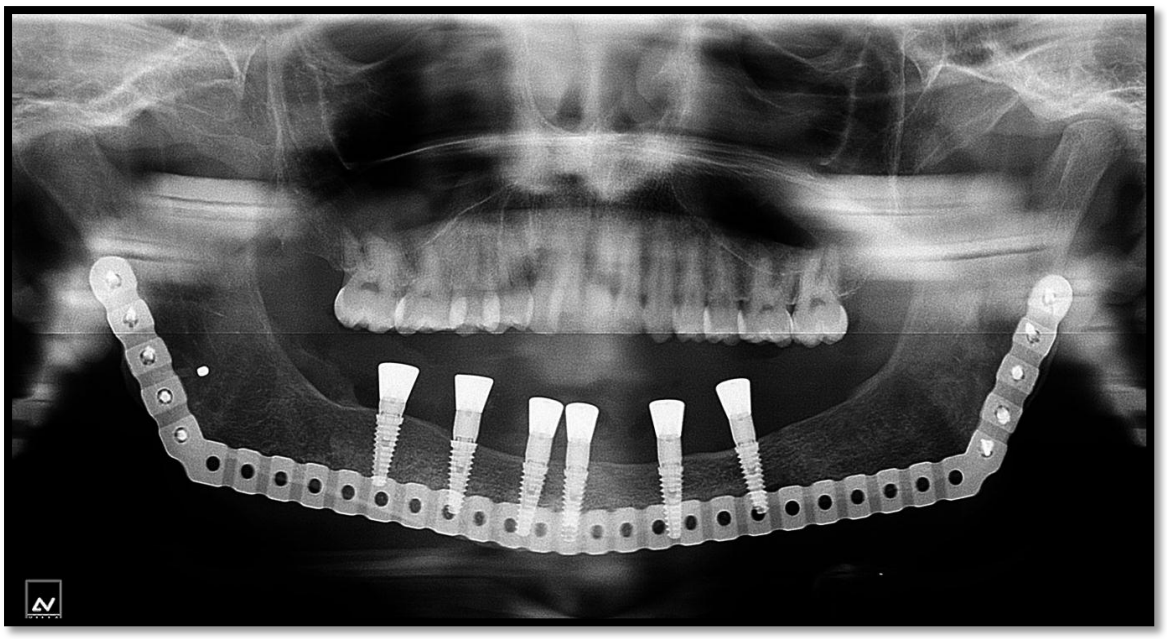


Fig. 2.3 Panoramic radiograph demonstrating a cortico-cancellous bone graft and implant placement for dental rehabilitation following an angle to angle resection of the mandible for treatment of a solid and multicystic ameloblastoma

Alternative and adjuvant therapies, including radiotherapy and chemotherapy have been found to have little effect on the tumour.[1,23-25] It has also been reported in a canine model that radiation can induce malignant transformation of the ameloblastoma.[24] In the latter study ameloblastomas were induced in canine subjects and subsequently treated with radiation. The detrimental effects of the radiation that may evoke radiation-induced malignancy also extend to the surrounding tissue and structures, as the tumours are generally located within bone.[1] This treatment modality is thus reserved for extreme cases that are irresectable and life threatening,[1] such as extensive maxillary ameloblastomas that encroach on the skull base and which cannot be surgically removed.

New treatment modalities obviating the need for surgery in the treatment of ameloblastoma are currently being researched. These treatment modalities are aimed at the molecular basis of tumour origin and may take the form of agents being delivered locally (directly into the

tumour), a process that will target specific signalling pathways.[26] Despite the myriad of treatment options suggested the consensus remains that aggressive treatment provides the best prognosis for solid and multicystic ameloblastomas.[1,2,4,8]

2.3 The inferior alveolar nerve

The inferior alveolar nerve is the main sensory nerve to the mandible, supplying the oral mucosa, the dentition and the skin overlying the chin and the lower lip. The third division of the trigeminal nerve exits the base of skull via the foramen ovale, after which it splits into an anterior and posterior trunk. The inferior alveolar nerve arises within the posterior trunk and then passes through the mandibular foramen into the mandibular canal on the medial side of the ramus of the mandible. It traverses the canal and exits at the mental foramen.[27-29]

The nerve consists of myelinated axons that make up nerve fibres. These fibres are encased in a thin connective tissue layer called the endoneurium. A group of fibres coupled together and encased by another layer of connective tissue, or perineurium, is called a fascicle. A couple of fascicles arranged together and surrounded by connective tissue, called epineurium, make up a nerve bundle (Fig. 2.4).[29]

Expanding tumours, cysts and other lesions of the mandible have been reported to involve the inferior alveolar canal.[4,11,12] This may include circumferential involvement and or destruction of the inferior alveolar canal, often with displacement of the canal away from its normal position.[30]

Nerve involvement by the tumour may lead to altered sensation (either hypoaesthesia or uncommonly hyperaesthesia), in the area of its distribution. As the inferior alveolar nerve runs within the bone in the ramus, angle and body of the mandible, it is commonly resected together with the tumour. The resulting loss of nerve sensation although most often benign may also lead to drooling, speech impediment, unintentional lip biting, residual food stagnation on the lip, burning pain, tingling and scalding of the lip with hot subtances.[5,27] This may be quite injurious in some patients. Preservation of the neurovascular bundle during ablative surgery to treat ameloblastoma in order to prevent the many resultant signs and symptoms of neural fallout is thus an extremely important consideration.

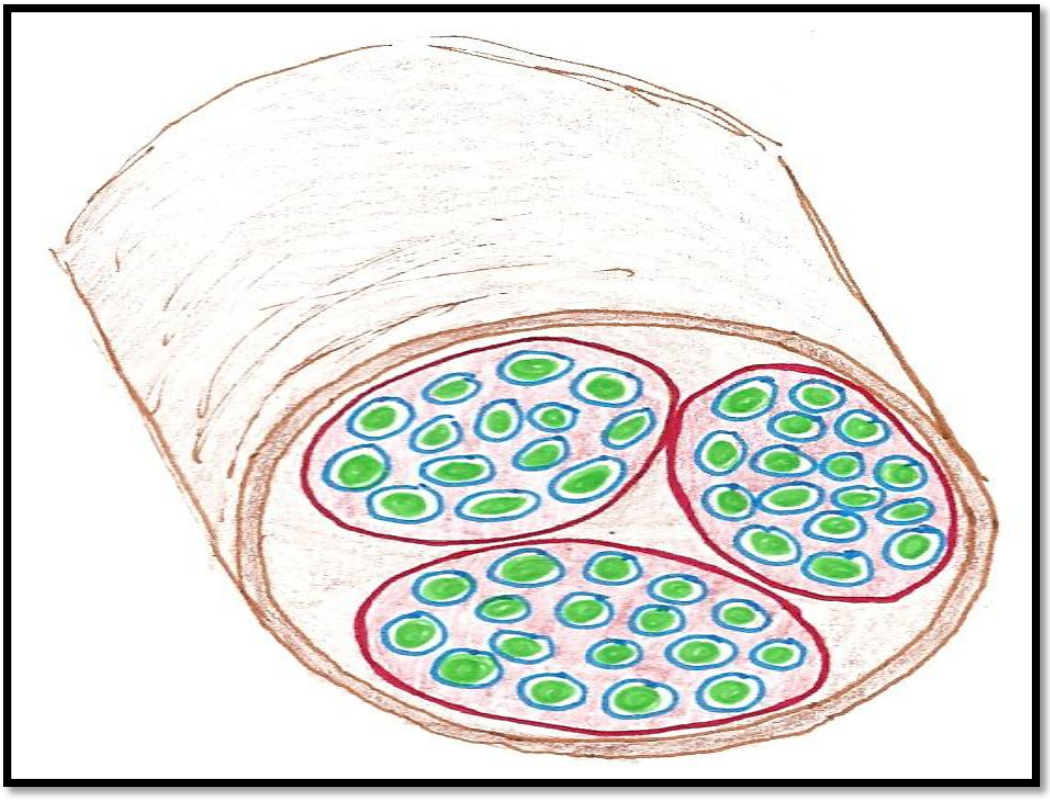


Fig. 2.4 Schematic illustration of a nerve: The brown outer layer is the epineurium, a connective tissue sheath surrounding the entire nerve. The red sheaths indicate the perineurium that encloses bundles of nerve fibres. The blue sheaths represent the delicate endoneurium that surrounds individual nerve fibres (green)

2.4 Management of the inferior alveolar nerve during ablative surgery

Great debate exists amongst maxillofacial and oral surgeons regarding preservation of the inferior alveolar neurovascular bundle during ablative surgery in the treatment of ameloblastomas.[5-7,11,12,14,30] Becker[7] first described preservation of the inferior alveolar neurovascular bundle during ablative surgery, but suggested that this technique not be used for the treatment of the solid and multicystic ameloblastoma.

Becker's technique[7] entailed sectioning of the mandible, with segmental removal of the tumour surrounding the nerve, preserving the nerve bundle in its entirety (Figs. 2.5 to 2.7). Subsequent to the piece-meal removal of the tumour from around the nerve, the defect is restored with a block graft from the iliac crest. A groove is prepared centrally within the graft to mimic the inferior alveolar canal and the nerve is placed within the graft. The graft is secured by using either wire or plates.

Becker[7] recommended that the technique be used for benign cystic lesions such as cystic ameloblastomas and dentigerous cysts, as well as other benign pathology including osteomyelitis of the mandible. However, he expressed concern for the use of this technique in solid and multicystic ameloblastomas in view of the possible seeding of tumour into surrounding soft tissue. In spite of the neurovascular bundle being left intact, some permanent sensory fall-out in a small area of the lower lip was reported.

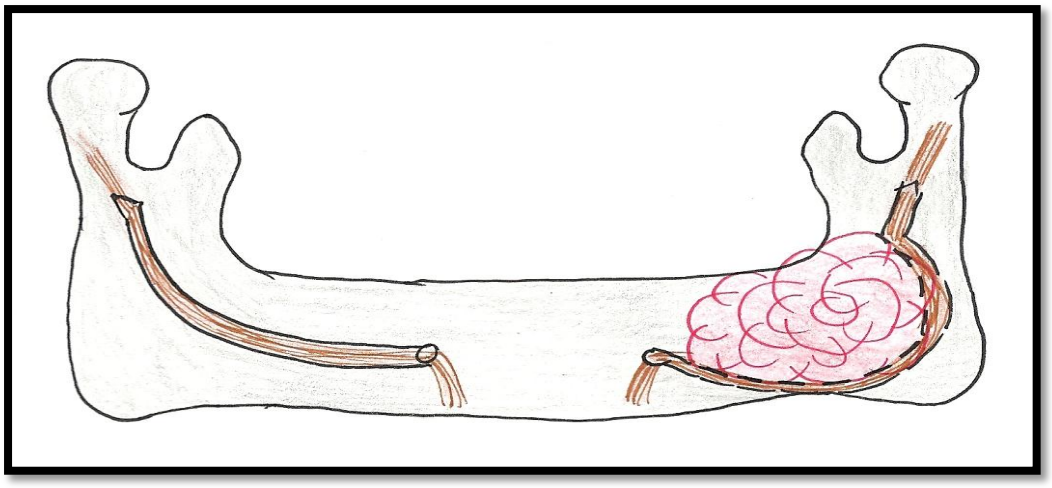


Fig. 2.5 Diagrammatic illustration of displacement of the inferior alveolar canal (brown) by a solid and multicystic ameloblastoma (red) of the left mandibular angle and body

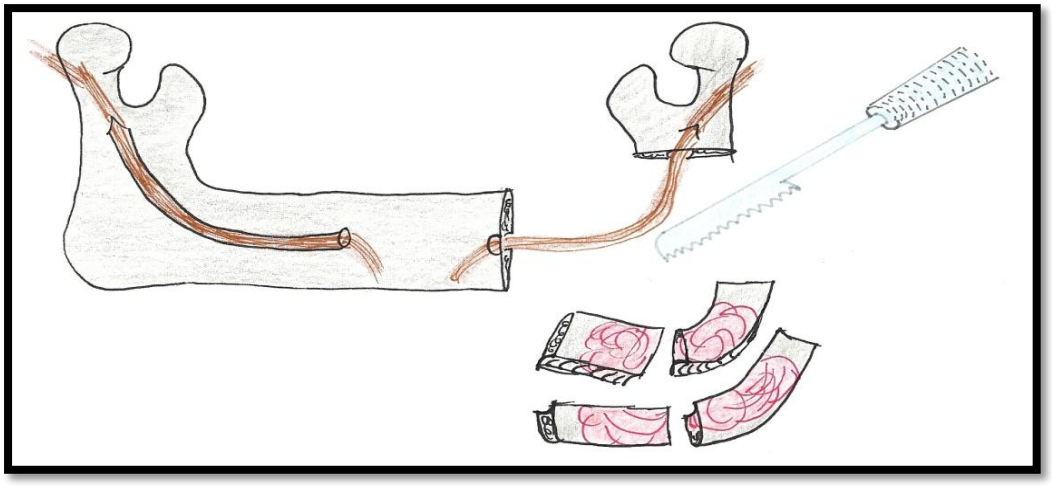


Fig. 2.6 Diagrammatic illustration of the particulate removal of the tumour, sparing the nerve in its entirety

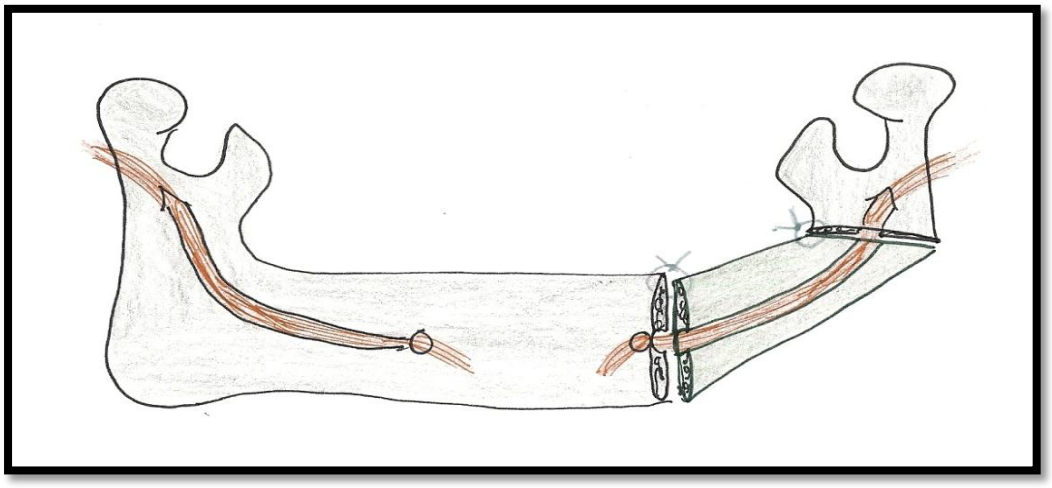


Fig. 2.7 Diagrammatic sketch showing the iliac crest block graft secured to the mandible and spanning the defect. The nerve lies centrally within the fabricated groove.

