

**The Pathological Outcomes Related to Symptomatic Impacted
Third Molars and Follicles as found in a Private Practice in
South Africa**

By

Brian Mark Berezowski

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Supervisors: Professor D. Kahn CH.M.F.C.S (SA)

Professor VM Phillips PhD

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Declaration

I, the undersigned, hereby declare that the work contained in this dissertation is my own original work and that I have not previously in its entirety or in part submitted it at any University for a degree.

Signed by candidate

Signature:

Date:

November 2013

ABSTRACT

The management of impacted third molar teeth remains controversial and unresolved. Arguments in favour and against removal of impacted third molar teeth are plentiful and convincing. Most publications do not specify whether the patient suffered systemic or local symptoms. Pathological lesions associated with impacted third molar teeth have been studied to a limited extent. Previous studies have been restricted to relatively small numbers of patients.

The aim of this study primarily was to review pathological reports of all symptomatic third molar teeth removed in a private practice, and to use the data to support or refute routine removal of third molar teeth.

All patients who underwent third molar tooth removal for symptoms, either systemic or local, in a private practice over a twenty year period between 1987 and 2007 were included in the study. Specimens were sent for histological assessment by Oral Pathologists. The patient records were reviewed retrospectively.

A total of 3427 third molar teeth were included in the study. There were 68.75% specimens which had some sort of pathology. Only 0.3% of specimens were reported as normal dental follicular tissue. There were 31.25% specimens of hyperplastic follicular tissue which was considered non pathologic as they consisted of normal dental follicular tissue with a mild chronic inflammatory cell infiltrate. However the 68.75% pathologic lesions consisted of 14.44% specimens with early

dentigerous cysts, 8.11% with dentigerous cysts, 42.80% of paradental cysts and the remainder with other pathologies. The majority of the patients were in the second and third decades and mostly female. The age distribution of the patients suggested a progression from hyperplastic follicular tissue with a peak occurring at 17 years, to early dentigerous cysts at 19 years, to dentigerous cysts at 21 years. Paradental cyst formation, with a peak incidence at 19 years of age formed a large number of the pathological lesions found, and accounted for a large number of patients seeking treatment, owing to the symptoms associated.

This study represents an analysis of the largest number of symptomatic third molar teeth submitted for histological assessment known. The data obtained was used to review the guidelines for the management of third molar teeth. From this study it can be concluded that symptomatic impacted third molar teeth should be removed early in the third decade in order to avoid general or local symptoms suffered by these patients

The role of the Oral Pathologist in the accurate diagnosis and treatment of patients was emphasized.

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CHAPTER 1

(1) Hypothesis

Symptomatic impacted third molar teeth and follicular tissue are associated with specific pathological changes which are progressive and which therefore supports the removal of symptomatic impacted third molar teeth.

(2) Aims of the study

(a) The problem.

The management of third molar or wisdom teeth whether impacted or not, remains a controversial issue to large extent unresolved. The arguments both for and against removal are convincing and there is no clear evidence to support either option. Many countries have developed guidelines which dictate how third molar teeth should be managed.

Furthermore the pathological changes and pathological lesions associated with third molar teeth have been studied to a limited extent only. The literature contains mainly case reports, case series and studies consisting of relatively small numbers of patients. As a consequence, there are few analytical studies of the pathological changes associated with third molars.

(b) Aims of the Study.

Thus the aims of the study were:

(i) To review the histological reports of all symptomatic third molar teeth removed over a 20 year period between 1987 and 2007 in a private maxillofacial practise in Cape Town.

(ii) To assess the progression of the pathological changes from follicular / hyperplastic follicular tissue to dentigerous cysts and to other pathoses.

(iii) To assess the impact of the age and gender of the patients and the location of the third molar teeth on the progression of the pathological changes.

(iv) To use the data from the analysis to try to support or refute the removal or retention of third molar teeth.

(v) To evaluate the need for removal of soft tissues associated with third molar teeth and to submit them for histological examination by preferably Oral Pathologists.

(vi) To briefly describe the current trends in treatment of the lesions examined.

CHAPTER 2

Review of the literature of management of third molar teeth and classifications.

(1) Management of third molar teeth.

In general third molars (Wisdom teeth) erupt between 17 to 24 years of age, but can remain unerupted and sometimes undiagnosed in older individuals. They can be seen as radiolucencies on orthopantomographs, with little or no calcification, from as early as 8 years of age. No specific literature concerning the local or systemic symptoms associated with third molars could be found. Symptoms from partially erupted wisdom teeth are either systemic or localized. Systemic complaints include temporal headaches, otalgia which sometimes is described as “scratchy ears”, submandibular lymphadenopathy and sore throat. These symptoms may well be in relation to temporomandibular joints also. Local symptoms include pericoronitis seen in partially erupted third molars, retromolar pain and swelling often in combination with some or all of the systemic symptoms, either unilaterally or bilaterally, and crowding of the anterior teeth. The problem of crowding is still a cause of debate among Orthodontists and remains controversial. Intra oral bad taste of a bitter/sour nature is also sometimes found with pericoronitis.

The exact percentage causing symptoms, unerupted or impacted, has not been determined. From clinical findings and orthopantomograms, impacted third molars do not remain unerupted due to lack of space, either in the mandible or in the maxilla, as bone growth has generally ceased at their time of eruption. Fully erupted third molars not causing symptoms should be left in situ. After an extensive review of the literature there appears to be no clear resolution as to whether wisdom teeth, impacted or not, should be removed. There are numerous articles which promote routine third molar removal, especially in the American literature. In contrast, there are

numerous articles which oppose routine third molar removal, albeit under strict guidelines, in British literature.

(a) Evidence in support of retention of third molar teeth.

The literature has many articles dealing with various aspects related to impacted wisdom teeth and recommending their retention. Van der Linden et al^[1] examined 1001 orthopantomographs of 2872 impacted third molars. They found dental caries to be the most common pathology in 7.1% of all impacted third molars and 42.7% of adjacent teeth. This was followed by supernumerary teeth, loss of alveolar bone height and coronal radiolucencies. The presence of pathological conditions was low and this radiological survey recommended non-removal of third molars.

Lopez et al^[2] found that almost all the patients who underwent third molar removal were satisfied, but that in over half the indication for surgery was initially unclear. They argued that the medico-legal aspects, especially with regard to nerve dyesthesia, as well as subjecting patients to general anaesthesia and the costs involved, did not justify routine removal of third molar teeth. The prophylactic removal of third molars was considered a question so controversial that it was reviewed in the British Journal of Orthodontics^[3]. The impact of local factors such as pericoronitis, dental decay, root resorption of the second molars, as well as incisor crowding and cyst development were analysed. It was concluded that only wisdom teeth with associated pathology should be removed.

The costs involved were also investigated by Edwards et al^[4]. They suggested the retention of third molars to be more cost effective for the NHS (National Health System) in the United Kingdom, but stated that should caries or recurrent pericoronitis develop then removal was the more cost effective treatment.

According to Liedholm et al.^[5] age was the only factor which influenced the removal of pathology-free third molars. Using a visual analogue scale, they assessed the indications for the removal of wisdom teeth, including age, angular position and eruption as well as the presence of disease which included caries, pericoronitis, root resorption, cyst and tumour formation. As far as age was concerned 71% of the patients were between 15 and 29 years. Statistically age was the only factor which had a significant relationship ($P < 0.05$) for the indication of removal of molars without disease. The indication for third molar removal was highest in young patients (15-19 yr) and lowest for the older group (40-49 yr).

Song et al.^[6] considered the effects of impacted wisdom teeth on incisor crowding by undertaking a systematic review of the available research literature in which 40 studies were reviewed. This study suggested only a weak association between crowding and the presence of third molars and they said that retention of third molars may be more cost effective than prophylactic removal in the short to medium term.

An audit of the appropriateness of referrals for third molar removal by General Dental Practitioners was published by Westcott et al.^[7]. The study was undertaken after the introduction of the NICE guidelines. They found 92% referrals followed the NICE guidelines. Of the 166 patients referred there were only 13 inappropriate referrals, of which 3 patients were asymptomatic, 9 had a single episode of pericoronitis and 1 had lower anterior crowding. They suggested that this compliance might stem from the original guidelines issued by the Royal College of Surgeons, prior to implementation of the NICE guidelines. They also concluded that the NICE guidelines contributed to cost reduction, waiting list time reduction and decrease in patient morbidity.

The question of dental research was debated by the United Kingdom parliament in 2005. The NICE Guidelines were praised for the reduction of routine removal of third molars by two thirds as found in The United Kingdom Parliament Lords Hansard text ^[8].

Adeyemo ^[9] reviewed the literature with reference to prophylactic removal of third molars and pathologies. He considered the risk of cyst and tumor development and concluded this was relatively low at 2.31% and stated that this small number did not justify the removal of third molars prophylactically. He also investigated the risks of mandibular fracture in the presence of impacted lower third molars and found that impacted third molars did not reduce the chance of angle fracture in these patients. Furthermore he endorsed the NICE principals as an indication for the removal of impacted third molars and recommended that "removal of impacted third molars should be limited to those teeth with well defined medical, surgical or pathological indications."

Freidman ^[10] also endorsed the NICE guidelines. As the risk factors for developing pathology in third molars appeared to be low, they suggested financial considerations and legal decisions might be implicated in third molar removal. In their opinion third molar removal was a health hazard.

The question was once again investigated by Krishan et al ^[11]. Their limited study of 439 patients found pericoronitis to be the most common problem, followed by caries and orthodontic reasons, with the formation of cysts and tumours occurring in only 5%. They concluded that patients do not readily agree to the removal of impacted wisdom teeth and they should only be removed when symptomatic, due to the costs involved as well as the manpower required.

(b) National Institute for Clinical Excellence (NICE) guidelines for England and Wales.

There were no clear cut guidelines for the removal of impacted third molars prior to the mid 1990's. This problem was recognized by the Royal College of Surgeons of England ^[12] (FDSRCS) who convened a small expert working panel in conjunction with the British Association of Oral Surgeon (BAOMS). This group worked with the American Association of Oral and Maxillofacial Surgeons (AAOMS), who had published their parameters of care ^[13].

The report of the Dental Faculty of the Royal College of Surgeons of England ^[14] was released in 1997 and was quickly followed and incorporated into a landmark publication entitled "Prophylactic Removal of Impacted Third Molars: Is it Justified?" ^[15].

This document was important for decision making for both practitioners and the National Health Service (NHS) in England and Wales. The NICE guidelines on extraction of wisdom teeth was published in March 2000 ^[16].

(NICE) guidelines for extraction of wisdom teeth (2000).

These guidelines stated emphatically that:

- 1 The practice of prophylactic removal of pathology free impacted third molars should be discontinued in the NHS.
- 2 Routine dental care needs to be no different in general for pathology free impacted third molars.
- 3 Surgical removal of impacted third molars should be limited to patients with evidence of pathology.

This included:

- Unrestorable caries.

- Non treatable pulpal and periapical pathology.
- Cellulitis.
- Abscess and osteomyelitis (sic).
- Internal/external resorption of the tooth or adjacent tooth.
- Fracture of teeth.
- Disease of follicles including cyst or tumour.
- Teeth impeding surgery or reconstructive jaw surgery.
- Tooth that is involved within the field of tumour resection.

4 The first episode of pericoronitis was not regarded as an indication for surgery unless extremely severe. The second episode or subsequent episodes were an indication for surgery. The NICE guidelines for removal of impacted wisdom teeth were clear. Since they were introduced there have been numerous audits done in order to ascertain whether they were being met. Bristol Dental Hospital ^[17] conducted an audit which found 48.2% of General Dental Practitioners (GDP) followed the NICE guidelines as published. However 32% gave inadequate or incorrect information. It was stressed that a detailed account of pericoronitis should be included in the letter of referral so that the correct treatment could be undertaken. The NICE guidelines were reiterated in a Complication Summary ^[18] issued to NHS in England and Wales. Subsequently this was issued again to the NHS in 2009 ^[19]. The guidelines remain unchanged.

Guidelines ^[20] are typically written in statement form by a reputable organisation.

In the United Kingdom these include:

- NICE – National Institute for Clinical Excellence.
- Scottish Intercollegiate Guidelines Network.
- Prodigy.
- Professional Organisations and Royal Colleges.

It was noted that even in the original NICE guidelines special mention was made of “individual responsibilities of the health care worker to make appropriate decisions in the circumstances of the individual patient in conjunction with the patient and/or the guardian or carer”.

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(c) Evidence in support of the removal of impacted third molar teeth.

The American Association of Oral & Maxillofacial Surgeons (AAOMS) published a landmark paper on the removal of impacted teeth: AAOMS position statement ^[21]. In this study all impacted teeth were viewed as potential pathologic entities and surgery was considered the treatment of choice. It stated categorically that “impaction or malposition of a third molar was an abnormal state and may justify its removal. Such treatment was not considered prophylactic.” Furthermore the paper recommended that other impacted teeth be removed at the same surgical intervention, in order to reduce costs and unnecessary subsequent anaesthesia. They stated that the incidence of pathology related to impacted teeth including cysts and tumours, increased after 30 years of age.

In a white paper on third molar data ^[22] published by the American Association of Oral & Maxillofacial Surgeons various parameters were considered. These included the natural history of third molars, periodontal considerations, age, orthodontic and prosthodontic considerations as well as nerve damage. There was no mention of cyst or tumour development, except under the section dealing with asymptomatic third molars under a planned or existing prosthesis. The conclusions reached were that “the disposition of unerupted teeth has been found to be dynamic and unpredictable”. It further stressed that each individual case should be examined and assessed by the clinician and treated accordingly. As far as crowding following orthodontic treatment was concerned, the white paper stated that wisdom teeth were only one factor in crowding and stressed that the clinician should make the ultimate decision. In the section dealing with age considerations, increased post-operative morbidity in patients over 25 years was noted, as well as an increase in periodontal defects and caries. No specific recommendations as to third molar removal due to cyst or tumour development could be found in this paper.

In the study by Bagheri et al ^[23] which was purely a literature review, they analysed the available literature from 1966 to 2004. This did not involve seeing any patients. The evidence for and against the prophylactic removal of third molars was investigated. Their recommendation was that there was overwhelming support for removal of asymptomatic third molars in young adults, considering the likelihood of cysts and tumours developing later in life.

They also found impacted third molars unlikely to be the cause of the temporomandibular joint syndrome. Furthermore, third molar removal was found to be cost effective and safe. In the editorial entitled "Impacted Teeth: Reflections on Curran, Kugelberg and Rood ", Assael ^[24] reported that the incidence of pathological findings was higher than previously found and stated that all follicular tissue should be submitted for histological examination. Due to pressure from medical insurance companies and third party funders, this was not the case, especially in the office setting and this would not be tolerated when treated in hospital. Furthermore he also recommended the early removal of third molars in order to decrease nerve injury as well as periodontal disease.

Periodontal pathology associated with asymptomatic third molars was investigated by Blakey et al ^[25]. In their clinical examination of 329 patients they found that 25% of patients with asymptomatic third molars had considerable periodontal pathology. They further found that unerupted molars, close to the occlusal plane were likely to have periodontal pathology similar to vertically impacted third molars. It was emphasised that symptoms from third molars were not a good indicator of periodontal pathology.

Curran et al ^[26] reported the largest series of histology of adult pericoronal lesions. They studied a total of 2646 specimens over a six year period. Results of this retrospective study showed an incidence of 67.1% nonpathologic follicular tissue. However there was an incidence of 28.4% dentigerous cysts, 2.68% keratocysts, 0.7% odontomata, 0.5% ameloblastomas and only 0.23%

carcinomas. Other pathology in small numbers included myxomas and calcifying odontogenic cysts and tumours. They concluded that there was a wide spectrum of pathology in the tissue submitted. This included malignant lesions, especially carcinomas; with these developing later in life in the 5th to 8th decades. Unfortunately they did not specify the exact location of the lesions. Furthermore they found that there was no correlation between radiographic findings and pathology diagnosed in routine follicular tissue submitted. They stressed that there was strong correlation between increasing age and pathology found. They recommended that the removal of impacted teeth was indicated.

The document pivotal to most of these papers was the NIH Consensus Development Conference for removal of third molars ^[27]. Firstly; it established well defined criteria for the removal of impacted third molars. Secondly; it was noted that there was an increase in morbidity with age and thirdly, that growth studies at that stage were not adequate for clinical action.

Güven et al ^[28] found that the incidence of malignant tumours associated with impacted third molars was very low, but that there was an increase in pathological conditions with an increased age. Furthermore they suggested that “considerable pathology may occur in a relatively small proportion of patients” and that often there was a lack of associated symptoms.

The question of removal of impacted mandibular third molar, the complications and their risk factors was investigated prospectively by Blondeau et al ^[29]. They reviewed 550 impacted mandibular third molars and found 20 cases of alveolitis, 12 cases of infection and 6 cases of paraesthesia of the inferior alveolar nerve of which 3 resolved and 3 were permanent. Females were found to be more affected than males with the three complications, namely alveolitis, infections and paraesthesia. As far as post operative anaesthesia was concerned age also appeared to be important. It was recommended that removal of impacted third molars took

place before 24 years of age. In addition the surgeon's experience could also be a factor in post-operative complication rates.

(d) The view of of the South African Society of Maxillo Facial Surgeons.

In the position paper on the removal of impacted third molars ^[30] the South African Association of Maxillofacial and Oral Surgeons emphasized and recommended that each case should be assessed on its own merits. Furthermore there were convincing arguments both for and against the removal of impacted third molars. In the interests of the patient it was recommended that impacted third molars be removed when the root formation was 2/3 complete or when there was a high probability of disease or pathology. It also suggested that pericoronitis was more likely in vertical or distoangularly impacted teeth, and that the risk of caries was increased in mesioangular and horizontal impactions. It went on to state that completely embedded third molars could well be left alone but stressed that they must be reassessed at regular intervals to ensure no subsequent pathological processes were taking place. It also agreed with the view that other impacted wisdom teeth should be removed at the same time if the patient was undergoing general anaesthesia in order to reduce morbidity and costs. It did not prescribe any clear guidelines for the removal of impacted wisdom teeth with or without pathology. It stressed that clinical independence of the practitioner was paramount and that the interests of the patient should come first.

This view concurred with that of Mercier and Precious ^[31] who stated the risks of non-intervention, intervention, as well as the benefits of both. The criteria for the removal of impacted third molars have been set out in the NICE protocols ^[16]. However the absolute indications and contra indications for the removal of asymptomatic third molars have not been established, as no long term studies exists to validate the benefits of removal or retention to the patient. As far as the development of infections, cysts and tumours was concerned, Mercier and Precious ^[31] agreed with the earlier findings of Stephens et al ^[32] who stated that the risks were low. Both papers concluded that the interest of the patient must remain the paramount concern of the practitioner.

(e) Scottish guidelines for the removal of impacted third molars.

Guidelines for the removal of impacted third molar teeth have also been issued by the Scottish Intercollegiate Guidelines Network, Sign Guideline 43 ^[33]. These guidelines were based on the same or similar literature search which produced the NICE (National Institute of Clinical Excellence) guidelines as described in detail previously. However it differed from the NICE guidelines as issued in England and Wales in a number of respects.

The Scottish guidelines allowed for a greater acceptance for prophylactic removal of third molars, whilst long term studies continued. The guidelines emphasized the importance of lingual nerve retraction and protection as well as the use of steroids in the peri-operative period and lower anterior crowding following orthodontics. All these entities required long term studies and further research before they could be included in the guidelines. However it was emphasized that this was only a guideline and personal guidelines should be developed by the attending practitioner.

(f) Risks and morbidity of removal of impacted third molar teeth.

Almost all publications concerning impacted third molars make mention of risks and post-operative morbidity.

Mercier et al ^[31] classified the risks and benefits of non-intervention as well as Intervention for the removal of third molar teeth. These were listed in detail in his paper as shown in Table (1).

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Risk of Non-intervention.

- a Crowding of the dentition based on growth prediction.
- b Resorption of the adjacent teeth and periodontal status.
- c Development of pathological conditions such as infections, cysts and tumours.

Risk of Intervention.

- a Minor transient: sensory nerve alterations, alveolitis, trismus and infections, haemorrhage, dento-alveolar fracture and displacement of teeth.
- b Minor permanent: periodontal injury, adjacent tooth injury, temporomandibular joint injury.
- c Major: altered sensation, vital organ infection, fracture of the mandible and maxillary tuberosity, injury and litigation.

Benefits of Non-intervention.

- a Avoidance of risk.
- b Preservation of functional teeth.
- c Preservation of ridge.

Benefits of Intervention.

- a In relation to age.
- b In relation to different therapeutic measures.

Table (1). Risks and morbidity following removal of impacted third molar teeth.