Ishikawa *et al*.[5] proposed an alternative technique (Figs. 2.8 to 2.11) whereby the nerve is severed together with one of the resection margins and pulled through the mandibular and mental foramina. The nerve endings are subsequently anastomosed microsurgically.

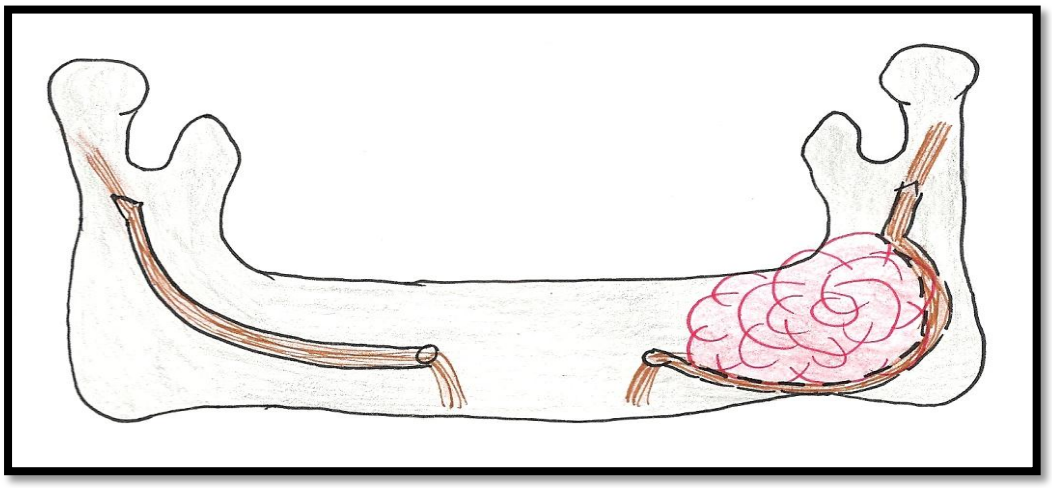


Fig 2.8 Diagrammatic illustration of the displacement of the inferior alveolar canal (brown) of a solid and multicystic ameloblastoma (red) of the left mandibular angle and body

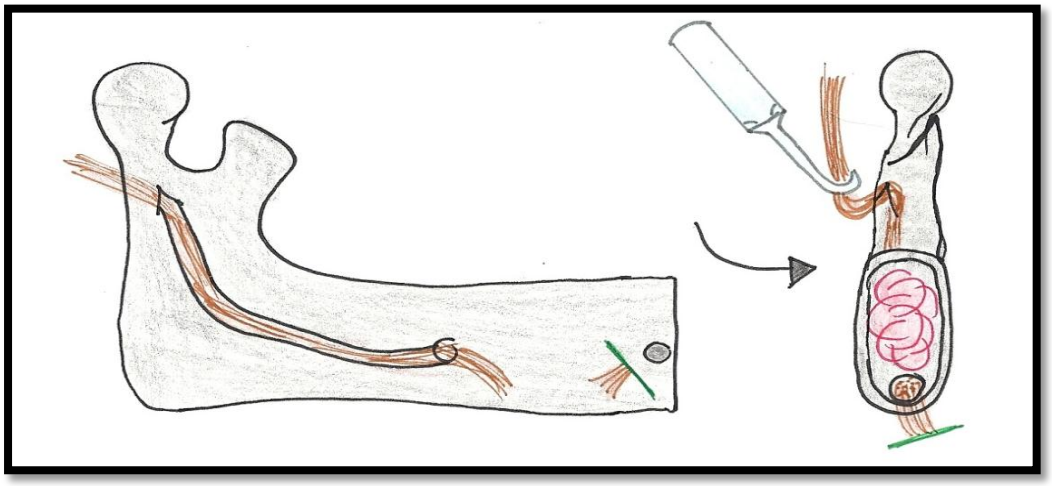


Fig. 2.9 Diagrammatic illustration of the Ishikawa *et al*.[5] technique. The mandible is sectioned anterior to the tumour margin and the nerve is cut (green lines). The proximal segment is reflected open (black arrow) and the nerve is pulled out of the mandible with a hook, via the mandibular foramen at the lingula

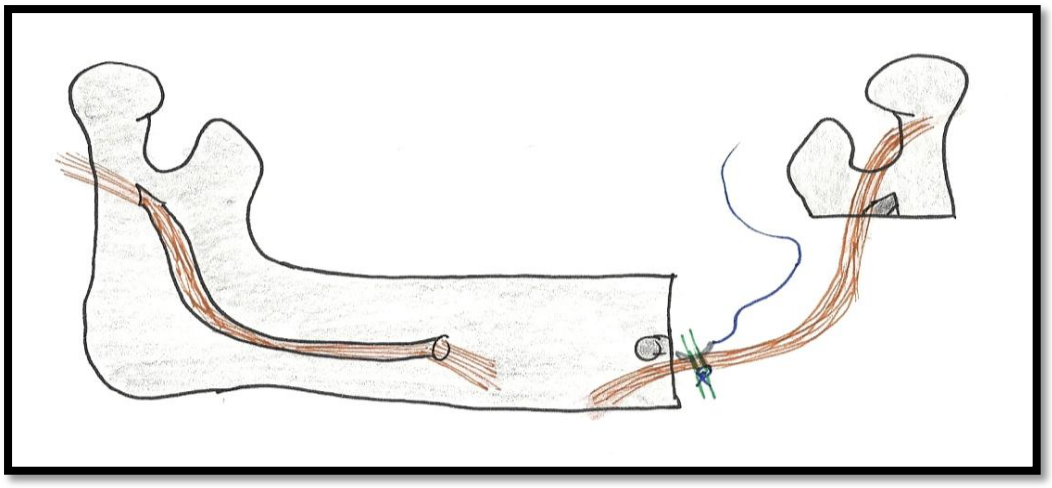


Fig. 2.10 Diagrammatic sketch showing the anastomosis of the cut inferior alveolar nerve ends after resection of the ameloblastoma

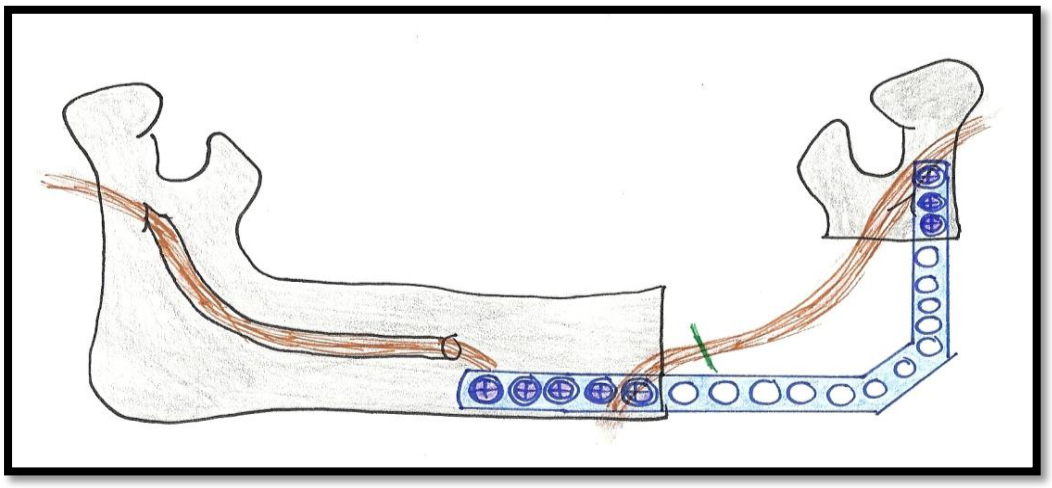


Fig. 2.11 Diagrammatic illustration showing interim reconstruction of the defect using a reconstruction plate (blue); note the nerve anastomosis (green)

The following criteria for the use of this technique were recommended by Ishikawa *et al.*[5]

- There should be no pre-operative loss of sensation in the area of distribution of the inferior alveolar nerve
- The nerve must be pulled through with ease, showing no signs of pathologic adhesion
- The nerve trunk should exhibit normal elasticity
- The neural sheath should appear smooth, glossy, uniform and regular

A case of resection of a solid and multicystic ameloblastoma following Becker's technique[7] coupled with the simultaneous placement of a bone graft was published by Wu *et al*.[6] in 1984. The patient showed good sensory recovery and had no recurrence at the time of publication (after 2 years).

The sensory recovery of the inferior alveolar nerve following multiple insults during ablative surgery, including sectioning, tension on the nerve to remove it and anastomosis has not been formally described. However, there are numerous reports in the literature regarding trigeminal nerve recovery following surgical intervention to restore function, where nerve ends were anastomosed following trauma, or partial resection with anastomosis was done for paraesthesia. In these reports recovery approached levels of well above 75%.[31,32] From this we can deduce that the nerve will recover well following Ishikawa's technique.[5] This would have a great impact on relieving morbidity post-operatively.

Zehm *et al*.[33] examined the nerve and its relation to the tumour and found tumour cells to be in close proximity to the epineurium, although it did not penetrate deeper than the epineurium. Pourian *et al*.[14] also examined and measured the distance between the neurovascular bundle (epineurium) and the closest ameloblastoma tumour cells and found this to be 120µm. The latter report stressed that the tumour cells were too close to the neurovascular bundle to consider pulling out the nerve, resulting in tumour cells being removed together with the nerve leading to eventual recurrence.

Based on the findings of Zehm *et al*.,[33] Tung-Yiu *et al*.[34] reported a case where an epineural dissection of the inferior alveolar nerve was performed at the time of resection of a plexiform ameloblastoma affecting the mandibular angle. The patient had an immediate reconstruction

of the defect utilising a block graft from the iliac crest. The dissected nerve was placed next to the block graft and covered by mucosa. Sensory recovery was acceptable, with a good two-point discrimination test and only mild paraesthesia subjectively reported by the patient.

Alternatives to saving the inferior alveolar nerve during resection and aimed at restoration of sensation to the lower lip have been described.[35-37] Reconstruction by means of autogenous grafting with local or distant nerves has been advocated, most commonly the great auricular nerve,[35] the sural nerve[36] and the long thoracic nerve.[37] The nerves are harvested and anastomosed to the cut ends of the inferior alveolar nerve. This is ideally done at the time of the initial resection, as atrophy and fibrosis of the surgical bed creates surgical problems if grafting is performed secondarily. The rate of recovery is variable, ranging from good patient satisfaction rates to continued paraesthesia. Donor site morbidity remains a worry too, as the donor site skin may show paraesthesia or complete anaesthesia. Unnecessary scarring of the patient is also a concern.

Chou *et al*.[28] reported that no attempt at reinstating sensation should be considered as the patients in their study group all had favourable outcomes with regard to sensory recovery and acceptance. They noted some adaptation to the fall-out, generally in the form of sensory perception to touch.[28] Some patients even displayed signs of neurosensory recovery in the affected area, most likely due to collateral sprouting of surrounding nerves. This phenomenon has been widely described and can result in complete sensory recovery in children.[38] It should be noted that the patients in the study by Chou *et al*.[28] were generally younger patients.

Nakamura *et al.*[11] and others[5] suggested that the pull-through technique with end-to-end anastomosis of the inferior alveolar nerve be used only for unicystic ameloblastomas and certain sub-types of solid and multicystic ameloblastomas such as the plexiform variant. They found no perineural infiltration in their evaluation of the proximity of all types of ameloblastic tumour cells to the mandibular neurovascular bundle, but found that the follicular pattern of ameloblastoma in particular showed tumour cells in direct apposition to the nerve sheath. Nakamura *et al*.[11] postulated that the nerve, if pulled through, would be tumour free. Follow-up studies revealed that apposition of ameloblastomatous cells to the nerve sheath was not restricted to the follicular pattern specifically, but rather correlated to the size of the tumour.[9]

The preservation of the inferior alveolar neurovascular bundle during ablative surgery in the treatment of ameloblastoma is contentious. In the absence of the great risk for recurrence of the lesion, preserving the nerve during resection would be the treatment modality of choice. Many studies report on the recurrence rates of ameloblastomas,[3,4,9-11] there are however unfortunately no studies which review and compare the recurrence rate in patients following treatment of ameloblastomas with and without preservation of the nerve.