Mercier et al ^[31] thought that the risks of non-intervention included over-crowding, resorption of the adjacent teeth and the development of pathological conditions such as infections, cysts and tumours. However the benefits of non-intervention included the avoidance of the surgical complications, preservation of functional teeth, and the preservation of the alveolar ridge.

The risks of intervention for the third molar include minor complications, which can be transient or permanent and major complications. The transient minor complications include sensory nerve alterations, alveolitis, trismus, haemorrhage, dentoalveolar fracture and displacement of teeth. Permanent minor complications include periodontal injury, adjacent tooth injury and temporomandibular joint injury. Major complications include altered sensation, infection of vital organs and fracture of the mandible or maxilla. There is also the risk of litigation. However the benefits of intervention are age related as well as in relation to different therapeutic measures. Long term complication relating to the age of the patient, temporomandibular joint function, inferior alveolar nerve function and fracture were described.

Blondeau et al ^[29] reported a low incidence of postoperative complications which included alveolitis, infections, and anaesthesia or paraesthesia of the inferior alveolar nerve. The incidence of complications investigated was 6.9%. As far as the neurosensory defects were concerned 50% were temporary and 50% were permanent. Risk factors for the development of complications included age and health of the patient, the difficulty of the impaction, experience of the surgeon, the surgical technique employed, smoking and the use of oral contraceptives. Although temporomandibular joint problems are included as one of the complications after third molar removal, the precise relationship is complex. Haung et al ^[34] found that both age and third molar extraction were risk factors for temporomandibular joint disorders. De Angelis et al ^[35] noted that 14% of patients referred for third molar removal had temporomandibular joint disorders preoperatively, and 23.3% had symptoms related to third molar tooth impaction. They

emphasized that temporomandibular joint disorders were common in patients referred for third molar removal.

Inferior alveolar nerve and lingual nerve injuries following removal of third molars are uncommon with incidences ranging from 0.5% to 5% and 0.6% to 2% respectively. Robert et al ^[36] surveyed maxillofacial surgeons in California and found an incidence of 0.04% for temporary injury and 0.01% for permanent injury to the inferior alveolar and lingual nerves. Although recovery rates were high, they emphasized the need for careful evaluation and the importance of a detailed informed consent.

Fractures of the mandible were also a problem following third molar removal. Characteristics common to most patients suffering mandibular fracture after removal of third molars include age (older than 30 to 40 years) and if the roots of the teeth were superimposed on or near the inferior alveolar canal on orthopantomograph as described by Lizuka et al ^[37]. They recommended that such patients be warned of the possibility of fracture of the mandible and that a soft diet for two weeks post-operatively be implemented. Surgical operative technique with minimal bone removal should also be employed.

Krimmel et al ^[38] also found that advanced age (between 42 to 50 years) was associated with fracture to the mandible after third molar removal, although half of the patient also had a pre-existing cystic lesion. It would appear that fully dentate patients were more at risk of mandibular fracture due to increased biting forces. Libersa ^[39] investigated immediate and late mandibular fractures following third molar removal. Again age was found to be a factor, with the mean age being 40 years. He also stated that patients with a full dentition were most at risk and two thirds of the fractures occurred whilst eating within two weeks of the post-operative period. He observed the risk was greater in males older than 25 years of age and suggested prophylactic removal of third molars should be performed before 20 years of age. Meisami et al ^[40] undertook

a study of all patients presenting with fractured mandibles. Assaults appeared to have been the most common aetiological factor (67%) with contact sports accounting for 14% and falls for 30%. Angle fracture of the mandible was the most common site. A significant number of these patients were below 30 years of age. They also suggested prophylactic removal of third molars be performed in the second or third decades in order to reduce angle fractures. It is debatable whether impacted third molars count as anatomically or pathologically weak spots, but certainly following blunt trauma, the mandible is likely to fracture through impacted wisdom teeth at the angle of the mandible. This is not the same thing as saying that if the wisdom teeth were to be removed the mandible would not break. It is likely that the mandible would still be fractured by the same energy transfer but that it would break elsewhere such as the condylar necks. Zhu et al^[41] compared the position of fractures with or without unerupted third molars. They found that in poly-trauma involving the mandible, those patients without impacted third molars often sustained condyle fractures, whilst those with embedded third molars often sustained angle fractures.

(g) Post-operative recovery following third molar removal.

Relatively little has been written about the alleviation of discomfort immediately following third molar surgery. Symptoms which patients suffered included pain, swelling, oral function and lifestyle alteration. White et al ^[42] addressed this problem and devised a health related quality of life questionnaire, (HRQOL) which was given to 740 patients about to have all four third molars removed. Eighty five percent of patients responded. Although 96% of these patients took analgesics after the operation, pain was considered most severe in the first post-operative day. By the 9th post-operative day 63% of patients considered the pain minimal or nil. By day 7 in the postoperative period chewing had resumed and normal diet was found in more than 66% of patients. It was concluded that health-related outcome data was useful in detailing the typical post-operative course.

This study was augmented to investigate the impact of delayed clinical healing. Ruvo et al ^[43] confirmed the clinical impression of surgeons that delay in clinical healing significantly affected health-related quality of life rates. They found that female patients, prior symptoms and more difficult surgery all contributed to delayed healing. This delayed healing influenced recovery, lifestyle, oral function and pain.

(2) Classification of cystic lesions and tumours of the maxillofacial regions.

Pathological lesions associated with impacted third molar teeth include odontogenic cysts and tumours and are by far the most important entities but can develop from the follicles of all developing teeth. These have been formalised as found below and do not apply to third molar teeth only.

(a) Cysts of the Oral and Maxillofacial regions 2007.

Shear and Speight^[44] in their textbook Cysts of the Oral and Maxillofacial Regions, classified cystic lesions of the jaws and oral areas as shown in Table (2).

(i) Cysts of the jaws.

Cysts of the Jaws can be divided into Epithelial and Non-Epithelial Cysts.

The Epithelial cysts can be further classified into developmental and inflammatory lesions. The developmental epithelial cysts include odontogenic cysts; gingival cysts of infants, odontogenic keratocysts, dentigerous cysts, eruption cysts, lateral periodontal cysts, gingival cysts of adults, botryoid odontogenic cysts, glandular odontogenic cysts and calcifying odontogenic cysts. The non-odontogenic cysts include the nasopalatine duct cysts, nasolabial cysts, mid palatal rafe cysts of infants, medial mandibular cysts as well as globulomaxillary cysts. The inflammatory epithelial cysts include radicular cysts, residual cysts, paradental cysts and inflammatory collateral cysts. Non-epithelial cysts of the jaws include the solitary bone cyst and the aneurysmal bone cyst.

(ii) Cysts associated with the maxillary antrum.

Cysts associated with the maxillary antrum include the benign mucosal cyst of the maxillary antrum and the post operative maxillary cyst (surgical ciliated cyst of the maxilla).

(iii) Cysts of the soft tissues of the mouth face and neck.

This includes a spectrum of cystic lesions of the mouth, face and neck as shown in Table (2).

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Cysts of the Oral and Maxillofacial Regions

CLASSIFICATION

I Cysts of the jaws

A. Epithelial-lined cysts

1. Developmental
 - (a) Odontogenic
 - i. Gingival cysts of infants
 - ii. Odontogenic keratocyst
 - iii. Dentigerous cyst
 - iv. Eruption cyst
 - v. Gingival cyst of adults
 - vi. Developmental lateral periodontal cyst
 - vii. Botryoid odontogenic cyst
 - viii. Glandular odontogenic cyst
 - ix. Calcifying odontogenic cyst
 - (b) Non-Odontogenic
 - i. Midpalatal raphe cyst of infants
 - ii. Nasopalatine duct cyst
 - iii. Nasolabial cyst
2. Inflammatory origin
 - i. Radicular cyst, apical and lateral
 - ii. Residual cyst
 - iii. Paradental cyst and juvenile paradental cyst
 - iv. Inflammatory collateral cyst

B. Non-epithelial-lined cysts

- 1 Solitary bone cyst
- 2 Aneurysmal bone cyst

II Cysts associated with the maxillary antrum

1. Mucocele
2. Retention cyst
3. Pseudocyst
4. Postoperative maxillary cyst

III Cysts of the soft tissues of the mouth, face and neck

1. Dermoid and epidermoid cysts
2. Lymphoepithelial (branchial) cyst
3. Thyroglossal duct cyst
4. Anterior median lingual cyst (intralingual cyst of foregut origin)
5. Oral cysts with gastric or intestinal epithelium (oral alimentary tract cyst)
6. Cystic hygroma
7. Nasopharyngeal cysts
8. Thymic cyst
9. Cysts of the salivary glands: mucous extravasation cyst; mucous retention cyst; ranula; polycystic (dysgenetic) disease of the parotid
10. Parasitic cysts: hydatid cyst: *Cysticercus cellulosae*; trichinosis

Table (2). Mervyn Shear and Paul M. Speight. Cysts of the Oral and Maxillofacial Regions
Fourth edition, Blackwell Munksgaard 2007.

(b) WHO histological classification of tumours of the oral cavity 2005.

The WHO introduced a system of classification of oral lesions in an attempt to standardise research and clinical approach to this area. The latest classification was produced in 2005 and changes considerably compared to earlier versions. This also does not involve only third molar teeth but the whole of the oral cavity. Cystic lesions have been removed totally.

(i) Tumours of the odontogenic apparatus.

Tumours of the Odontogenic Apparatus can be divided into benign tumours which contain ameloblastoma of the solid or multicystic type, extraosseous/peripheral types, desmoplastic and unicystic types, squamous odontogenic tumour, calcifying epithelial odontogenic tumour, adenomatoid odontogenic tumour and keratocystic odontogenic tumour. Malignant tumours include metastasising ameloblastoma, ameloblastic carcinomas of primary and secondary type, primary intraosseous squamous cell carcinoma of the solid type or derived from keratocystic odontogenic tumours or odontogenic cysts, clear cell and ghost cell carcinomas. Saromas contain ameloblastic fibrosarcoma and ameloblastic fibrodentinosa. Tumours of odontogenic mesenchyme and epithelium are ameloblastic fibroma, ameloblastic fibrodentinoma, ameloblastic fibro-odontome-odontoma, complex and compound odontoma, ontoameloblastoma, calcifying cystic odontogenic tumour and dentinogenic ghost cell tumour.

(ii) Tumours related to bone.

Tumours relating to bone include ossifying fibroma, osseous dysplasias, central giant cell lesion and cherubism.

(iii) Tumours of odontogenic mesenchyme only.