The possibility of recurrence is undoubtedly the biggest cause for concern when considering preservation of the inferior alveolar nerve during ablative surgery. There is thus a very clear need to establish histologically whether a preserved nerve will be free of tumour cells.

Currently there are no South African or global studies that have histologically examined the association of ameloblastoma tumour cells to the inferior alveolar nerve following surgical removal of the nerve from the tumour. Furthermore there are no studies that have explored

the possibility of preserving the inferior alveolar nerve during segmental resection of the mandible, with adequate follow-up to evaluate possible recurrence rates. Only studies that have measured the distance between tumour cells and the nerve with the neurovascular bundle left in situ have been reported.[11,30,33]

CHAPTER 3

3.0 AIM AND OBJECTIVES

3.1 Aim

The aim of this study was to determine the histological association of the solid and multicystic ameloblastoma in hemimandibular specimens to the inferior alveolar nerve, both in situ within the tumour as well as in separately removed segments of the nerve in order to determine the feasibility of preserving the inferior alveolar nerve during ablative surgery for mandibular ameloblastomas.

3.2 Objectives

This will be achieved by a histological measurement of the distance between the ameloblastomatous tumour cells and the epineurium of the inferior alveolar nerve, as well as determining whether tumour cells are removed together with the pulled out nerve.

3.3 Comment

The findings of the study will guide the surgical treatment protocol for patients with mandibular ameloblastomas, especially with regards to preservation or removal of the inferior alveolar nerve. This is a highly relevant study as there are currently no treatment guidelines pertaining specifically to the management of the inferior alveolar nerve during ablative surgery for mandibular ameloblastomas.

CHAPTER 4

4.0 MATERIALS AND METHODS

4.1 Study design

A prospective study was carried out, examining resected hemimandibular specimens in patients diagnosed with solid and multicystic ameloblastoma over a one year period [2010 – 2011]. All patients were treated at the Charlotte Maxeke Johannesburg Academic and the Chris Hani Baragwanath Hospitals, Johannesburg, South Africa. The current treatment standard for this type of ameloblastoma is resection of the involved mandible, including removal of the associated inferior alveolar nerve. Thus there was no change to the current accepted treatment protocol for patients with solid and multicystic ameloblastoma in the Division of Oral and Maxillofacial Surgery at the University of the Witwatersrand.

4.2 Study sample

Following routine surgical treatment of patients with solid and multicystic ameloblastomas, 13 resected hemimandibulectomy specimens, which included the inferior alveolar canal, were microscopically examined. The course of the inferior alveolar canal and nerve as well as tumour association to the inferior alveolar canal were imaged and studied using plain film radiographs prior to serial sectioning of the resected specimen. This was done only as a guide to locate the histologic pathway of the nerve. The specimens were divided into 2 groups as outlined below, with 8 patients in the first group and 5 patients in the second group.

- Group 1 included cases where the portion of the mandible containing the tumour was resected leaving the inferior alveolar nerve in position, and thus allowing an in situ histological examination of the nerve and tumour (Figs. 4.1 and 4.2). The closest

distance between the neurovascular bundle (epineurium) and the tumour cells were measured. The canal was examined to determine whether it was merely displaced or whether there was any erosion by the tumour, on those portions of the canal that were present on the serial sections examined. The closest distance between the neurovascular bundle (epineurium) and the tumour cells were measured.

- Group 2 comprised of the resected mandibular specimens in which the investigator mimicked the surgical pull-through technique as described by Ishikawa *et al*.[5] on the unfixed specimen, immediately after resection in theatre, prior to submission in formalin for histopathological examination. The nerve and the tumour were examined separately (Figs 4.3, 4.4 and 4.5). The presence or absence of tumour cells in or on the nerve was evaluated. In the ameloblastoma specimen, the closest distance between tumour cells and the inferior alveolar canal (devoid of the explanted nerve) was measured.



Fig. 4.1 Group 1: patient with a solid and multicystic ameloblastoma of the right body, symphysis, left angle and body of mandible

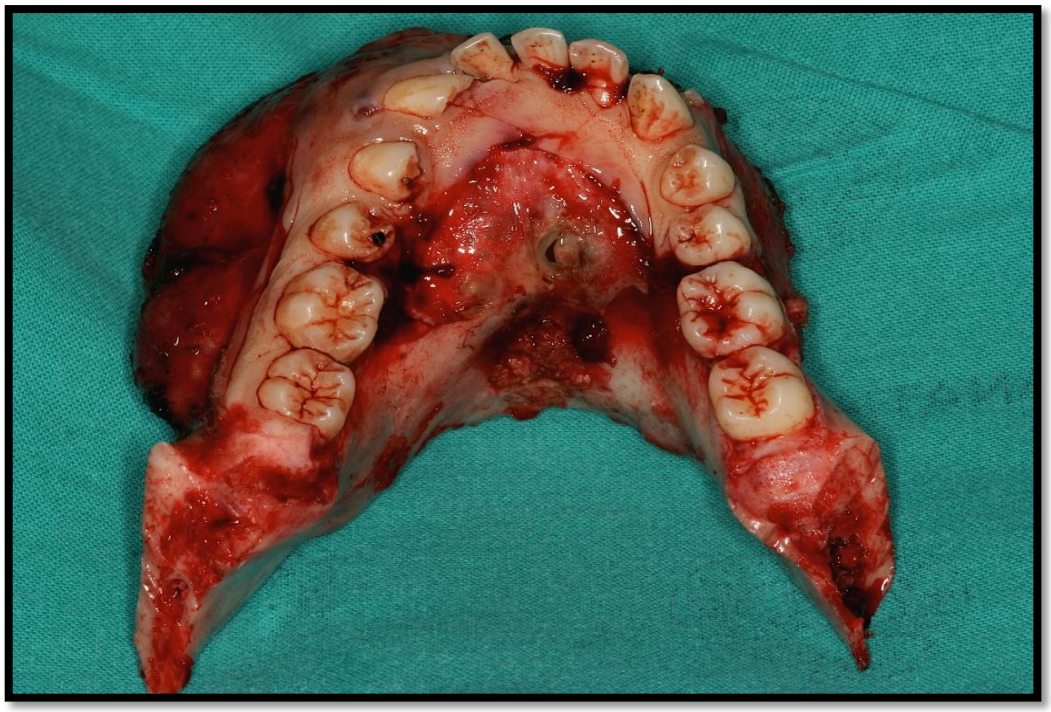


Fig 4.2 Group 1: mandibulectomy specimen of the solid and multicystic ameloblastoma from patient in Fig 4.1 above

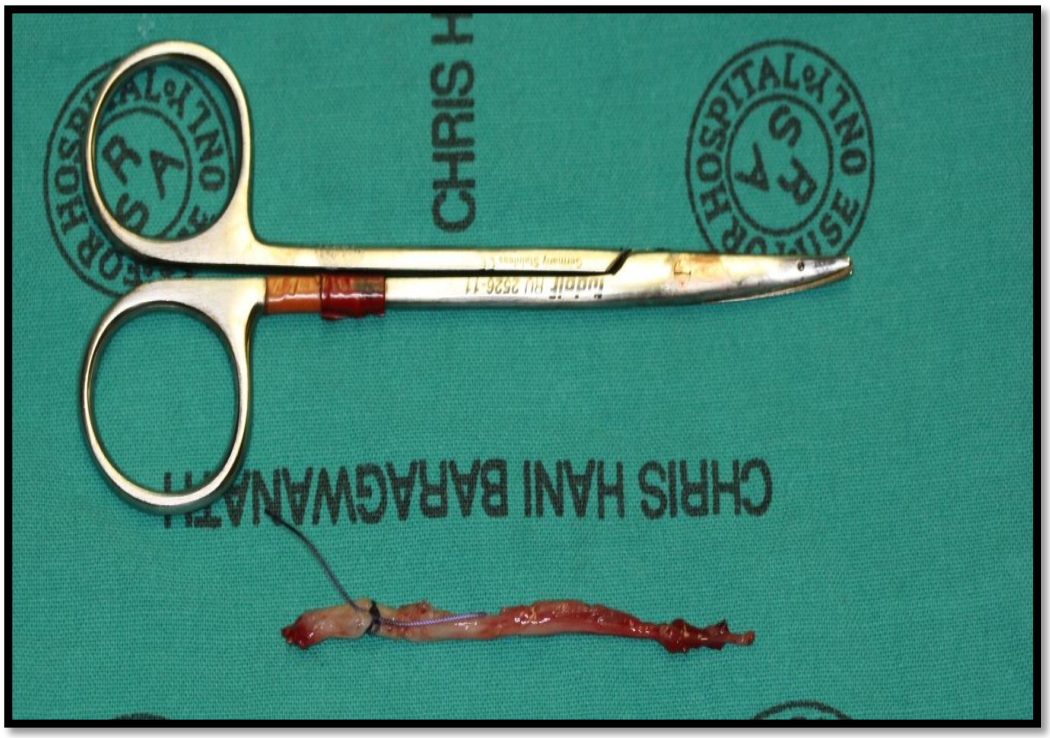


Fig 4.3 Group 2: inferior alveolar nerve from the hemimandibulectomy specimen, which was pulled out of the tumour immediately after resection. The proximal end of the nerve is marked with suturing material

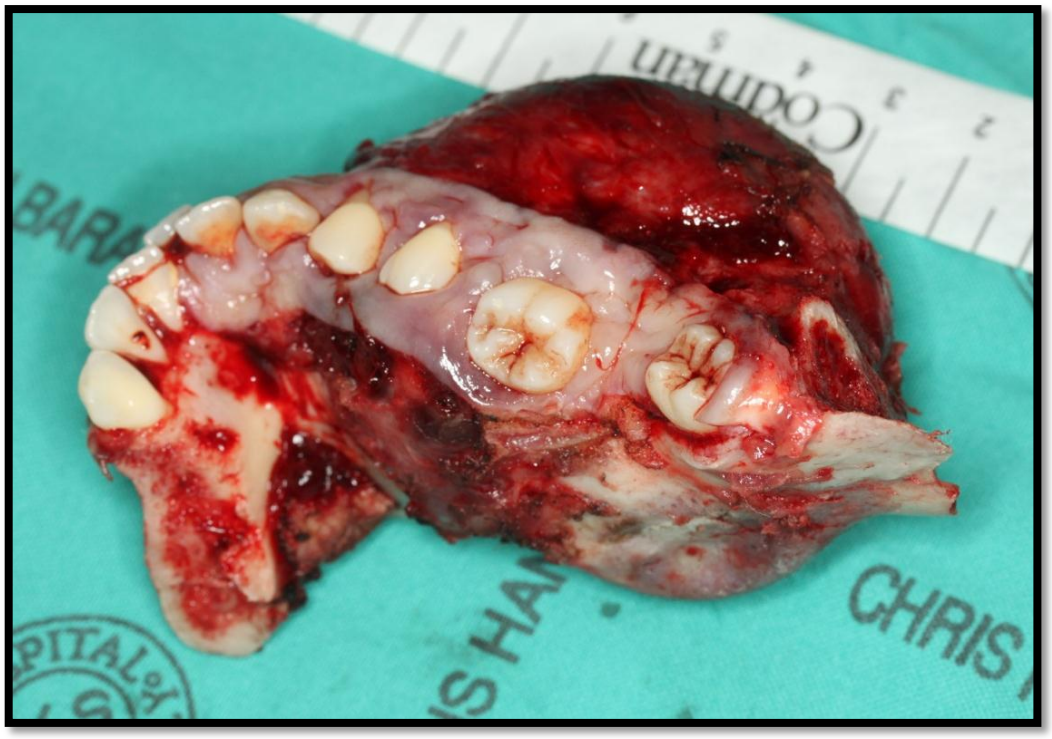


Fig 4.4 Group 2: resected hemimandibulectomy specimen prior to removal of the inferior alveolar nerve



Fig. 4.5 Group 2: resected hemimandibulectomy specimen after removal of the inferior alveolar nerve; note the violation of the tumour on the distobuccal aspect due to difficulty in removing the nerve

4.3 Method

Following fixation in 10% neutral buffered formalin (18-48 hours) and decalcification in hydrochloric acid/formic acid working solution (EDTA) 20 times the specimen volume, the mandibular resection specimens were serially sectioned and then routinely processed and embedded in paraffin wax. Only the bone specimens were decalcified, and whilst the separate segments of pulled-through inferior alveolar nerve were not decalcified, they were subjected to a similar preparation technique. The orientation and serial sectioning of the gross resection specimen was done by the investigator under the supervision and guidance of a trainee histopathologist in the Division of Oral Pathology.

The portion of the mandibular bone containing the inferior alveolar canal, as determined on pre-operative CT scan, post-operative plain film radiographs and macroscopic orientation of the specimen, was serially sectioned into 10mm blocks using a band saw. These blocks were sequentially numbered, to facilitate correlation with the radiographs. Radiographic examination of the specimen was purely to determine the path of the inferior alveolar nerve, and radiographic data did not form an integral part of the study. 4µm haematoxylin and eosin (H&E) stained histological sections were reviewed by the principal investigator in conjunction with an oral histopathologist using a dual headed conventional light microscope [Nikon Eclipse 80*i* (Nikon Corp, Tokyo, Japan)] fitted with 10x oculars and a 40x objective for specific measurement of the distance between the ameloblastoma cells and the inferior alveolar nerve histologically.

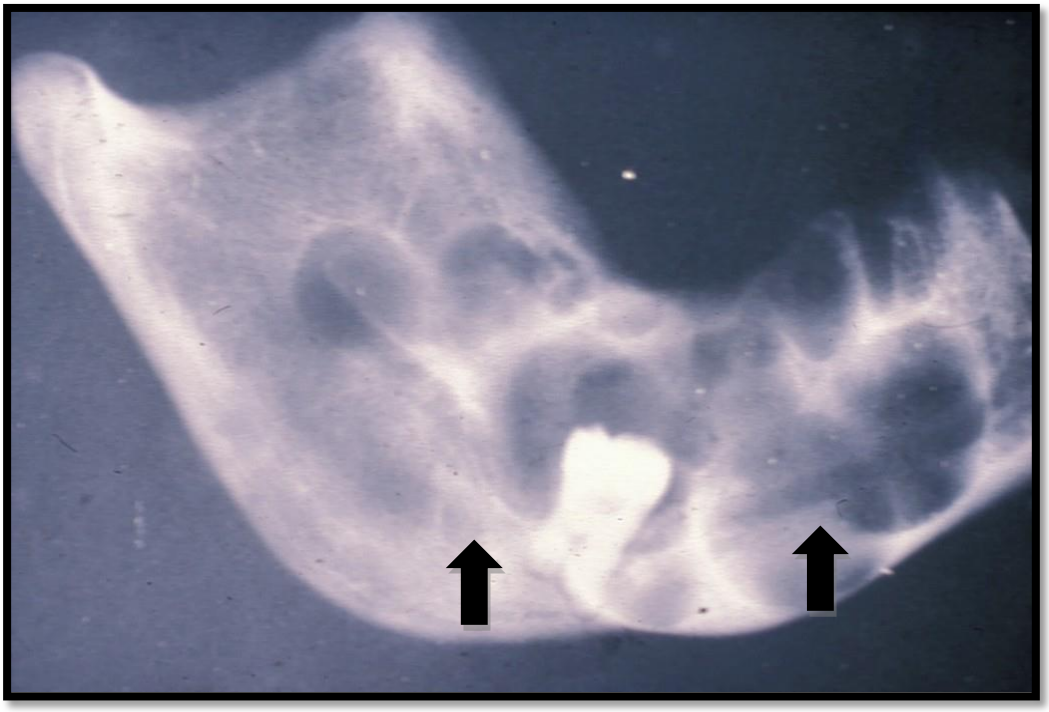


Fig. 4.6 Group 1: plain film radiograph of a resected hemimandibulectomy specimen; note the loss of continuity of the inferior alveolar canal (arrows)

4.4 Evaluation

The deparaffinised 4μm H&E histological sections of both Groups 1 and 2 were examined to evaluate the presence and proximity of ameloblastoma cells to the inferior alveolar nerve, more specifically examining whether any tumour cells remained attached to and were removed with the nerve, as well as to examine the corresponding portion of the canal within the tumour to correlate the proximity of the cells to the canal and the inferior alveolar nerve.

In Group 1, where the nerve was examined in situ, the closest distance between the main nerve (epineurium) and the tumour was measured. The presence of intra-neural tumour deposition was recorded. Furthermore, the histological variants of ameloblastoma were documented in view of the possibility that certain histological variants being more likely to infiltrate the nerve bundle. The proximity of the tumour cells to the nerve were measured histologically in millimetres and the measurements of the closest distance between tumour

and nerve were measured independently by 2 histopathologists. The closest distance of ameloblastomatous cells to the inferior alveolar nerve for each case was recorded.

For cases in Group 2, the nerve was examined independently of the tumour but in a similar manner. The presence or absence of tumour cells within isolated inferior alveolar nerve was noted. The closest distance of ameloblastoma tumour cells to the inferior alveolar canal was measured in the hemimandibulectomy specimen and recorded. The data for both Groups 1 and 2 were recorded on data sheets and statistically analysed.

4.5 Ethical considerations

An ethics clearance certificate specific for this project (No: M10555) was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand for the use of the patient specimens needed for this study (Appendix 1). The identities of the patients were kept confidential. Furthermore, the ethics code M080850 used for this research adheres to international ethical criteria for research. This is a blanket code for use on archival block material obtained from human tissues allocated to the Division of Oral Pathology, Department of Anatomical Pathology and covers the review of the histological sections.

CHAPTER 5

5.0 RESULTS

5.1 Inter-observer reliability

The measurements obtained by two different observers at two separate occasions were compared with each other using the paired sample t-test for parametric data. There was no statistically significant difference between the means of the two variables; $p = 0.1168$.

5.2 Clinicopathologic data results

The study population consisted of 13 patients in total, with 8 patients in Group 1 and 5 patients in Group 2. The demographic data of the patients in Groups 1 and 2 are listed in Table 5.1. Of the study population, 46.2% were male and 53.8% female. African blacks accounted for 92.3% of the study population.

Table 5.1 Study population demographics

	Age	Sex	Race
Patient 1	35	M	African
Patient 2	17	F	African
Patient 3	19	F	African
Patient 4	51	M	African
Patient 5	61	F	African
Patient 6	49	F	African
Patient 7	61	M	African
Patient 8	57	M	Caucasian
Patient 9	18	M	African
Patient 10	14	F	African
Patient 11	29	M	African
Patient 12	27	F	African
Patient 13	37	F	African

5.3 The histologic association of ameloblastoma cells to the inferior alveolar nerve

5.3.1 Histologic association of ameloblastoma to inferior alveolar nerve in situ

Perineural and intraneural ameloblastoma in the form of either direct involvement (Fig. 5.1) or apposition of tumour cells to the inferior alveolar nerve (Fig. 5.2) respectively, was noted in 5 of the 8 patients in Group 1 (62.5%), irrespective of the histological variant of ameloblastoma (Table 5.2). Intraneural tumour deposition was present in 2 of the 8 patients (25%) and ameloblastoma tumour cells were noted abutting directly onto the nerve in 3 cases (37.5%). The average closest distance between ameloblastoma cells and the inferior alveolar nerve in specimens taken from the patients in Group 1 was 0.437mm.

The histological variants in these 5 cases comprised follicular, plexiform, granular, adenoid and basaloid ameloblastomatous patterns. In this study, 10 of the 13 solid and multicystic

ameloblastomas (76.9%) showed mixed histological growth patterns, with the follicular and plexiform patterns predominating. Irrespective of the histological variant of the ameloblastoma, 7 of the 13 cases (53.8%) showed neural involvement by the ameloblastoma. Thus there appears to be no correlation between the histological subtypes of the tumour and the proximity of tumour cells to the nerve.

Table 5.2 Histological association of ameloblastoma to inferior alveolar nerve in patients in Group 1

Case	Histologic variant	Proximity of closest tumour cells to nerve (mm)	Presence of intraneural/ perineural tumour
Patient 1	Plexiform, Granular	0.25	No
Patient 2	Follicular, Plexiform	0.25	Tumour abutting onto nerve
Patient 3	Follicular, Plexiform, Adenoid	0	Yes
Patient 4	Follicular	1	No
Patient 5	Follicular, Basaloid	1.5	No
Patient 6	Plexiform, Granular	0.25	Tumour abutting onto nerve
Patient 7	Follicular, Plexiform	0	Yes
Patient 8	Basaloid	0.25	Tumour abutting onto nerve

In cases of intraneural tumour involvement, ameloblastoma follicles were noted permeating the epineurium (Fig. 5.1). One case of perineural involvement showed the nerve to be sheathed by plexiform and follicular arrangements of ameloblastoma (Fig. 5.3). Immunohistochemical staining in the presence of adequate preparations and controls was performed where necessary to confirm the presence of the inferior alveolar nerve with S-100 protein (Dako, Glostrup, Denmark) (Figs. 5.4 and 5.5) and the islands of ameloblastoma with calretinin (Dako, Glostrup, Denmark).

In some cases, even though there was no direct intraneural or perineural involvement of the inferior alveolar nerve by ameloblastoma, tumour was noted in close proximity to the nerve (Fig. 5.6). Some tumours were separated from the inferior alveolar nerve by a shelf of bone (Fig. 5.7), whilst in other cases the mandibular bone encasing the inferior alveolar bone was totally destroyed allowing infiltration of the ameloblastoma islands and subsequent abutment of tumour onto the inferior alveolar nerve (Figs. 5.2 and 5.3). Other cases showed separation of ameloblastoma from the nerve only by a few strands of collagenous fibrous connective tissue with no intervening bone (Fig. 5.6). In yet another case, the inferior alveolar nerve was noted "dipping" into and between the ameloblastoma (Fig. 5.8).

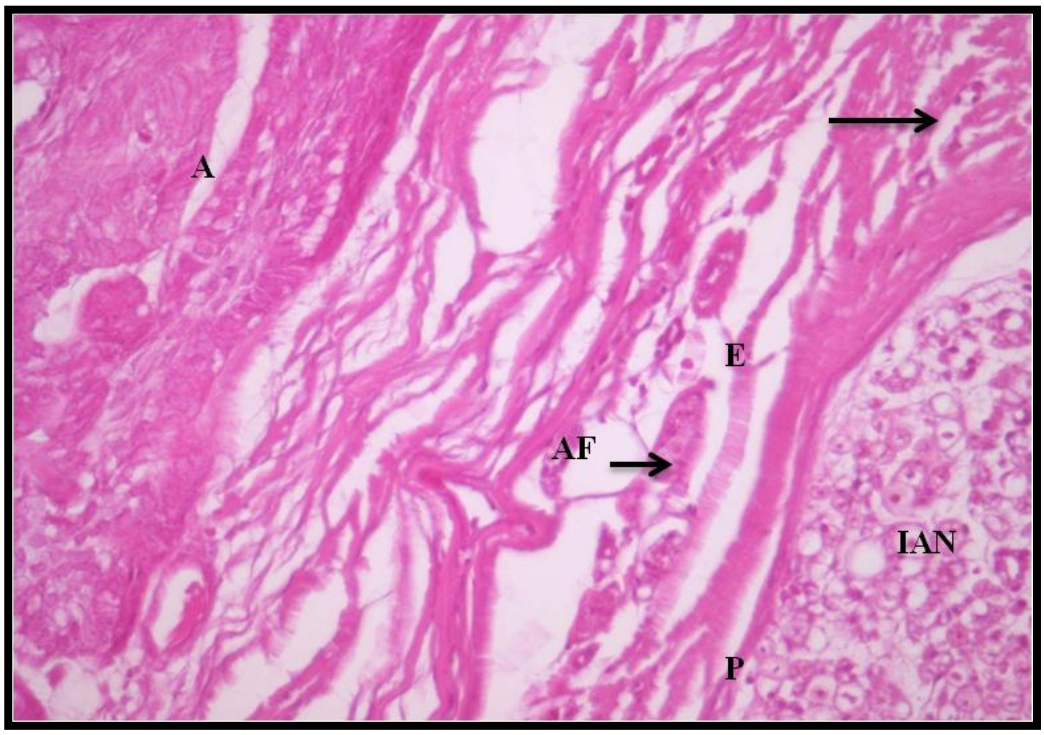


Fig. 5.1 Ameloblastic follicles (AF - small arrow) within the epineurium (E) of the inferior alveolar nerve (IAN); solid ameloblastoma (A) abutting onto the perineurium (P) of the IAN (large arrow) (H&E stained section of case 8 (Group1), x400 original magnification)

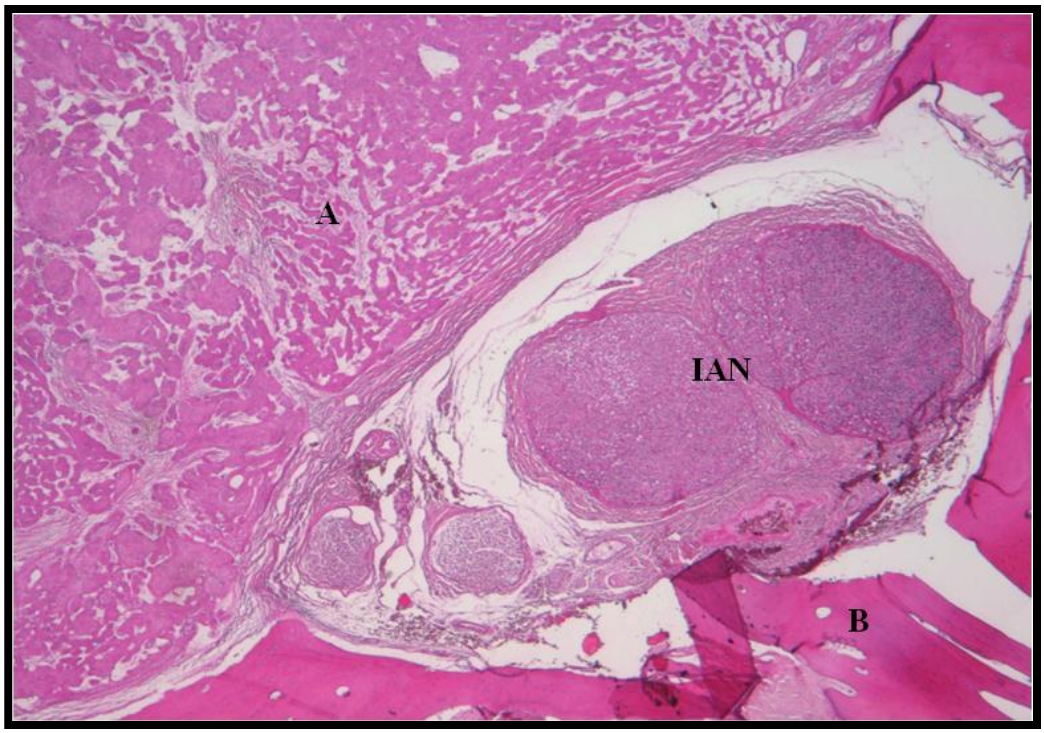


Fig. 5.2 Solid and multicystic ameloblastoma (A) noted abutting directly onto the epineurium of the inferior alveolar nerve (IAN) which is partially encased by the mandibular bone (B). The ameloblastoma exhibits both a follicular and plexiform growth pattern (H&E stained section of Case 8 (Group1), x40 original magnification)