These include cementoblasoma, odontogenic fibroma, myxoma and fibromyxoma.

WHO Histological classification of odontogenic tumours 2005

MALIGNANT TUMOURS

Odontogenic Carcinomas

Metastasizing (malignant) ameloblastoma	9310/3
Ameloblastic carcinoma – primary type	9270/3
Ameloblastic carcinoma – secondary type (dedifferentiated), intraosseous	9270/3
Ameloblastic carcinoma – secondary type (dedifferentiated), peripheral	9270/3
Primary intraosseous squamous cell carcinoma – solid type	9270/3
Primary intraosseous squamous cell carcinoma derived from keratocystic odontogenic tumour	9270/3
Primary intraosseous squamous cell carcinoma derived from odontogenic cysts	9270/3
Clear cell odontogenic carcinoma	9341/3
Ghost cell odontogenic carcinoma	9302/3

Odontogenic sarcomas

Ameloblastoma fibrosarcoma	9330/3
Ameloblastic fibrodentino-and fibro-odontosarcoma	9290/3

BENIGN TUMOURS

Odontogenic epithelium with mature, fibrous stroma without odontogenic ectomesenchyme

Ameloblastoma, solid/multicystic type	9310/0
Ameloblastoma, extraosseous/peripheral type	9310/0
Ameloblastoma, desmoplastic type	9310/0
Ameloblastoma, unicystic type	9310/0
Squamous odontogenic tumour	9312/0
Calcifying epithelial odontogenic tumour	9340/0
Adenomatoid odontogenic tumour	9300/0
Keratocystic odontogenic tumour	9270/0

Odontogenic epithelium with odontogenic ectomesenchyme, with or without hard tissue formation

Ameloblastic fibroma	9330/0
Ameloblastic fibrodentinoma	9270/0
Ameloblastic fibro-odontoma	9290/0
Odontoma	9280/0
Odontoma, complex type	9282/0
Odontoma, compound type	9281/0
Odontomeloblastoma	9311/0
Calcifying cystic odontogenic tumour	9301/0
Dentinogenic ghost cell tumour	9302/0

Mesenchyme and/or odontogenic ectomesenchyme with or without odontogenic epithelium

Odontogenic fibroma	9321/0
Odontogenic myxoma/myxofibroma	9320/0
Cementoblastoma	9273/0

Bone-related lesion

Ossifying fibroma	9262/0
Fibrous dysplasia	
Osseous dysplasia	
Central giant cell lesion (granuloma)	
Cherubism	
Aneurysmal bone cyst	
Simple bone cyst	

OTHER TUMOURS

Melanotic neuroectodermal tumour of infancy

9363/0

Table (3). WHO 2005 histological classification of odontogenic tumors. IACR, Lyon France.

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(c) Pathological lesions of the third molar area.

(i) General findings.

Rakprasitkul ^[46] examined histologically pericoronal tissues of completely unerupted third molars. There were 104 specimens. These consisted of 65.4% of mandibular and 34.6% maxillary wisdom teeth. Normal dental follicular tissue was found in 41.39% of patients but pathoses in 58.65%. Of these dentigerous cysts comprised the bulk of nearly 51% whilst other entities included odontogenic keratocysts and ameloblastomas. They were commonly found in patients older than 20 years and he recommended removal of wisdom teeth in this age group.

Mesgarzadeh et al ^[47] examined the histological appearance of 185 impacted third molars in 170 patients with normal follicles less than 3mm in size radiologically. The incidence of pathology was highest in the 20-30 year age group, more often in men and occurred predominantly in the mandible. There were 38% dentigerous cysts and 5.8% ameloblastomas. They concluded that radiological examination was not a reliable indicator of the presence of pathology. They recommended prophylactic removal of all third molar impactions in young people in the third decade.

Yildirumm et al ^[48] from Turkey examined 120 dental follicles histologically. All the teeth were covered by mucosa or bone. Normal dental follicles were found in 77% but 23% had some sort of pathological lesion. There were 61% dentigerous cysts, 6.6% calcifying odontogenic cysts and 2.5% keratocysts. The angular positions of the impacted teeth as well as gender were not associated with the presence of pathological lesions. However 89% of patients with cystic change were older than 20 years and prophylactic removal prior to this was recommended even in the absence of symptoms. They also recommended that all tissue should be sent for histological analysis.

Ngeow et al ^[49] reported a paradental cyst associated with an unerupted wisdom tooth. They stated that a paradental cyst was an odontogenic cyst near the cervical margin of the tooth which occurred as a result of an inflammatory process related to a periodontal lesion. In their case this was an incidental finding after removal of an unerupted wisdom tooth. They postulated that paradental cysts were possibly under reported as they were thought to be part of the dental follicle.

(ii) Radiology and third molar teeth.

Polat et al ^[50] studied 1914 panoramic radiographs retrospectively. They considered four radiological pathological changes which included caries on the impacted third molar, caries on the distal aspect of the second molar, periodontal damage to the second molar and bone loss on the distal aspect of the third molar. They found that horizontal and mesio angular impacted molars had more abnormalities as seen on radiographs. However no histological examination was performed.

Al-Khateeb et al ^[51] also reported a radiographic study of third molars. These included caries, radiolucent areas both peri-apically and peri-coronally, caries of the second molar, external resorption of roots of the second molar and odontomata. Analysis included age, gender and the radiographic lesions mentioned. They found an incidence of radiological abnormalities of 46%. Caries was most often seen radiographically. Histologically peri-apical areas were most often peri-apical infections while pericoronal areas were either cysts or neoplasms. The most common cyst found was a dentigerous cyst whilst ameloblastomas were the most common neoplasm. They did not specify the specific percentages of each.

Saravana et al ^[52] examined both radiographs and histology of "follicles" of 2.4mm or less. Their study comprised 100 patients. Cystic changes were seen in 60% of men and 28% in women. They also reported a higher incidence in the 3rd decade. The total incidence of cystic change

was 46% overall, with the common diagnosis being that of dentigerous cysts. They concluded that there was a place for prophylactic removal of impacted third molars.

A radiological study based on orthopantomograms by Werkmeister et al ^[53] showed abnormal changes related to impacted wisdom teeth and their position. A high “position” score was significantly associated with teeth in aberrant positions, and corresponded with cyst formation. A lower score was associated with teeth in a less aberrant position and was associated with abscess formation as well as angle fracture. They recommended that wisdom teeth with high “position” scores be removed to avoid cyst formation.

Chu et al ^[54] from Hong Kong retrospectively studied orthopantomograms of patients who had symptoms related to impacted teeth. They found that 82.5% of the patients had impacted mandibular wisdom teeth followed by impacted maxillary molars in 15.6% with only 0.8% of impacted canines. They stressed the need for full clinical records in order to verify the findings of the orthopantomograms and stressed that orthopantomograms were not to be used as the only diagnostic method. No histological analysis was included in their study.

Radiographic images of follicles were also investigated by Baykul et al ^[55] to determine the incidence of associated cystic change. They looked at the type of impactions of lower third molars in relation to cyst formation as well as contact with adjacent teeth. All cases were examined radiographically and histologically. Fifty percent of the specimens showed cystic change with most occurring at the 20-25 year range. There was a significant association between cystic change and position of impactions, with vertical impactions having the greatest possibility of cyst development. They concluded that cystic changes in the asymptomatic molars were greater in patients older than 20 years whose impactions were in a vertical position. These were considered as early dentigerous cysts.

(iii) Rare lesions associated with third molars.

A rare case of squamous cell carcinoma arising in a dentigerous cyst was reported by Yasuoka et al ^[56]. They stressed that carcinoma arising in dentigerous cysts was extremely rare and their extensive review of the literature showed less than 20 cases. In their particular case an impacted molar tooth together with a cyst was removed under general anaesthetics after swelling in the area had not resolved after antibiotic treatment from the dentist. Subsequent histological examination revealed a well differentiated squamous cell carcinoma in part of the cyst wall. Treatment involved chemotherapy, resection and reconstruction with a titanium plate as well as radiotherapy. The patient fulfilled Gardeners criteria ^[57] for the diagnosis of carcinoma arising from a dentigerous cyst, which included change from benign cystic epithelium to invasive squamous cell carcinoma, no carcinomatous change in the overlying epithelium and no source of carcinoma in the adjacent structures or the rest of the body. The average age of patients with squamous cell carcinoma arising in a dentigerous cyst wall was in the sixth decade whilst the average age for dentigerous cysts was in the second or third decade. The most common site involved was the mandibular third molar area.

Malignant metastasis of breast carcinoma to a third molar was reported by Chatterjee et al ^[58]. The patient had a previous breast carcinoma and presented with parasthesia of the lower lip. On orthopantomogram this appeared to be a dentigerous cyst associated with an impacted third molar. The tooth was removed and histological examination showed a dentigerous cyst containing adenocarcinoma in the cyst wall. This was presumed to have been a metastasis from the original disease.

Chindia et al ^[59] reported a case of ameloblastoma which occurred about three and a half years after the removal of a third molar which originally had pericoronitis and was a bony impaction.

They noted that the “index of suspicion” should be high for all impacted teeth especially third molars and that their early detection minimized the need for surgery.

(iv) Importance of the Oral Pathologist.

Kim et al ^[60] undertook a study of dental follicular tissue. They investigated a total of 663 specimens from 1976 to 1988 which were referred to the Armed Forces Institute of Pathology (AFIP) in the United States by general pathologists seeking diagnostic clarification. Of these 84% of patients were in the second and third decades with over 70% of the specimens coming from third molar teeth. Of these 53% were correctly diagnosed by general pathologists 17% gave a description only, 10% had no diagnosis at all, whilst 20% were incorrectly diagnosed. The incorrect diagnosis included odontogenic cysts, myxomas, fibromas, ameloblastic fibromas and ameloblastomas. It was suggested that general medical pathologists needed to take into account the clinical and radiological features as well as the histology in order to differentiate the follicles from cysts and tumours. In her discussion of this paper Eisenberg ^[61] stressed that General Pathologists should be specially trained in oral and dental pathology. The special relationship between Oral Pathologists and Oral and Maxillofacial surgeons was emphasized and General Pathologists were encouraged to seek specialized opinions. She stressed the need for diagnostic accuracy as this was more than only academic and had a large bearing on treatment delivered to the patient.

Glosser et al ^[62] investigated the histological abnormalities of tissues surrounding third molar teeth when there were no pathological conditions seen on radiographs. A higher number of dentigerous cysts were found histologically and hence they stressed the importance of histological investigation of all specimens.