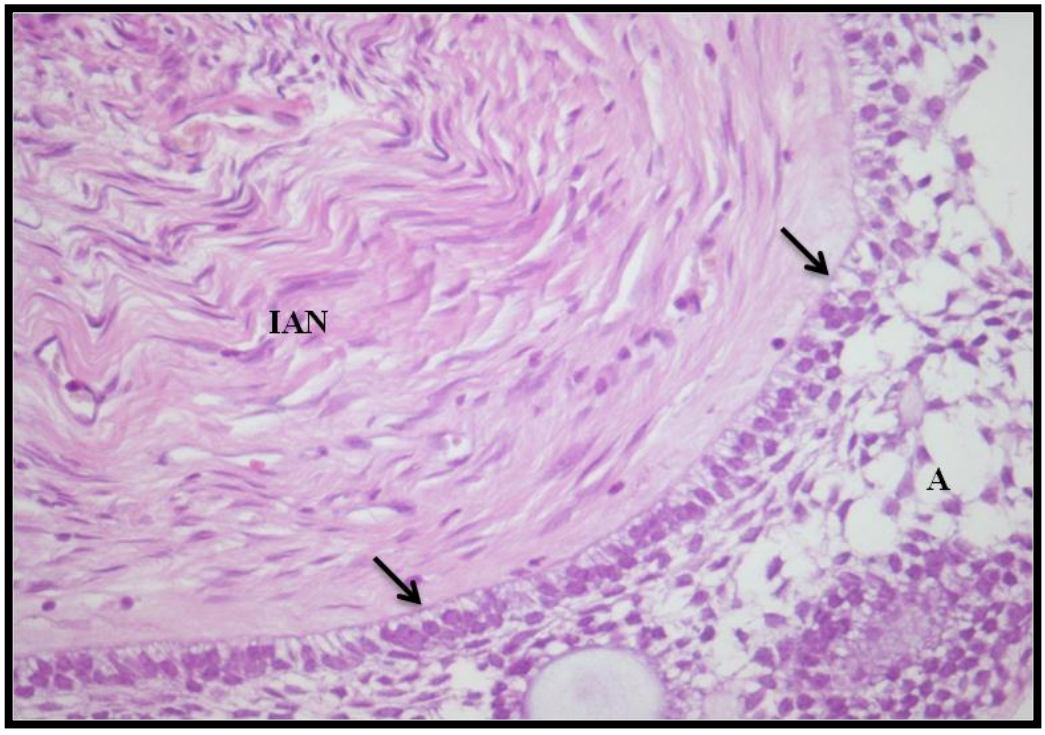


Fig. 5.3 Plexiform and follicular solid and multicystic ameloblastoma (A) enveloping and abutting directly onto the epineurium of the inferior alveolar nerve (IAN) (arrows) (H&E stained section of Case 8 (Group1), x200 original magnification)

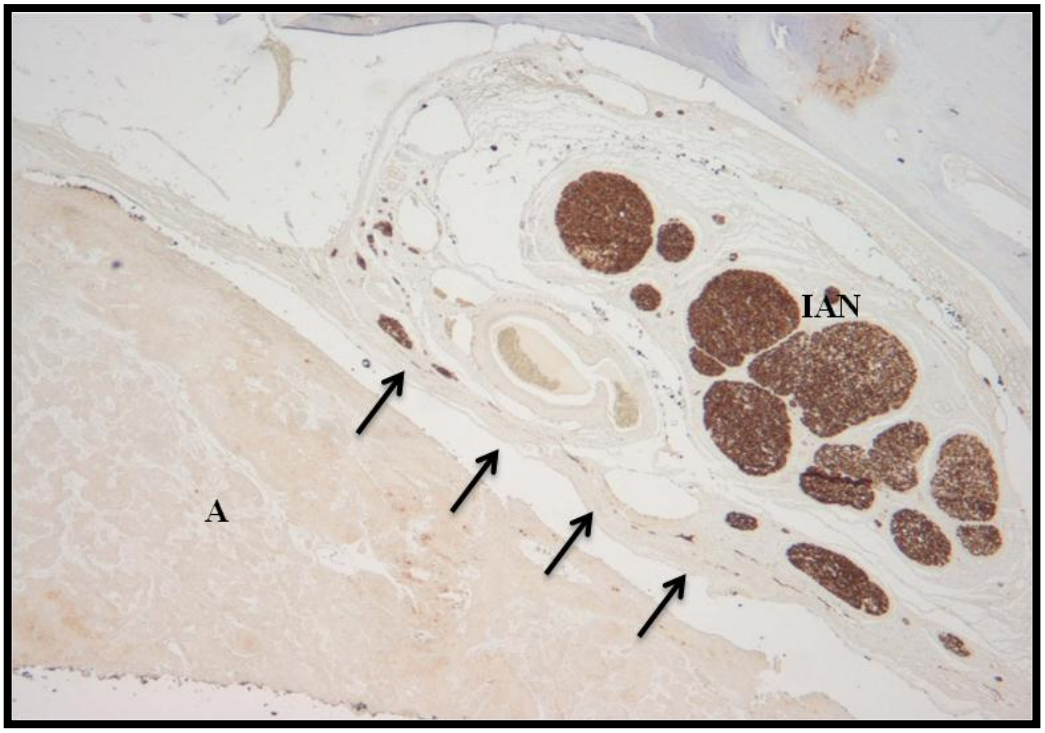


Fig 5.4 Solid and multicystic ameloblastoma (A) conjoined to the perineurium of the inferior alveolar nerve (IAN), which is highlighted by the brown immunopositivity with S-100 protein (A) (arrows) (S-100 immunostained section of Case 8 (Group1), x40 original magnification)

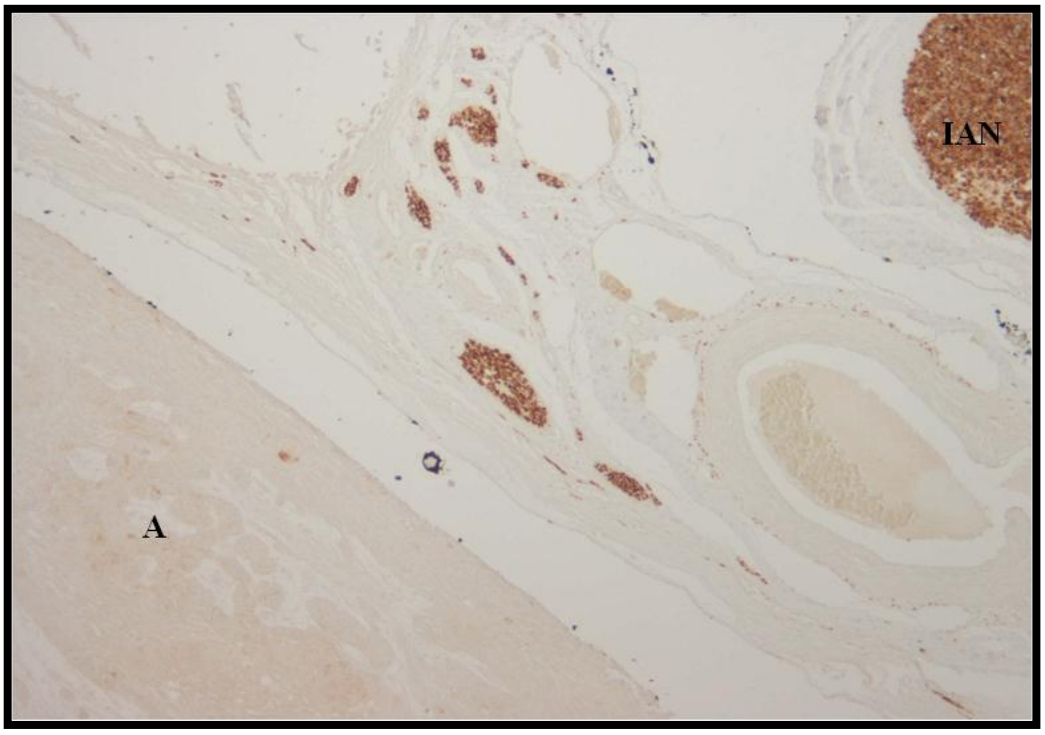


Fig. 5.5 S-100 immunostain highlights the inferior alveolar nerve (IAN) which is in close proximity to the ameloblastoma (A), separated from the tumour only by fibrous connective tissue with no bone barrier (S-100 protein immunostained section of Case 8 (Group1), x100 original magnification)

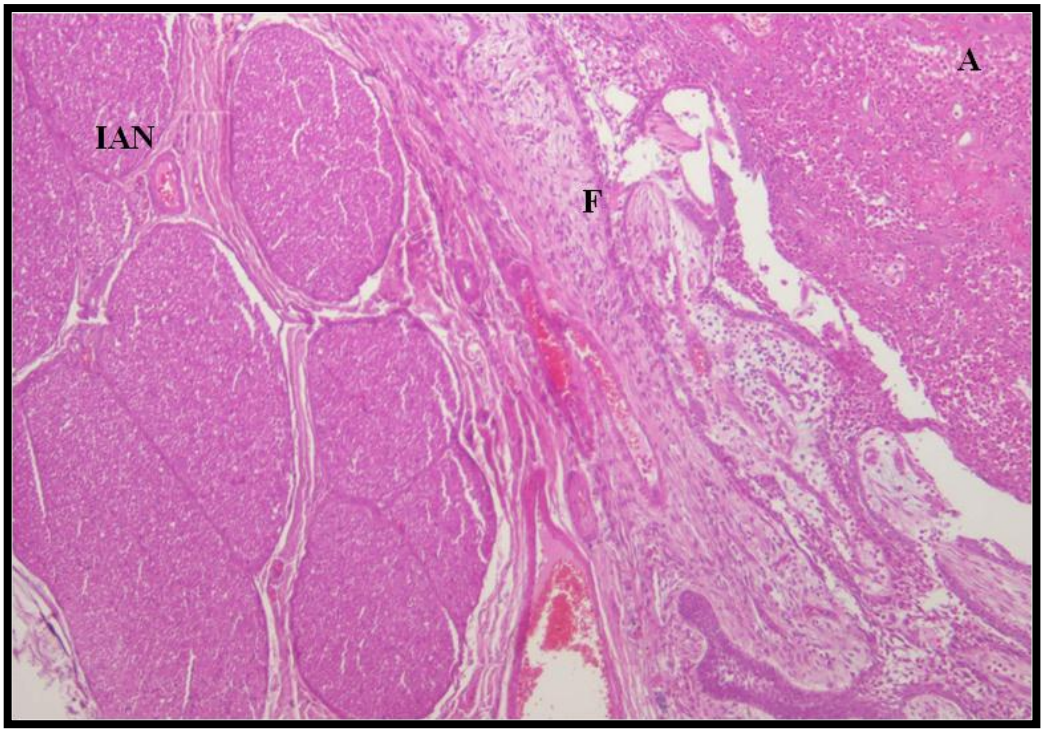


Fig. 5.6 The inferior alveolar nerve (IAN) which is in close proximity to the ameloblastoma (A), separated from the tumour by fibrous connective tissue (F) with no bone barrier. (H&E stained section of Case 1 (Group1), x100 original magnification)

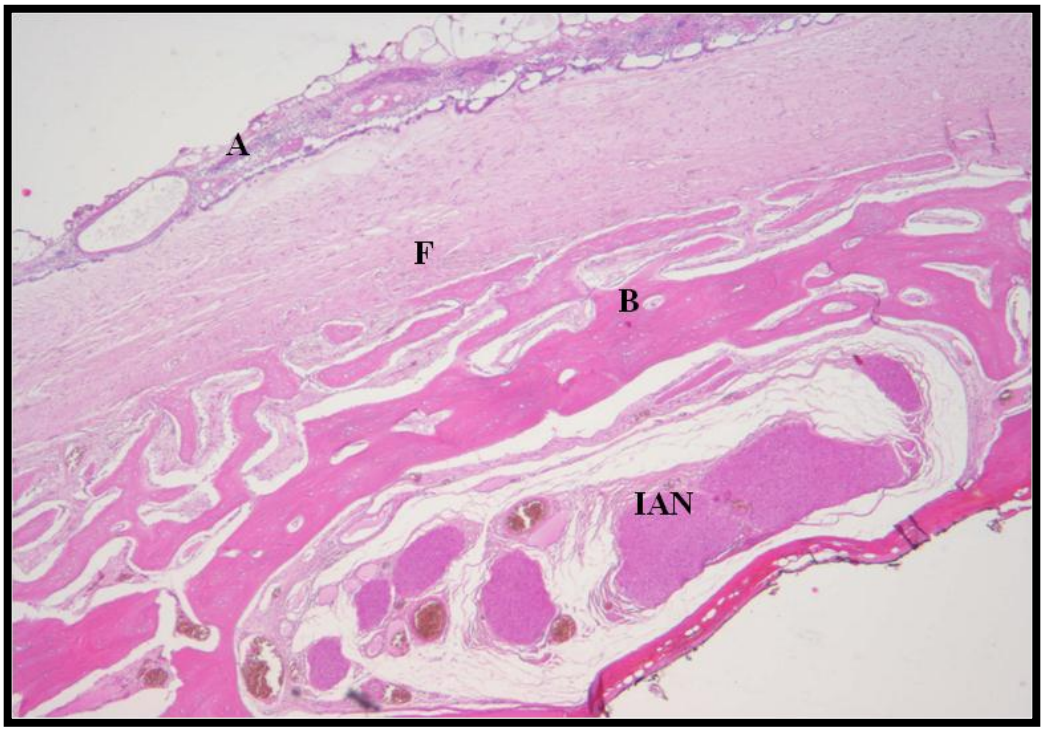


Fig. 5.7 The inferior alveolar nerve (IAN) is separated from the ameloblastoma (A), by fibrous connective tissue (F) and a bone barrier (B). (H&E stained section of Case 3 (Group1), x40 original magnification)