Franklin et al ^[63] reviewed the total number of oral pathology specimens over a 29 year period. Of the specimens received 12.46% were from General Dental Practitioners. During that period there was a four fold increase of the overall service, whilst cases referred from general practitioners only increased from 7% to 17%. Of the specimens submitted by general practitioners only 9 malignant neoplasms were seen but other entities included cysts, benign tumours and mucosal lesions. However this increase indicated more lesions were being sent by General Dental Practitioners and they recommended that the oral pathology service should be expanded.

Khorasani et al ^[64] reviewed the histology of 100 impacted third molars with radiographically normal follicular spaces. There were only 100 patients in the study, 74% female and 26% male. A significant relationship was found between patient age and the presence of squamous epithelium and metaplasia as well as inflammation ($P < 0.05$). As no significant pathological lesions were found in their sample it was recommended that third molars should be left, but radiological follow up was advised. This study suggests that the diagnosis of early dentigerous cyst was missed and the pathologist may not have interpreted the results correctly.

(d) Description of Individual Lesions.

(i) Dental follicle.

The dental follicle is a fibrous sac containing the developing tooth and its odontogenic organ. In addition it may be the precursor of other cells of the periodontium including osteoblasts and cementoblasts as described by Ten Cate ^[65]. It contains loose fibrous tissue and is lined with a reduced enamel epithelium (non-functional ameloblasts after enamel formation) that is situated on the surface of tooth enamel. The surrounding fibrous tissue may contain epithelial islands of odontogenic epithelium from the embryonal dental lamina. Radiographically the dental follicle appears as a radiolucent space around the tooth, with a thin outer radio-opaque border according to Farah et al ^[66]. Differentiation of stem cells in the dental follicle was studied by Yao et al ^[67] in rat mandibular molars. They hypothesised that stem cells may be present in the dental follicle and that these were pluripotential cells.

Völlner et al ^[68] demonstrated that the dental follicle consisted of ectomesenchymal tissue surrounding the developing tooth germ. They derived their source of precursor cells from human third molars and confirmed that these cells were unique and undifferentiated cells resided in the periodontium prior to tooth eruption. They demonstrated differentiation in vivo as well as in vitro conditions. They also found that the expression of the genes, runx 2, DLX-5 and MSX-2 in the dental follicle cells were unaffected during differentiation in vitro, but DLX-3 gene expression was increased in dental follicular cells during differentiation. Hence differentiation did occur after four weeks of culture. Furthermore they demonstrated differentiation of precursor cells in neural like tissue.

Investigation into the stages of tooth development was undertaken by De Olivera et al ^[69]. They studied 105 teeth histologically and radiographically from 13 to 24 years of age. They showed

the width of the dental follicle ranged from 0.0 to 4.0 mm radiographically on orthopantomographs but showed no significant association histologically between root formation and any morphological findings, with the exception of formation of a stratified squamous epithelium. There was little chronic inflammation present.

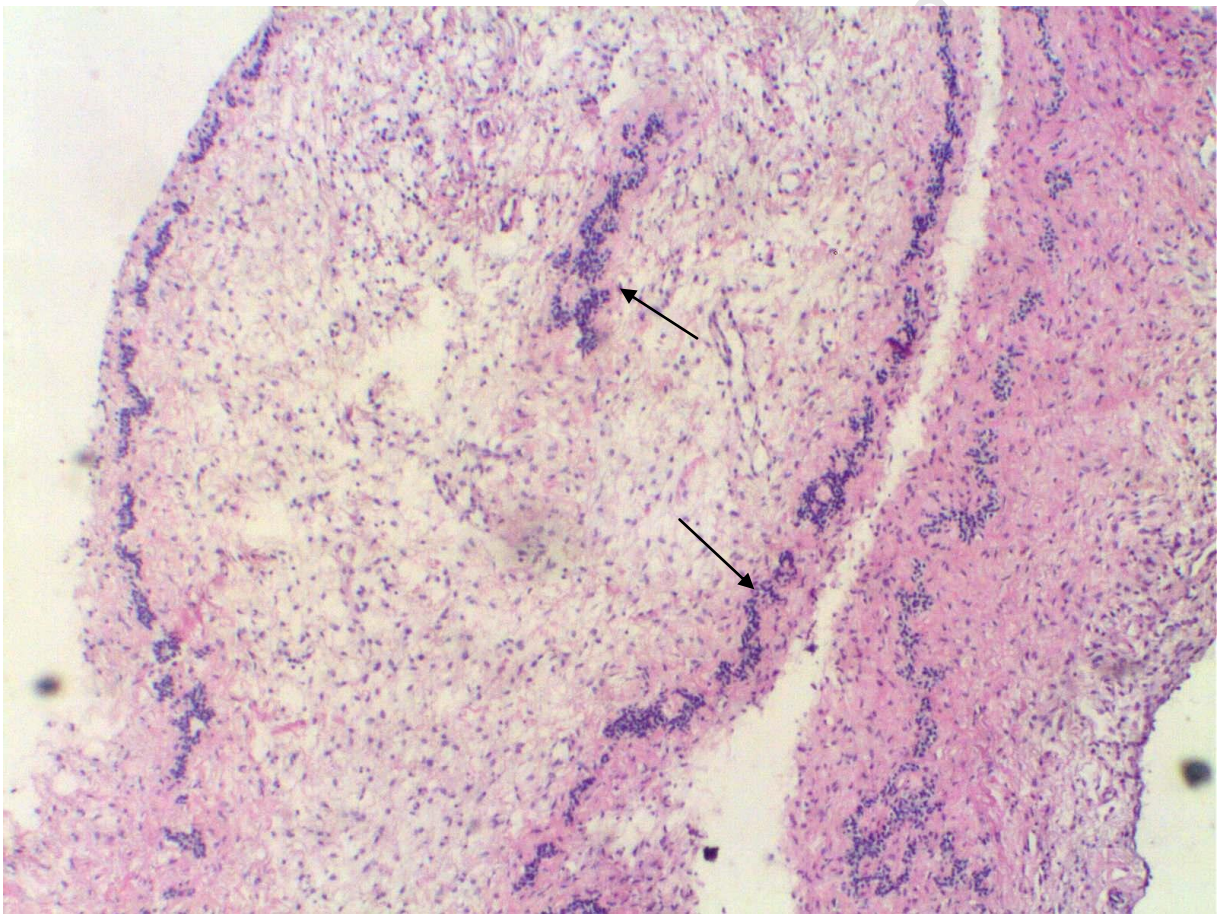


Figure (1). Strings and islands of odontogenic epithelium in the loose fibro-vascular connective tissue associated with the dental follicle of an unerupted 3rd molar. Haemotoxylin & Eosin (H&E) x40



Figure (2). Dental follicular tissue, normal orthopantomograph of a set of impacted 3rd molars.

(ii) Hyperplastic dental follicular tissue.

The hyperplastic dental follicle is seen histologically to have areas of fibrous connective tissue with areas of ground substance containing multiple odontogenic epithelial rests with some surfaces lined by reduced enamel epithelium as described by Sun et al ^[70]. The dental follicular tissue enlarges as a result of stimulation and results in a thicker than normal layer of fibrous tissue around the crown of the tooth and is lined with reduced enamel epithelium. The fibrous tissue contains numerous islands of odontogenic epithelium and shows a mild chronic inflammatory cell infiltrate.

The hyperplastic dental follicle and odontogenic fibroma are often misinterpreted in histological examination. Distinction between the lesions is based on clinical and radiological features as described by Hirschberg et al ^[71]. Picrosirius red stain and examination under polarising microscopy can be used to differentiate the two lesions. The thin fibres (<0.8mm) of both lesions stained the same, but the thicker fibres (1.62 – 2mm) stained more green or green-yellow in the case of odontogenic fibromas. In the past solid fibrous masses associated with the crown of an unerupted tooth, especially 3rd molars were considered to be odontogenic fibromas, but today these lesions are regarded as hyperplastic dental follicles.

A study of eleven specimens of hyperplastic follicle was undertaken by Fakuta et al ^[72]. The average age of the patients was 15.7 years, with a male to female ratio of 1:1. Radiographically most of the cases were diagnosed as dentigerous cysts but histological examination of the impacted teeth and follicles showed hyperplastic follicular tissue. The definitive difference between hyperplastic follicular tissue and early dentigerous cysts could only be made histologically and not only radiographically according to Shear et al ^[44].

Walker et al ^[73] reported an unusual case of an impacted second primary molar. It was treated by removal of the lesion, the second primary molar and second premolar and sent for histology.

This revealed hyperplastic dental follicle with areas probably representing the start of an adenomatoid odontogenic tumour because of duct like structures observed.

Hyperplastic dental follicle was considered an extremely rare lesion and the practitioner should be able to differentiate it from a dentigerous cyst according to Sun et al ^[70]. In their case report two brothers in their 2nd decade undergoing orthodontic treatment had all 8 canines exposed and the tissue removed sent for histology. All 8 were diagnosed as hyperplastic dental follicles.

However they stressed the difficulty in differentiating between hyperplastic dental follicle and odontogenic fibromas.

Meric et al ^[74] published a case in which there were supernumerary teeth in the maxilla on both sides, associated with impacted third molars in the maxilla and mandible. On radiograph it appeared as if a dentigerous cyst was associated with the supernumerary teeth of the right maxilla. However after removal of these lesions and submission for histology a diagnosis was made of hyperplastic dental follicular tissue. This occurred in a non-syndromic patient.

(iii) Early dentigerous cysts.

An early dentigerous cyst was defined as a developmental odontogenic cyst that has similar soft tissues to the hyperplastic dental follicle. The reduced enamel epithelium undergoes squamous metaplasia and a cystic cavity develops between the enamel of the tooth and the epithelial lining that increases in size due to fluid accumulation within the cyst.

(iv) Dentigerous cysts.

A dentigerous cyst is one which encloses the crown of an unerupted tooth by expansion of its follicle, and is attached to the neck according to Shear et al ^[44]. They stated that the radiograph should show a periodontal width of at least 3mm-4mm for the presence of a possible cyst. Histologic examination shows a thin fibrous cyst wall which consists of young fibroblasts widely

separated by stroma and ground substance rich in acid mucopolysaccharide. The epithelial lining, which is reduced enamel epithelium, consists of 2-4 cell layers of flat or cuboidal cells and is seldom keratinized as described by Shear et al ^[44]. Both non inflamed and inflamed examples of dentigerous cysts have been described by Neville et al ^[75].

The early dentigerous cyst is a developmental odontogenic cyst that has soft tissues similar to the hyperplastic dental follicle. The reduced enamel epithelium undergoes squamous metaplasia and a cystic cavity develops between the enamel of the tooth and the epithelial lining that increases in size due to fluid accumulation within the cyst.

The dentigerous cyst can be mistaken for a unicystic ameloblastoma since they have identical clinical and radiographic appearances. Dunsche et al ^[76] in their study of 101 specimens with clinical and radiographic features of dentigerous cysts did not detect any ameloblastomatous epithelium. They concluded that unicystic ameloblastomas can be differentiated from dentigerous cysts if two slides were prepared for routine diagnosis.

The extent of epithelium lining the dentigerous cyst wall was investigated by Villa ^[77]. He found that the epithelium was not only attached at the neck of the tooth but extended over the entire enamel of the unerupted tooth. He concluded that the classical theories of dentigerous cyst formation were inadequate and they have been further investigated since that time. Theories include osmotic relationships and inflammation of the of adjacent teeth as well as chronic inflammation in the cyst itself but the matter has not been resolved according to Shear et al ^[44].

Srinivasa et al ^[78] reported a case of an ectopic maxillary third molar in the maxillary sinus. They said that this was rare. It was diagnosed with plain radiographs and CT scans. They stressed that all soft tissue should be removed with the ectopic teeth and that histology on these should be done. They also stated that malignancy or ameloblastic transformation was rare but follow

up observation with radiographs was mandatory. In this case a histological diagnosis of dentigerous cyst was made.

A dentigerous cyst rarely causes paraesthesia of the inferior alveolar nerve according to Sumner et al ^[79]. They found 3 cases of this phenomenon in the literature. In their case a large dentigerous cyst with three impacted and displaced teeth was described. They hypothesised that the associated paraesthesia could be due to either simple compression of the inferior alveolar nerve by the expanded cyst or secondary infections of the cyst wall. In their case treatment was by enucleation of the cyst rather than by marsupialisation and sensation gradually returned.

Saravana et al ^[80] studied 100 patients with radiographically normal, asymptomatic lower third molars. They found cystic change in 46% of the follicles examined with a high proportion of dentigerous cysts. They recommended that histopathological evaluation of all specimens should be done. Sales et al ^[81] found odontomes to be the most common odontogenic tumour of the jaws. However dentigerous cysts arising from odontomes were very rare. They reported a complex odontome associated with a dentigerous cyst in the maxillary sinus and focused on differential diagnosis by means of radiographic imaging.

The otolaryngology literature also has reports of impacted teeth in the maxillary sinus. Amin et al ^[82] removed a very large dentigerous cyst associated with an ectopic unerupted right maxillary canine from the maxillary sinus. He performed this by way of a classical Caldwell- Luc approach.

According to Ben et al ^[83] three possible mechanisms exist for the development of the dentigerous cyst. The first was the classical theory of development from the dental follicle, which became secondary infected. Secondly it was postulated that a permanent tooth erupted into a radicular cyst of a non-vital primary tooth and hence the dentigerous cyst was extra-follicular.

Thirdly a non-vital primary tooth spread inflammation to a developing dentigerous cyst below it, associated with a permanent successive tooth. Shear et al ^[44] also considered the PTCH gene as well as an inflammatory aetiology in the development of dentigerous cysts.

The inflammatory origin of the dentigerous cyst was described by Bhayya et al ^[84] based on a case report of a dentigerous cyst of the second impacted pre-molar associated with non-vital deciduous molar. They also suggested an inflammatory origin of the dentigerous cyst because of the histology which showed a typical dentigerous cyst with non-keratinised squamous epithelium and the presence of an inflammatory cell infiltrate.

According to Pechalova et al ^[85] odontogenic cysts were the commonest type of cysts and accounted for 97.1% of all jaw cysts. Dentigerous cysts occurred more frequently in the lower jaw with 72.6%, in the body of the mandible. Cysts of the maxilla were more likely to become infected. The dentigerous cyst was the most common odontogenic cyst in the first decade and increased in the second and third decades, reaching a maximum at that time.

Furthermore the dentigerous cyst was associated with impacted teeth, especially the third molars. The standard recommended treatment of a dentigerous cyst consists of enucleation. However the conservative management of dentigerous cysts associated with deciduous teeth has been described in a case report by Shivaprakash et al ^[86]. In their first case of a 10 year old girl, the primary tooth was removed as well as the second premolar and dentigerous cyst in the third quadrant. Another cyst around a premolar tooth was marsupialised in the fourth quadrant two weeks later and the tooth subsequently erupted. They also described a case of a 10 year old boy who had a deciduous molar removed and the impacted second premolar exposed. The roof of the cyst was removed and marsupialisation performed. This healed successfully and uneventfully. Hence they recommended these techniques for elimination of pathology and maintenance of the dentition.

A rare case of an adenomatoid odontogenic tumour (AOT) associated with the crown of an unerupted canine in the maxilla was reported by Sandhu et al ^[87]. They reported the case of a 25 year old female who presented with a large lesion of the maxillary sinus. Initially a biopsy showed a dentigerous cyst only. After a definitive operation, the specimen of the soft tissue mass and the unerupted canine was sent for histological examination. This showed a dentigerous cyst with areas of adenomatoid odontogenic tumour in its walls. They reported that very few cases of adenomaotoid odontogenic tumour occurring in a dentigerous cyst wall had been reported in the maxillary antrum. They strongly recommended histological evaluation of all enucleated cysts.

(v) The Paradental cyst.

The paradental cyst is an inflammatory odontogenic cyst, arising in conjunction with partially erupted vital teeth associated with pericoronitis in the paper by Fowler et al ^[88]. These occur in conjunction with mandibular third molars primarily and present radiologically as well defined radiolucencies associated with the affected teeth.

Paradental cysts contain hyperplastic non-keratinizing stratified squamous epithelium with an intense inflammatory response. Paradental cysts have also been called collateral inflammatory cysts, inflammatory lateral periodontal cysts, and mandibular infected buccal cysts according to Vedtofte et al ^[89]. They found 27 cysts occurred in the mandible and only 2 in the maxilla in their study.

The term mandibular infected buccal cyst was also used by Wolf et al ^[90] because of the presence of a mixed inflammatory cell infiltrate seen histologically. It was thought that it had an important role in the pathogenesis of these cysts. It was postulated that the inflammation might

lead to pocketing, hyperplasia and cyst formation arising from the remnants of the reduced enamel epithelium or cell rests of Malassez.

The occurrence of paradental cysts in the first molars in children was reported by Packota et al^[91]. Only 5 cases were reported but as the histological features were non specific and stressed the importance of clinical and radiographic features. Treatment was by enucleation without disturbing the associated teeth.

The classification published by the World Health Organization on the Histological typing of odontogenic tumours which included cystic lesions was published in 1992. This has since been changed and occurs in the classification of cysts of the maxillofacial regions by Shear et al^[44].

Magnussen et al^[92] described only 26 of 2700 jaw cysts (0.9%) as paradental cysts. They commented that the true incidence was probably greater due to misdiagnosis. Furthermore they described an equal sex distribution and swelling associated with the first and second molars especially and histologically a non-keratinized squamous epithelium which was hyperplastic and infiltrated by chronic inflammatory cells.

The differentiation of the small dentigerous and paradental cyst was attempted by Damante et al^[93]. They measured the periodontal space of 130 unerupted and 35 partially erupted teeth. The width of the pericoronal space varied from 0.1 – 5.6mm. They confirmed a lining of reduced enamel epithelium in unerupted teeth and hyperplastic stratified squamous epithelium in partially erupted teeth with inflammatory cells in 82% of this group. They concluded that the primary diagnosis of the enlarged periodontal space was “inflammation of the follicle”, but that the final diagnosis between a small dentigerous cyst and paradental cyst depended on the clinical behaviour, cystic content and surgical findings.

Colgan et al ^[94] reviewed 15 paradental cysts, which comprised 25% of all cysts associated with mandibular third molars. According to them there was a close association between the angle of the impaction of the third molar and the development of a cyst. Most of their cases had linings resembling radicular cysts. They proposed that food impaction played a part in development of paradental cysts.

A paradental cyst of the second molar on its buccal and mesial aspects affected the apical area of the first molar according to Silva et al ^[95]. Their cyst had typical clinical and radiographic features but the microscopic features were similar to those found in other odontogenic inflammatory cysts. They found difficulties in diagnosis, treatment and terminology.

The diagnosis of paradental cyst was confirmed by Philipson et al ^[96]. They confirmed a frequency of 0.19 – 4.7%. These occurred mainly in mandibular permanent molars with a history of pericoronitis, with the third molar contributing 64.9% of the cases. They concluded that inflammation, reduced enamel epithelium, cell rest of Malassez and remnants the dental lamina all contributed to the established diagnosis of inflammatory periodontal cysts. They also stated that the histological features were indistinguishable from those of radicular cysts.

Vedtofte et al ^[97] investigated 8 cysts between the lateral incisors and canines in the maxilla. Radicular cysts were excluded by virtue of positive vitality of the teeth concerned and odontogenic keratocysts excluded by histological investigation. Histology revealed features seen in inflammatory paradental cysts and they suggested that the lesions previously described might be paradental cysts.

A case report involving the second molar but not showing an inflammatory reaction diagnosed as a paradental cyst was published by Naclerio-Homen et al ^[98]. They confirmed that this was

unusual as paradental cysts are related to an inflammatory process often associated with pericoronitis involving impacted or semi-erupted teeth.

Thikkurissy et al ^[99] reported a buccal bifurcation cyst (paradental cyst) in a 7 year old male patient. There was no caries involved but a swelling in the area and probing depth was 15mm. After simple surgical enucleation of the cyst and a 14 month follow up probing was only 4mm and the tooth no longer was displaced. They concluded that simple enucleation of the cyst provided good short and long term results without disturbing molar development. Further paediatric occurrence of 2 cases was reported by Borgonovo et al ^[100]. These cases occurred in a 7 year and 8 year old male patients respectively in the first mandibular area. Both had histology indicative of paradental cysts and were treated by enucleation and thorough curettage of the cysts without removal of the teeth.

(vi) The Primordial cyst, odontogenic keratocyst and keratocystic odontogenic tumour.

These three terms all refer to a previously classified cystic lesion by Shear et al ^[44]. The term primordial cyst was initially used. It was one of the three kinds of odontogenic cyst which contained an epithelium lined sac filled with fluid. It appeared radiographically as a radiolucent area in the affected jaw. It developed from the dental enamel organ before the formation of dental hard tissues as found in the Mosby Medical Dictionary ^[101]. It developed through cystic degeneration of the stellate reticulum in the enamel organ before dental hard tissues were formed and hence was found in place of a tooth according to Shear et al ^[44].