Fig. 5.8 Ameloblastoma (A) noted "dipping" into the nerve (IAN); the nerve appears divided by tumour (dotted line) (H&E stained section of Case 3 (Group1), x100 original magnification)

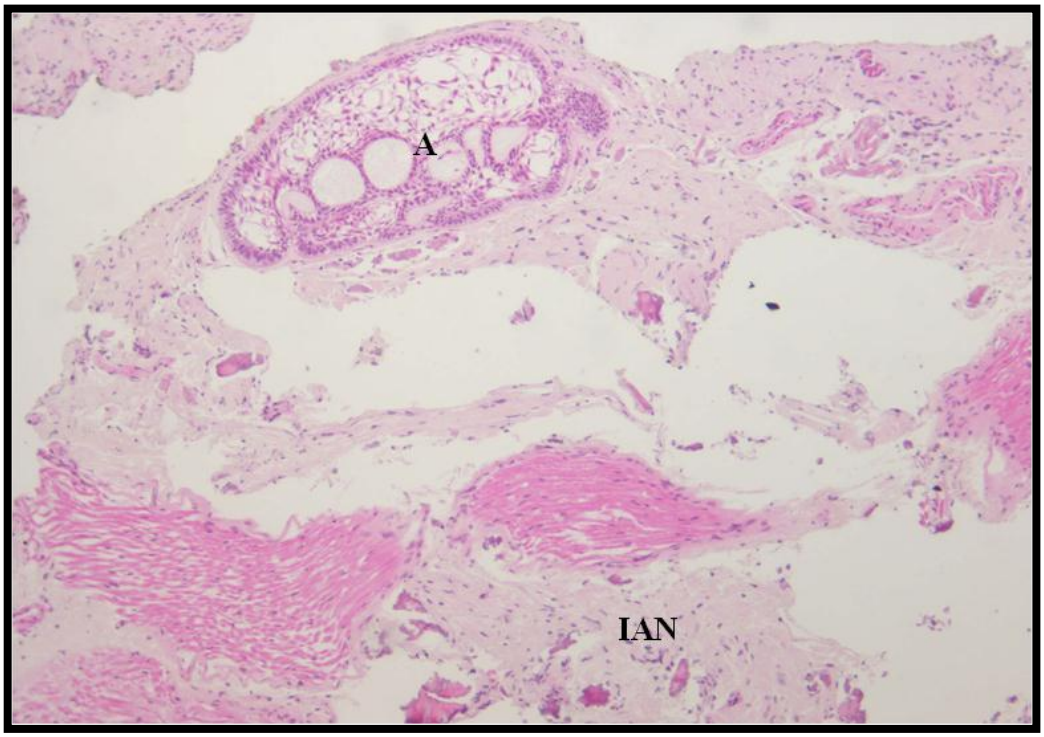


Fig. 5.9 Islands of ameloblastomatous tumour (A) noted within the nerve bundle of the pulled out inferior alveolar nerve (IAN) (H&E stained section of Case 13 (Group2), x40 original magnification)

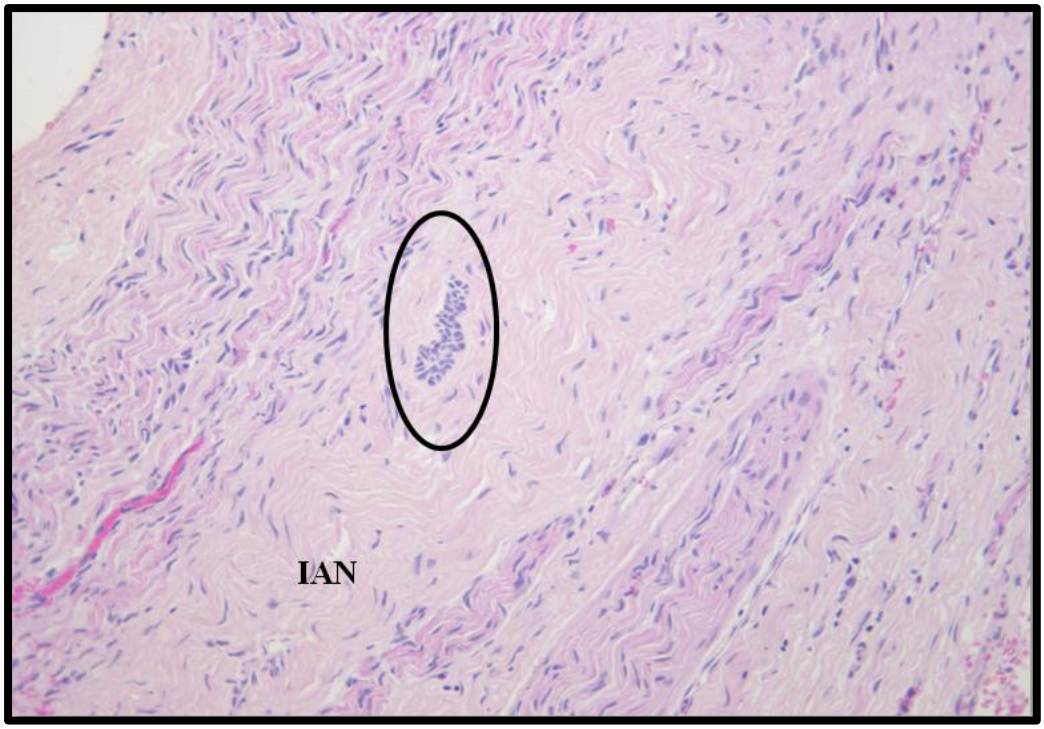


Fig. 5.10 An island of active odontogenic epithelium (encircled) noted within the inferior alveolar nerve bundle (IAN) (H&E stained section of Case 11 (Group2), x200 original magnification)

5.3.2 Histologic association of ameloblastoma to the pulled through inferior alveolar nerve and the inferior alveolar canal

As for Group 1, there was perineural and intraneural ameloblastoma cells in and around the inferior alveolar nerve and canal (Table 5.3 and Figs. 5.9 and 5.10 respectively). Intraneural ameloblastoma was evident in 2 of the 5 patients in Group 2 (40%), irrespective of the histological variant of ameloblastoma (Table 5.2). In 2 of the 5 cases (40%) no canal could be identified in close proximity to the nerve, both radiographically and histologically. Similar to Group 1, there was no correlation between the histological variants of ameloblastoma and the presence of tumour within the pulled-out nerve bundle.

The raw data for both Groups 1 and 2 are presented in Appendices 2 and 3.

Table 5.3 Histological association of ameloblastoma to inferior alveolar nerve in patients in Group 2

Case	Histological variant	Presence of tumour cells in pulled out nerve	Distance of tumour cells to nerve canal (mm)
Patient 9	Plexiform	No	No canal identified in relation to tumour
Patient 10	Follicular, Plexiform	No	No canal identified in relation to tumour
Patient 11	Follicular, Plexiform	Yes	0.5
Patient 12	Plexiform, Granular cell	No	1
Patient 13	Plexiform [Recurrence]	Yes	0,3

CHAPTER 6

6.0 DISCUSSION

6.1 Statement of the principal findings

This study confirmed neural involvement in 53.8% of cases of mandibular ameloblastomas in which the inferior alveolar nerve was removed together with the resected mandibular specimen as well as when pulled through separately from the mandibular resection specimen.

In this study, in order to validate a surgical procedure advocated by some surgeons,[5,11] the surgical technique of pulling the inferior alveolar nerve out of the ameloblastoma at the time of resection was mimicked and the association between the nerve and tumour histologically examined. A totally unexpected finding was that of peri- and intraneural involvement of the inferior alveolar nerve in the mandibular ameloblastoma since cells from a benign tumour generally do not show neural infiltration.

As expected of most benign tumours, a clear demarcation or delineation between the ameloblastoma tumour cells and the unaffected inferior alveolar nerve bundle was anticipated. Even though ameloblastomas are locally aggressive and often reach very large proportions with displacement and erosion of local structures, there is still a distinct demarcation in most cases between the tumour and the nerve. Perineural invasion is not characteristic of benign lesions.

This study demonstrated the presence of ameloblastoma tumour cells not only in very close proximity to the inferior alveolar nerve bundle, but also within the nerve itself. In addition to

actual ameloblastoma tumour cells, benign odontogenic epithelial cell rests within the inferior alveolar nerve canal was also an unexpected finding. This however cannot be ignored, bearing in mind that ameloblastomas can arise within odontogenic epithelial cell rests. Even though these odontogenic cell rests were inactive and showed no features of ameloblastomatous differentiation, there is a high probability of recurrent or de novo ameloblastoma arising within this satellite or daughter island at some stage following differentiation should the nerve be spared. There is absolutely no way to determine or predict exactly how these aberrant cell rests will behave.

Exactly why the ameloblastoma is noted infiltrating or "dipping" into the nerve, is not known. It can however be postulated that the nerve is slowly splayed by the pressure from the expanding tumour, especially if the inferior alveolar canal has already been eroded. Our hypothesis is that following an incisional biopsy to confirm the diagnosis of ameloblastoma, and decompression of the lesion, the release of pressure allows the nerve some freedom of movement, and in an attempt to regain its original shape, it recoils and closes up around the tumour entrapping tumour islands. Another possible explanation is that the section viewed is through a U-loop of the nerve, either towards or away from the viewer, caused by a tumour locule. The presence of this "dipping effect" of the tumour with ameloblastoma present in between the nerve bundle and flanked on either side by inferior alveolar nerve poses a further threat in the management of these lesions as there is no guarantee that the nerve, when being pulled out, would not pull along or seed the tumour cells that are noted "dipping" into it. This finding shows that the recommendation by Nakamura *et al*.[11] to first shrink the tumour by means of marsupialisation, followed by pull-through of the nerve upon resection is not a safe or viable treatment option. Marsupialisation results in decompression and the nerve may

very well recoil and "pinch" the tumour with resultant tumour tissue being removed together with the nerve.

Gortzak *et al*.[12] and Slootweg *et al*.[15] stated that if there are signs of bone breakthrough, the dissection should be extended to the next tumour free tissue plane. This raises the question as to whether the epifascicular plain is an adequately safe plain for dissection (as described by Tung-Yiu *et al*.[34]) as odontogenic epithelium was clearly demonstrated within the inferior alveolar nerve in the present study. Thus, the absence of a clear plane necessitates removal of the nerve.

The surgical treatment planning of a mandibular ameloblastoma necessitates not only delineation of the full extent of the tumour within bone and soft tissue, following cortical bone perforation, but also consideration of the management of the inferior alveolar nerve bundle. Any residual tumour within the nerve bundle may be a source of recurrence following conservative management.[14] Wide resection is the recommended and accepted treatment protocol for mandibular solid and multicystic ameloblastomas.[4] This however results in the sacrifice of the inferior alveolar nerve which results in permanent numbness of the region innervated by the mental nerve. It is with this in mind that authors[5,6,11] have recommended avoidance of resection of the nerve.

Based on the findings of their study which showed no invasion of the nerve or nerve sheath by ameloblastoma, Nakamura *et al*.[11] recommended that a more conservative approach and proper follow up is acceptable if the canal wall is not destroyed. Ishikawa *et al*.[5] reported a method to preserve the inferior alveolar nerve when the wall of the bony canal is intact. However, Nakamura *et al*.[11] found that even when the bony wall of the mandibular canal was

destroyed the ameloblastoma was clearly separated from the nerve by bone or connective tissue. This certainly was not the case in the current study where there was at least 53.8% neural involvement by ameloblastoma.

Whilst computed tomography may give an indication as to the relationship between the tumour and the inferior alveolar nerve, definitive confirmation of tumour in and around the nerve and micro-destruction of the inferior alveolar canal can only be done histologically. In the present study it was apparent that it is impossible to confirm neural or mandibular canal involvement via radiographs and in tissue taken from an incisional biopsy. Moreover, involvement of the nerve and canal by tumour is only evident on serial sectioning of the entire resected mandibular specimen. It is not standard practice to serial section the entire tumour after resection has been carried out. Normal protocol dictates that the mucosal, soft tissue and bone, surgical margins are checked for tumour clearance and random sections for confirmation of tumour and subtype.

In a review of treatment modalities, Pogrel *et al*[4] conclude that surgical resection of the solid and multicystic ameloblastoma should be aggressive. One of the main reasons for this is the high recurrence rate and unpredictability of the tumour's biologic behaviour. Pourian *et al*.[14] also reported that tumour adjacent to or within the mandibular canal may destroy and grow into the canal, involving the epineurium and ultimately the nerve itself. In this regard, an aggressive treatment approach to the management of the nerve should be maintained. In determining the possible surgical approach to the treatment of the mandibular ameloblastoma, there is no doubt that prevention of a recurrence in the patient far outweighs the limited morbidity of permanent numbness in the area of innervation.

Nakamura *et al*.[11] advocated that histological variant is important in determining the biological behaviour of the ameloblastoma, and that the growth characteristics of the tumour must be considered in the surgical treatment planning of solid and multicystic ameloblastomas. Consequently they recommended a more conservative approach with meticulous follow up in ameloblastomas with a plexiform growth pattern, provided that there is no destruction of the canal wall. Most ameloblastomas in our study (76.9%) showed a mixed histological growth pattern, however neural involvement by ameloblastoma occurred irrespective of the histologic variant. Thus inferior alveolar nerve involvement was not dependent on the gross or histologic type of the ameloblastoma. Furthermore, accurate histological sub-typing as well as the aggressive versus non-aggressive nature of the tumour cannot be made on an incisional biopsy as the tissue submitted may not be representative of the histologic type of the entire ameloblastoma.

Whilst the nerve pull through technique has been promoted by Nakamura *et al*.,[11] Wu *et al*.[6] and Ishikawa *et al.*[5] we encountered technical difficulty with the surgical removal of the inferior alveolar nerve in patients of Group 2. In contrast to the relative ease of this pull through surgical technique described by Ishikawa *et al*.,[5] we found that it was extremely difficult to deliver the nerve from the tumour. The inferior alveolar nerve could not be freed easily by pull and manipulation from the mental or mandibular foramina. In fact, in 2 cases the tumour had to be cut open in order to deliver the nerve intact. The technique is extremely difficult, and if done in situ, seeding of tumour cells is a distinct possibility. Even in cases where the canal appeared well corticated on pre-operative radiographic views, the inferior alveolar nerve appeared to be well attached to the adjacent structures and proved to be extremely difficult to remove.

The treatment modality is the most important prognostic indicator for treatment to be curative in ameloblastomas.[4] There is a likelihood of tumour recurrence, especially if the surgery is not aggressive. As was noted, the nerve cannot always be reliably delivered free of tumour cells and hence, being conservative and sparing the inferior alveolar nerve in the treatment of ameloblastomas will be detrimental to the patient. In all instances, the best chance at successful treatment will always remain the first chance.

6.2 The strength and the weakness of the study

The strength of the study is the histologic demonstration of tumour cells that have adhered to and infiltrated the inferior alveolar nerve. Even though the sample size is small, evidence of neural involvement by ameloblastoma even in one case is sufficient to mitigate against the nerve pull through surgical technique as encouraged by Ishikawa *et al*.[5] The evidence of neural involvement by ameloblastoma in this study is sufficient to show that there is no doubt that the proposed technique is unsafe and unfeasible, and would lead to recurrence of the tumour. Ideally, more patients from each group need to be evaluated.

6.3 The meaning of the study and surgical application

This is a highly relevant and pertinent study as it forms the basis of a protocol for the effective surgical management of the mandibular solid and multicystic ameloblastoma. Maxillofacial and oral surgeons can be confidently guided in the treatment planning for patients with mandibular ameloblastoma by the findings in this study, in which there is sound evidence for the inferior alveolar nerve to be removed together with the ameloblastoma.

6.4 Future research

A similar prospective study on a much larger cohort of patients will scientifically and statistically seal the findings of this study. However, this cohort is sufficient to recommend that future research be focused on devising new methods to reinstate sensation in areas innervated by the inferior alveolar nerve, rather than investigating techniques to spare the nerve.

CHAPTER 7

7.0 CONCLUSION

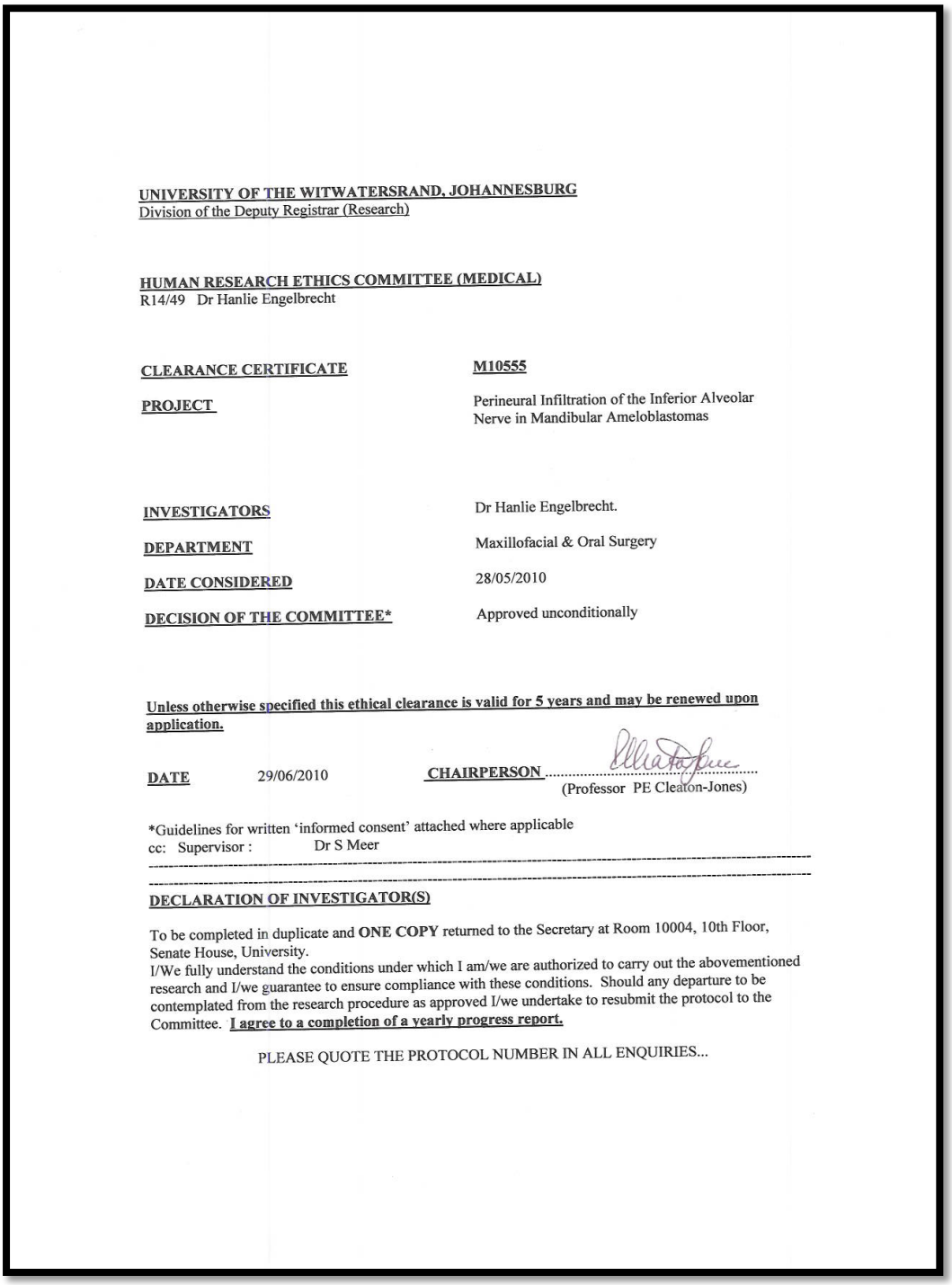
Both peri- and intraneural involvement of the inferior alveolar nerve was histologically confirmed in solid and multicystic hemimandibular specimens both in situ within the tumour as well as in separately removed segments of the nerve.

Preservation of the inferior alveolar nerve during ablative surgery for mandibular ameloblastomas cannot be advocated.

CHAPTER 8

8.0 APENDICES

8.1 APPENDIX 1:



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

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Hanlie Engelbrecht

CLEARANCE CERTIFICATE	**M10555**
PROJECT	Perineural Infiltration of the Inferior Alveolar Nerve in Mandibular Ameloblastomas
INVESTIGATORS	Dr Hanlie Engelbrecht.
DEPARTMENT	Maxillofacial & Oral Surgery
DATE CONSIDERED	28/05/2010
DECISION OF THE COMMITTEE*	Approved unconditionally

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

DATE 29/06/2010 **CHAIRPERSON**.....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr S Meer

DECLARATION OF INVESTIGATOR(S)

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

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

8.2 APPENDIX 2:

Individual patient slide descriptions

1) Patient 1
   - A1: Granular plexiform variant tumour. Close proximity to nerve at 0.25mm (next to blue line)
   - A2: Tumour in close proximity to nerve, at 0.25mm
   - A3: Tumour noted
   - A4: Tumour noted, margins clear
   - A5: Tumour noted in soft tissue but margin clear.
   - A6: Inferior alveolar canal noted, surrounded by bone and separated from tumour by bone
   - A7: Slide missing
   - A8: Granular plexiform pattern tumour, no nerve noted
   - A9: Granular plexiform pattern tumour, no nerve noted
   - A10: Inferior alveolar nerve less than 0.25mm away from tumour, break in bone continuity at canal, nerve is only separated from tumour by soft tissue
   - A10: Tumour noted, no nerve
   - A11: Nerve surrounded by bony chips interspersed with ameloblastomatous islands
   - A12: Inferior alveolar nerve noted, tumour noted not too close proximity (2mm)
   - A13: Tumour noted, no nerve
   - A14: Tumour noted, no nerve
   - A15: Tumour separated from nerve by bone

2) Patient 2
   - A1: Plexiform pattern tumour noted within bone, no nerve noted
   - A2: Nerve encased by bone, but lingually there is bone destruction noted. In some areas there is no separation by bone of tumour and nerve. 0.5mm distance between bone and tumour.
   - A3: Bone separating nerve and tumour. 0.75mm distance. See "Folded locule": IAN and second nerve twig is not separated from tumour by bone, and is 0.25mm away. The cystic structure is large and folded over and very close to nerve twigs within the wall.
   - A4: No tumour or nerve noted
   - A5: No tumour or nerve noted
   - A6: No tumour or nerve noted
   - A7: No tumour noted, nerve seen
   - A8: Nerve surrounded by extensive marrow tissue. Tumour is quite a distance away.
   - A9: No tumour noted, nerve seen
   - A10: No tumour or nerve noted
   - A11: Nerve noted at the apex of the tooth, surrounded by marrow.
   - A12: No tumour noted, nerve seen
   - A13: No tumour noted, nerve seen
   - A14: At the inferior border the nerve bundle is pushed away by tumour, and is sitting right up at the cortex, 0.5mm from the epithelial lining and 0.25mm from the wall of the Ameloblastoma.
   - A15: Slide missing
   - A16: Slide missing
   - A17: Nerve twigs noted, no bundle or tumour seen
   - A18: Tumour noted
   - A19: Nerve is 0.25mm from the epithelial lining but abutting onto the tumour cyst wall
   - A20: Plexiform and follicular pattern
   - A21: Islands away from main tumour illustrates infiltrative nature of tumour.
   - A22: Tumour noted
   - A23: Nerve twigs in close proximity to tumour (0.25mm)
   - A24: Tumour noted

3) Patient 3
   - A: Free mucosal margin
   - B: Tumour noted, margin clear, no nerve seen
   - C: Tumour noted, margin clear, no nerve seen
   - D: Tumour noted, margin clear, no nerve seen

E: Tumour noted, margin clear, no nerve seen
F: No tumour or nerve noted
G: Tumour noted, margin clear, no nerve seen
H: Tumour noted, margin clear, no nerve seen
I: No tumour or nerve noted
J: Tumour noted, margin clear, no nerve seen. Adenoid pattern
K: Tumour noted, margin clear, no nerve seen. Plexiform pattern
L: Tumour noted, margin clear, no nerve seen
M: Tumour noted, margin clear, no nerve seen. Plexiform pattern
N: No tumour noted. Medium sized nerve twigs seen
O: Medium sized nerve twigs with muscle and vessels. Tumour present, but not involving nerves
P: Medium sized nerve twigs with muscle and vessels. No tumour.
Q: Nerves noted, no tumour
R: Nerve separated from tumour by cortical bone
S: Proliferative periosteal bone reaction noted. No nerve
T: Nerve separated from tumour by cortical bone
U: No nerve
V: No nerve
W: Nerve separated from tumour by cortical bone and muscle
X: Tumour noted in between roots of teeth
Y: No nerve
Z: Small nerve seen close to epithelium, separated from tumour by a tooth
AA: Tumour either side of bone and against tooth. 0.5mm away from tumour
AB: Nerve "dipping into" tumour (S100)
AC: Nerve 0.5mm away from tumour
AD: Nerve separated from tumour by cortical bone
AE: Tumour noted, no nerve seen
AF: Nerve within marrow bone, no tumour
AG: Slide missing
AH: Nerve bundle separated from tumour by bone (2mm)
AI: Nerve bundle separated from tumour by bone
AJ: Tumour noted, no nerve seen
AK: Nerve encased in bone, pushed aside by tumour
AL: Tumour noted, no nerve seen
AM: Nerve separated from tumour by bone
AN: Nerve close to tumour cyst, no bone separating it, 0.5mm
AO: Nerve encased in bone
AP: Nerve on either side of tumour. Tumour dipping into bundle
AQ: No nerve, Follicular mixed plexiform pattern
AR: Nerve close to tumour
AS: Tumour noted, no nerve seen
AT: Nerve/smooth muscle next to cyst (S100)
AU: Tumour noted, no nerve seen
AV: Tumour noted, no nerve seen
AW: Tumour noted, no nerve seen