The Odontogenic Keratocyst (OKC) developed from cell rests in the dental lamina as found in Neville et al ^[75]. In 1972 the World Health Organisation originally used the term primordial cyst but in 1992 changed the term to odontogenic keratocyst and subsequently to keraocystic

odontogenic tumour in the latest classification by the WHO of 2005^[45] as it had a distinct clinicopathological character and a higher tendency for recurrence. The odontogenic keratocyst often had a more aggressive course than other cystic lesions of the jaw and for this reasons they were sometimes known as benign cystic neoplasms according to the article by Purkait^[102].

The Keratocystic Odontogenic Tumour is a benign uni- or multicystic intraosseous tumour of odontogenic origin with a characteristic lining of parakeratinized stratified squamous epithelium and a potentially aggressive infiltrative behaviour. It may be solitary or multiple with the latter usually one of the stigmata of the inherited Naevoid Basal Cell Carcinoma Syndrome as described by Philipson^[103]. It was also often associated with sporadic keratocystic odontogenic tumour development as found in the article by Madras et al^[104]. Terminology has changed over the years. Today in journals of Head and Neck Surgery and Otolaryngology, the term odontogenic keratocyst (OKC) has been replaced by keratocystic odontogenic tumour and calcifying odontogenic cyst replaced with calcifying odontogenic tumour owing to the recurrence of the lesions as seen in the paper by Press et al^[105].

Shear et al^[44] reported an incidence of odontogenic keratocysts to be 11.2 % of all jaw cysts. Various series have reported 3% to 11% of all odontogenic cysts as in the publication by Neville et al^[75]. There is general agreement that nearly twice as many males as females were affected. The lesion occurs more often in the mandible especially at the angle area and ascending ramus (50%). Those found in the maxilla have a greater propensity for recurrence as found in the publication by Shear et al^[44] and Neville et al^[75].

Odontogenic keratocysts occurred at all ages but particularly in the fourth and the fifth decades of life. They varied from small to very large in size spreading in the medullary spaces. Radiographic images of large lesions may have a scalloped margin. There could be

multilocularity and occasionally resorbed adjacent tooth roots. Borders could be sclerotic. They seldom caused symptoms except if infected and could grow to a large size causing bone expansion and tooth migration according to Neville et al ^[75]. Multilocularity is usually due to multiple cysts (daughter cysts).

The cyst lining is reported to be thin, and the lumen is lined by stratified squamous epithelium. This is typically 6 to 8 cells thick with a palisaded basal layer. The surface is often parakeratotic and there is a lack of rete peg formation. The lumen of the cyst could contain a white cheesy keratin substance or serous like straw coloured fluid with a low protein count according to Neville et al ^[75].

Recurrences and growth is thought to be due to the following factors and described by Soames et al ^[106]. These are hydrostatic forces, active epithelial growth, production of bone resorbing factors by the capsule, accumulation of mural squames and incomplete removal owing to the thin fibrous wall. With the advent of genetic investigation and the changes of the name to keratocystic odontogenic tumour genetic factors have been identified. This is specifically in relation to the PTCH Supressor Gene as found in the paper of Madras et al ^[104]. Over-expressed and amplified genes in 12q13 may be a contributing factor to the persistent growth characteristics seen in the keratocystic odontogenic tumour as described in the paper by Helkinheimo et al ^[107].

(vii) Odontogenic fibroma.

The central odontogenic fibroma is a rare benign odontogenic tumour described in the paper by Hwang et al ^[108]. It is more common in adults, with the average age being 40 years. It is likely to

affect twice as many women than men. It can occur either in the anterior maxilla or posterior mandible according to Khan ^[109].

An attempt at classification of the central odontogenic fibroma was made by Gardner ^[110]. He identified three entities previously seen. These were associated with (a) the hyperplastic dental follicle; (b) fibrous neoplasm with similar histological appearance of a dental follicle and (c) a more complicated lesion with fibrous tissue, odontogenic epithelium, and possible cementum. The third lesion could be confused with the calcifying epithelial odontogenic tumour. Furthermore he stated that the central fibroma of the jaws should be considered a desmoplastic fibroma, as it does not appear to have arisen from odontogenic origin.

Hwang et al ^[108] reported a case of central odontogenic fibroma in the left canine/premolar area in a 52 year old female patient. They considered the tumour rare but benign and derived from mesenchymal tissue of dental origin. It has been infrequently reported in the literature.

A report by Daniels ^[111] described the first reported case of a central odontogenic fibroma associated with an impacted lower first molar. The radiological appearance was that of a dentigerous cyst. He also considered the lesion rare, accounting for less than 0.1% of all odontogenic tumours.

Covani et al ^[112] had a six year follow up following the removal of a central odontogenic fibroma. In his discussion he stated that the incidence was higher in women and occurred predominantly in the anterior maxilla. Most lesions were unilocular and easily removed by enucleation and curettage. Furthermore he described the typical histology of his case being of the simple variety containing various amounts of fibrous tissue and collagen with the absence of odontogenic epithelium. This might have been misdiagnosed.

Khandekar et al ^[113] found that these lesions had only been rarely reported. Their case was of a 12 year old female patient with a swelling in the posterior mandible near the first molar area.

The lesion was not encapsulated, 1cm in diameter, unilocular and associated with an impacted second premolar tooth. The lesion was treated by enucleation. The patient was followed for 18 months with no radiological or clinical recurrence. They emphasised long term follow up, as recurrences of up to 13% could occur up to nine years after initial treatment.

Daskala et al ^[114] stated that the central odontogenic fibroma was rare, accounting for 1% of all odontogenic tumours. Their case was in a 71 year old male patient and that the lesion was related to the root of an erupted mandibular canine tooth. Furthermore it was described radiologically as multilocular. The lesion was enucleated under local anaesthetic. They recommended that these lesions should be considered in the differential diagnosis of jaw neoplasms, even though they were rare.

Radiological diagnosis was considered extremely difficult. In a paper published by Araki et al ^[115] they investigated by radiological methods a 40 year old man who had an unerupted lower left third molar with a mixed radio-opaque radiolucent lesion. This showed what looked like a calcifying odontogenic tumour. Their differential diagnosis contained calcifying cystic odontogenic tumour; calcifying epithelial odontogenic tumour or ossifying fibroma. After operation, histology reported a central odontogenic fibroma. They stated that diagnosis by radiographic investigation alone was extremely difficult.

(viii) Odontoma.

Odontomata are considered to be hamartomas because once the hard tissues are formed they do not grow any further. If the lesion grows then it is due to odontogenic epithelial proliferation. There are three distinct varieties described: complex odontoma, compound odontoma and

ameloblastic fibro-odontoma. Most are diagnosed in the first 2 decades of life. They can occur at any site in the maxilla or mandible but compound odontomata form in the anterior areas and the complex odontomata in the posterior areas predominantly ^[75]. Referral for histological examination is recommended in order to exclude the ameloblastic odontoma and the ameloblastic fibro odontoma from the common odontoma.

Douglas et al ^[116] described a case of a 16 year old male patient with removal of a developing odontoma in the right premolar area of the mandible. There was associated failure of eruption of permanent teeth in that area. He postulated that the odontoma removed was connected to a regional disturbance in that area.

Owens et al ^[117] confirmed that there were three types of odontomata. They reviewed 104 cases retrospectively and found that 85% had been radiographically diagnosed correctly by Dentists prior to histological examination. The majority occurred in the second decade of life in caucasians and occurred more in the maxilla. Most (64.4%) were compound odontomata consisting of denticles, whilst the rest were complex odontomata, consisting of a mass of calcified tooth material. No ameloblastic fibro-odontoma was found in their study.

The rare ameloblastic fibro-odontoma was reported in two cases by Favia et al ^[118]. Both cases occurred in young people in the posterior mandible as asymptomatic swellings. They were enucleated and histology revealed dental hard tissues, as well as odontogenic epithelium and mesenchymal tissue. No recurrence of the tumour was noted after follow up for some years.

Zoremchhing et al ^[119] reported failure of an upper right central incisor to erupt. The patient was a nine year old female who had a radio-opaque mass over the 11, diagnosed as an odontoma on radiograph. The lesion was removed under local anaesthetic. Subsequent examination on radiograph showed that the 11 had only half of its root formed but there was a substantial

change in its position, although it had not fully erupted after twelve months. It was suggested that all specimens should be submitted for histological examination by Oral Pathologists.

Singh et al ^[120] reviewed the classification and features of odontomata. All odontomata had varying degrees of tooth material, including pulp and cementum, and most were associated with impacted or unerupted teeth. They reported an eleven year old girl with unerupted 21 and 22 and a lump in the area on the buccal aspect of the maxilla. A provisional diagnosis of compound odontoma was made with subsequent enucleation of the lesion. The tissue was submitted for histological examination and the clinical diagnosis confirmed. They stated that after conservative enucleation there was little chance of recurrence.

Jeryaraj et al ^[121] said that odontomata were hamartomas which contained all the materials present in tooth development. Furthermore they found the majority in the first and second decades of life and they postulated that there might be genetic or environmental factors associated with their etiology. Their case report was of a 58 year old male patient who presented with paraesthesia of the right mental nerve area. Intra-oral palpation revealed a 2cm x 1cm bony hard swelling in the area. Radiographically two complex odontomata were diagnosed with the one periapical to the central incisor. Aspiration as well as incision biopsy revealed the presence of a dentigerous cyst combined with complex odontomas. The lesion was treated by enucleation of the cyst and odontomas under local anaesthetic. They stressed the need for histological examination to exclude other entities.

Shekar et al ^[122] described the presence of intra and extraosseous odontomas. They considered the extraosseous odontoma rare. They presented a case of a 15 year old female who presented with a missing 47. In its place was a single rooted radio-opaque structure above the level of the alveolar bone. They extracted the lesion and on subsequent histology found it to be a

compound odontoma. They found that enucleation was curative and chances of recurrence minimal.

Further confirmation of the nature of odontomas was made by Barros et al ^[123]. They said that it was a benign lesion and occurred mainly in patients in the first and second decades. They reported a case of a complex odontoma preventing the eruption of a permanent successive second molar tooth. After enucleation of the odontoma the second molar erupted normally after a period of five months. They followed up the case for five years. They stressed the need for histological examination post-operatively.

(ix) Ameloblastoma.