4) Patient 4
A: Clear mucosal margin
B: Clear mucosal margin
C: Clear mucosal margin
D: Clear mucosal margin
E: Clear mucosal margin
F: Clear mucosal margin
G: Clear mucosal margin
H: Clear mucosal margin
I: Clear mucosal margin
J: Clear mucosal margin
K: Clear soft tissue margin
L: Clear soft tissue margin

M: Tumour very infiltrative, small follicles very spread out. No nerve seen.
N: Tumour noted, no nerve seen
O: Nerve separated from tumour by bone, tumour "chomping up" bone. 1mm
P: Tumour noted, no nerve seen
Q: Tumour noted, no nerve seen
R: Nerve encased in bone
S: Tumour noted, no nerve seen
T: Tumour noted, no nerve seen
U: Tumour noted, no nerve seen
V: Tumour noted, no nerve seen
W: Tumour noted, no nerve seen
X: Nerve separated from tumour by bone
Y: Nerve noted, no tumour seen
Z: Tumour noted, no nerve seen
AA: No nerve or tumour seen
AB: Nerve seen, tumour far removed
AC: No nerve or tumour seen
AD: No nerve or tumour seen

5. Patient 5
$A1_1$: Nerve noted, away from tumour
$A1_2$: Nerve separated from tumour by bone
$A2_1$: Nerve separated from tumour by bone. Follicular basaloid appearance
$A2_2$: Nerve separated from tumour by bone. Very solid tumour
A3: Nerve separated from tumour by bone
A4: Nerve separated from tumour by bone. Basal cell variant
$A5_1$: Tumour noted no nerve seen
$A5_2$: Tumour noted no nerve seen
$A6_1$: Tumour noted no nerve seen
$A6_2$: Tumour noted no nerve seen
$A7_1$: Tumour noted no nerve seen
$A7_2$: Tumour noted no nerve seen, Very infiltrative
$A8_1$: Nerve separated from tumour by inflammatory connective tissue, 1.5mm
$A8_2$: Nerve separated from tumour by inflammatory connective tissue, 1.5mm
$A9_1$: Tumour noted no nerve seen
$A9_2$: Tumour noted no nerve seen
A10: No tumour or nerve seen
A11: No nerve seen

6. Patient 6
A: Clear mucosal margin
B: Clear mucosal margin
C: Clear mucosal margin
D: Tumour with overlying epithelium
E: Tumour with overlying epithelium
F: Tumour noted no nerve seen
G: Soft tissue
H: Clear mucosal margin
I: Tumour in soft tissue, solid. No nerve
J: Plexiform granular cell variant, no nerve seen
K: Tumour noted no nerve seen
L: Tumour noted no nerve seen
M: Tumour noted no nerve seen
N: Tumour noted no nerve seen
O: Tumour noted no nerve seen
P: No nerve or tumour noted
Q: Tumour noted no nerve seen
R: Tumour noted no nerve seen
S: Tumour noted no nerve seen
T: Tumour noted no nerve seen

U: Tumour noted no nerve seen
V: Tumour noted no nerve seen
W: Tumour noted no nerve seen
X: Tumour noted no nerve seen
Y: Tumour noted no nerve seen
Z: Nerve very close to tumour, 0.25mm away, separated only by fibrous connective tissue wall of tumour
AA: Infiltrative pattern noted, no nerve seen
AB: Tumour noted no nerve seen
AC: Nerve seen far away from tumour
AD: Tumour noted no nerve seen
AE: Inflammatory cells seen, suppuration noted

7. Patient 7
A: Clear mucosal margin
B: Clear mucosal margin
C: Clear mucosal margin
D: Clear mucosal margin
E: Clear mucosal margin
F: Clear mucosal margin
G: No tumour or nerve noted
H: No tumour or nerve noted
I: Nerve separated from tumour by fibrous connective tissue, 1mm
J: Tumour noted no nerve seen
K: Tumour noted no nerve seen
L: Tumour noted no nerve seen. Plexiform and follicular pattern
M: Tumour noted no nerve seen
N: Nerve twig separated from tumour cyst by fibrous connective tissue, 1mm
O: Nerve twig separated from tumour cyst by fibrous connective tissue, 1mm
P: Tumour noted no nerve seen
Q: Looks like nerve close to tumour (S100 ordered). Tumour within nerve at a different section on slide
R: Tumour noted no nerve seen
S: Tumour noted, small nerve twigs noted far away
T: Clear
U: Nerve separated from tumour by fibrous connective tissue

8. Patient 8
A: No tumour or nerve seen
A_x: Tumour noted no nerve seen
B: Tumour noted no nerve seen
C: No tumour or nerve seen
D: Tumour noted no nerve seen
D_{MC}: Tumour abutting onto nerve, fibrous connective tissue wall of tumour on nerve. 0.25mm from ameloblastomatous epithelium
E: Tumour noted no nerve seen
F: Tumour noted no nerve seen
G: Lots of basilar cells seen, little stellate reticulum, very solid, no nerve
G_{MC}: No nerve seen
H: Tumour within soft tissue
H_{MC}: No nerve seen
I: No nerve seen
J: No nerve seen
K: Nerve separated from tumour by bone, separate bundle abutting onto tumour
L: Nerve torn away from tissue
L_{MNF}: poor stain
L_{S100}: Nerve stained nicely but free lying
M: Tumour wall abutting onto tumour
M_x: Stain didn't work due to decal
N: Nerve onto tumour

N_X: Nerve onto tumour
O: Tumour wall abutting onto nerve
P: No nerve seen
Q: Tumour noted no nerve seen
Q_X: Tumour noted no nerve seen
R: No tumour seen
S: No tumour seen

9. Patient 9

Nerve:

A – D: (slides of nerve) Clear. Nerve only, no tumour seen. Areas of fibrous connective tissue show inflammation

Tumour:

E: Right Post bony resection margin, Clear.
F: Right Post bony resection margin, Clear. Nerve seen, but no tumour. Nerve totally encased by host bone, no evidence of tumour in vicinity. Tumour noted on surface of impacted tooth, but separated from nerve.
G: Left bony resection margin, Clear.
H: Clear
I: Clear
J: Tumour seen, no nerve noted. Plexiform variant
K: Tumour seen, no nerve noted.
L: Clear
M: Clear
N: Clear
O: Clear
P: Small nerve noted in bone, no tumour seen, posterior margin
Q: Clear

10. Patient 10

A: Lymph node
A1 – A2 and stained slide p24: Reactive lymphoid hyperplasia in keeping with chronic antigenic stimulation. P24 is negative. No evidence of a neoplastic infiltrate in any of the sections examined.

B: Nerve
B1 – B16: Nerve. No evidence of tumour or odontogenic cell rests Evidence of retained suture material on slide.

C: Tumour
C1: Muco-gingival margin clear
C2: Muco-gingival margin clear
C3: Muco-gingival margin clear, Inflammation noted
C4: Muco-gingival margin clear
C5: Muco-gingival margin clear
C6: Muco-gingival margin clear, Tumour in submucosa
C7: Muco-gingival margin clear
C8: Muco-gingival margin clear
C9: Muco-gingival margin clear
C10: Muco-gingival margin clear
C11: Muco-gingival margin clear
C12: Muco-gingival margin clear
C13: Muco-gingival margin clear, bacteria noted
C14: Muco-gingival margin clear
C15: Muco-gingival margin clear
C16: Muco-gingival margin clear
C18: Muco-gingival margin clear
C19: Soft tissue margin close to tumour
C20: Solid and plexiform variant of tumour. Tumour close to soft tissue resection margin, but

clear. Carry-over noted
C21: Tumour close to margin, but clear
C22: Tumour close to margin, but clear
C23: Tumour close to margin, but clear
C24: Soft tissue, clear
C25: Soft tissue, clear
C26: Tumour close to margin, but clear
C27: Soft tissue, clear
C28: Soft tissue, clear
C29: Soft tissue, clear
C30: Tumour close to margin, but clear
C31: Soft tissue, clear
C32: Soft tissue, clear
C33: Tumour, follicular and plexiform, no nerve noted
C34: Tumour, follicular and plexiform, no nerve noted
C35: Clear
C36: Clear

11. Patient 11
A: Tumour
A1: No tumour
A2: No tumour
A3: No tumour
A4: No tumour
A5: Plexiform pattern, close to margin but clear
A6: No tumour
A7: No tumour
A8: No tumour
A9: Plexiform and Follicular pattern. Stroma showing desmoplasia, very close to sublingual gland.
A10: Small follicles displaying distinctive ameloblastomatous features (reverse polarisation, infranuclear vacuolisation, subepithelial hyalinisation). Variable size diameter of follicles from 0.25mm to 2mm. Active and relatively far removed from larger tumour mass and cysts. 1mm away from largest tumour and 0.5mm away from nerve twig. Thus, in addition to the pulled out nerve there is accessory nerve supply in the area that is as close as 0.5mm to tumour.
A11: Tumour close to margin but clear
A12: Small follicles away from main tumour
A13: No tumour, tooth within bone noted

B: Nerve
B1: Clear
B2: Clear (lots of blood vessels)
B3: Clear
B4: Clear
B5: Clear
B6: Clear, Mast cells noted
B7: Inactive odontogenic cell rests noted. Has not developed all the features of an ameloblastoma, but can possibly cause recurrence. Cell rests not generally seen within tumour.
B8: Clear
B9: Clear
B10: Clear

12. Patient 12
A: Tumour
A1: Clear
A2: Clear
A3: Clear
A4: Tumour noted, no nerve seen

A5: Clear
A6: Clear
A7: Tumour noted, Plexiform Granular cell variant
A8: Nerve twigs in anterior region – incisive lingual branches – clear of tumour
A9: Clear
A10: Clear
A11: Clear
A12: Clear
A13: Clear
A14: Large nerve buccally, not affected by tumour, there is tumour medial to nerve, but separating tumour is cortical bone and fibrous connective tissue wall. Tumour cells 1mm away from nerve.
A15: Clear
A16: Clear
A17: Clear
A18: Tumour noted, no nerve seen
A19: Clear
A20: Clear
A21: Tumour noted, no nerve seen
A22: Tumour noted, no nerve seen
A23: Tumour noted, no nerve seen
A24: Tumour noted, no nerve seen
A25: Tumour noted, no nerve seen
A26: Tumour noted, no nerve seen
A27: Tumour noted, no nerve seen

B: Nerve
B1 – B10: Nerve seen, no tumour noted on any slides
B11: Inflammation noted with giant cells around nerve, no tumour noted
B12: Clear with carry over noted on slide
B13: Clear, nerve only
B14: Cleat, nerve only

13. Patient 13
A: Tumour noted
A1: No tumour
A2: No tumour
A3: Plexiform pattern, margins clear
A4: No tumour
A5: Tumour noted, margins clear
A6: No tumour
A7: Tumour noted, margins clear
A8: No tumour
A9: Plexiform pattern, margins clear
A10: Plexiform pattern, margins clear
A11: Nerve twigs noted close to tumour (shows proximity to tumour) 1mm
A12: No tumour
A13: No tumour
A14: No tumour
A15: Tumour noted, margins clear
A16: Tumour noted, margins clear
A17: Tumour noted, margins clear
A18: Tumour noted, margins clear
A19: Tumour noted, margins clear
A20: Tumour noted. Although the nerve was pulled through in this specimen, there are numerous smaller accessory nerves present. Here they are not involved by tumour.
B: Nerve
B1: No tumour
B2: No tumour
B3: No tumour

B4: No tumour
B5: No tumour
B6: No tumour
B7: No tumour
B8: No tumour
B9: 3 levels reviewed: tumour cells noted
B10: Tumour noted within the inferior alveolar canal, pulled out with the nerve (tumour in soft tissue attached to nerve) (not carry over)

8.3 APPENDIX 3:

Second observer measurements

Closest distances between ameloblastomatous epithelium and nerve bundles

1. Patient 1 (F) - tumour not identified.
2. Patient 11 (A10) – 0,25mm from closest nerve twig.
3. Patient 12 (A14) – 1mm from large nerve.
4. Patient 13 (A11) – 1mm.
5. Patient 13 (B10) – 0mm.
6. Patient 1 (A1) – 0.25mm.
7. Patient 1 (A2) – 0,25mm.
8. Patient 1 (A10) – 0,25mm.
9. Patient 1 (A12) – 1,1mm from smaller nerve twig and 2mm from large nerve in neurovascular bundle.
10. Patient 2 (A2) – 0,5mm.
11. Patient 2 (A3) – 0,7mm.
12. Patient 2 (A14) – 0,5mm.
13. Patient 2 (A19) – 0,25mm.
14. Patient 2 (A23) – 0,25mm.
15. Patient 3 (AA) – 0,5mm.
16. Patient 3 (AC) – 0,5mm.
17. Patient 3 (AH) – 2mm.
18. Patient 3 (AN) – 0,5mm.
19. Patient 4 (O) – 1mm.
20. Patient 5 (A8) – 1,3mm.
21. Patient 6 (Z) – 0,25mm.
22. Patient 7 (I) – 1mm.
23. Patient 8 (D) – 0,25mm.

CHAPTER 9

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