Ameloblastoma is defined as “a usually benign but locally invasive neoplasm of tissues of a type characteristic of the enamel organ but which does not differentiate to the point of enamel formation” as found in the Dorland Medical Dictionary ^[124]. It was further described as “a rare, highly destructive, benign, rapidly growing tumour of the jaws”. It was also called an adamantinoma, adamantoblastoma and epithelioma adamantinum as found in the Mosby Medical Dictionary ^[101].

According to Neville et al ^[75] the lesion is rarely found in the 1st and 2nd decades with a fairly equal distribution in numbers from the 3rd to the 7th decades. Only 15-20% lesions occur in the maxilla with the vast majority occurring in the molar-ascending ramus area of the mandible. Some studies shows a greater incidence in black patients but others show no racial predilection. Radiographically the lesions show a multilocular “soap bubble” appearance except for the rarer unicystic ameloblastma. They are non painful and can grow to a large size clinically. The histologic variant has little influence on the clinical behavior but the unicystic ameloblastoma has a more favourable prognosis.

Maia Campos ^[125] gave a philosophical approach to ameloblastomas. He stated it was a lesion with aggressive clinical behaviour with apparent benign histological features. He further stated the paradox of a neoplastic parenchyma with cells normally able to form enamel but that did not form dental hard tissues. He stated that the cell rests of Malassez usually led to periodontal cysts, which lack tumour characteristics whilst epithelial rests of Serres might lead to the formation of ameloblastomas which were extremely aggressive neoplasms. He suggested that the different tissues found in ameloblastomas, as well as autocrine and paracrine factors influenced individual cells and the parenchyma respectively. He concluded that ameloblastoma was probably no more than epithelial rests which remained in an embryonic state and were re-activated at a later stage but were unable to resume their intended original function.

The causation of ameloblastomas included neoplastic factors, irritation sources such as trauma and infection, nutritional deficit disorders, and a viral pathogenesis as found in the article by Kim et al ^[126]. Ameloblastomas might develop in the walls of dentigerous cysts. They reviewed 71 patients and found the mean age of the patients to be 30.4 years and that 55% of the patients were male. Eighty three percent of the ameloblastomas were located in the mandible. Swelling was found in 38%, whilst nearly 60% were found to be unilocular radiographically. Unilocular ameloblastomas tended to occur in the younger age groups and occurred in the mandible. Confirmation of the presence of ameloblastoma required a biopsy to be performed prior to definitive operation. Long term follow up following the definitive surgery was recommended.

Motamedi ^[127] reported an unusual case of a peri-apical ameloblastoma. Ameloblastomas were often benign but locally aggressive odontogenic tumours and small lesions might be mistaken for peri-apical granulomas or cysts. The tooth might be root treated or extracted without

treatment of the ameloblastoma. He recommended that a full differential diagnosis and biopsy of the lesion be obtained prior to treatment. He emphasized the high recurrence rate of the lesion and stressed the need to submit specimens for histological examination after operation. He recommended a wide resection margin and if appropriate removal of the inferior alveolar nerve en block with the tumour to avoid recurrences.

Ord et al ^[128] reported 38 cases of ameloblastoma seen in children, between 1991 and 1999. Almost 30% were younger than 20 years. The mean age of the children was 15.5 years with almost 50% being black. There were four boys and seven girls in this group and occurrence was almost always in the mandible, with 45% at the angle and the rest at the symphysis. Eight cases were unicystic and three recurrences occurred. They stated in their literature review from 1970 to 2002 that in Western reports 26 cases were reported in blacks and 37 in whites. All were treated with resection. They stated that the treatment of unicystic ameloblastomas remained controversial but multi-cystic ameloblastomas were treated by resection as they were in adults. They enucleated only those cases of unicystic ameloblastoma with intra-mural change, or ameloblastic change in the epithelium. In these cases they tried to keep a strut of bone of the lower border of the mandible to maintain continuity. In the textbook of Neville et al ^[75] it stated that "some studies indicate a greater frequency in blacks others showed no racial predilection".

Fine needle aspiration cytology has been used initially to obtain a diagnosis of ameloblastoma as described by Mukopadhyay et al ^[129]. Fine needle aspiration cytology showed a dark brown substance with smears showing low cellularity. The epithelial cells however appeared benign, elongated with abundant cytoplasm. There appeared to be some osteoblasts in the smear. No giant cells were seen and on this evidence a diagnosis of ameloblastoma was made. Subsequent to operation by resection histology confirmed the provisional diagnosis of ameloblastoma.

Bueno et al ^[130] reported the removal of a unicystic ameloblastoma in a 19 year old patient. It extended from the left angle of the mandible to the centreline. The inferior alveolar nerve was displaced but kept at operation. A reconstruction plate was applied to reinforce a free iliac crest bone graft, with platelet rich plasma and a fibrin membrane. Histology was of a unicystic follicular ameloblastoma with partial cystic transformation. Computrised Tomography was performed eight months after operation and re-operation approximately one year after the original surgery. The reconstruction plate was removed and four implants (Branemark) placed and prosthesis fabricated.

Stolf et al ^[131] investigated the changes in the expression of the genes associated with normal tooth development and ameloblastoma development. Normal tooth development involved four major families of genes and included transforming growth factors (TGF β), which included bone morphogenic protein (BMP), fibroblast growth factors (FGF), Hedgehog (Hh) and Wnt. Normal tooth development involved a series of events between active dermal and mesodermal components regulated by these molecules. It was suggested that ameloblastoma formation was related to aberrant activities of these genes.

(x) Lymphomas.

Lymphomas of the jaws are uncommon and only 2% of extra nodal lymphomas arise in the oral region according to Berezowski et al ^[132]. Lymphomas are malignant lesions of cells derived from lymphoid tissue. Lymphoid proliferations are divided into Hodgkin's disease in which Reed Sternberg giant cells are present and Non-Hodgkin's lymphoma that account for all other neoplastic lymphoid proliferations. Commonly histology shows a diffuse, often mixed inflammatory cell infiltrate, interspersed with large, atypical neoplastic lymphoid cells as described by Neville et al ^[75]. Classification systems have been changed and modified over the years. These have included the Working Formulation, Kiel classification and the Anne-Arbor staging system. The WHO Real Classification of Non Hodgkin's lymphoma according to clinical

aggressiveness is now used according to Berezowski et al ^[132]. Treatments include surgery, radiotherapy or chemotherapy or a combination of these. The prognosis was generally poor before modern cancer therapy and the survival rate being only 5%, but this has improved significantly recently according to Neville et al ^[75].

Azua-Romeo et al ^[133] said that extra-nodal lymphomata of the maxillofacial areas are rare but their accurate and prompt diagnosis and treatment is paramount to the welfare of the patient. They reported a 64 year old female who underwent treatment for a lesion of the mandible. They said that this was rare and mandibular lymphoma accounted for 0.6% of all lymphomas. Immunohistochemical analysis showed CD20, CD23 and BCL-2 were positive, but negative for CD10, CD5 and cyclin D1. They stressed the diagnosis was always histological with immunohistochemical support. They used the Anne-Arbor staging method.

Primary lymphoma of the mandible was investigated by Robbins et al ^[134]. They examined eleven patients in their department from 1947 to 1983. They said that the mandible was an uncommon site for lymphomas and misdiagnosis was common. Only one patient had surgery, with the others having radiotherapy, chemotherapy or a combination of both. They did not differentiate between Hodgkin's and Non-Hodgkin's lymphomas.

Bertolotto et al ^[135] reported a lymphoma presenting radiographically as widening of the right mandibular canal with ill-defined edges and absence of sclerosis. CT scan confirmed infiltration of the inferior alveolar canal. Extra nodal malignant lymphoma was considered relatively rare especially in the oral areas. A case report occurring in the right mandibular area was reported by Kawasaki et al ^[136]. They said that lymphoma was often misdiagnosed as inflammatory disease.

A case of non-Hodgkin's lymphoma following tooth extraction was reported by Sarda et al ^[137]. Biopsy of a non healing ulcer following the extractions revealed an undifferentiated non-Hodgkins lymphoma. This was treated with hemi-mandibulectomy and radiation. The patient was reported asymptomatic two and a half years after treatment.

Gusenbauer et al ^[138] published a case report of primary lymphoma of the mandible and emphasized difficulties of that pathology in particular. They stated that the condition should be considered in the differential diagnosis when considering swelling, ulceration and unexplained dental pain and radiological evidence of rarefaction.

Three patients with T-Cell lymphoma were described by Blayney et al ^[139]. There were multiple lytic bone lesions, natural serum antibodies to disrupted HTL human cell lymphoma virus and to one or both structural proteins p19 and p24. Transformation from a low to a medium or high grade lymphoma was investigated by Yuen et al ^[140]. They did not restrict themselves to lymphomas of the mandible but lymphomas in general. They concluded that change from low grade to a medium or high grade lymphoma was related to a relatively long survival time and the patient who had not undergone chemotherapy or had limited disease had the best prognosis.

Four cases in a five year period of extra nodal non-Hodgkin's lymphoma of the mandible were reported by Rosodo et al ^[141]. The median age of their patients was 51 years and there was an equal distribution between males and females. Common presenting features were swelling in 58%, pain in 53% and dyasthesia in 20%. Most patients were treated with a combination of radio and chemotherapy with an estimated five years survival rate of 60%. A case report and discussion of treatment modalities was published by Steinbacher et al ^[142]. They said that lymphoma was rare in the mandible often leading to a delay in diagnosis and treatment. Their

two cases were treated by radio and chemotherapy and the disease totally eradicated. They stated that the role of surgery was for biopsy initially and control of persistent or recurrent disease. Radiotherapy may be curative in early disease. Stage 1E had a median survival time of ten years for all cases but in the maxillo facial areas this was only five years.

Wen et al ^[143] reported 32 cases of lymphoma of bone from 1945 to 1985. There were only three cases in the mandible and hence the condition was considered very rare.

Kini et al ^[144] reported a case of a 55year old male with a large painless swelling of the mandible for four months increasing in size. A differential diagnosis of residual cyst was made and a biopsy performed. The histology suggested a large cell lymphoma with immunohistochemical chemistry positive for CD 45 and CD 20 but negative for CD 3. This was diagnostic for B-Cell lymphoma. The patient was treated successively with chemotherapy and followed up for one and a half years. They said that although rare, lymphomas should be considered in the differential diagnosis of swellings of the mandible.

Primary lymphoma of the mandible was also described by Berezowski et al ^[132] who agreed that primary lymphomas of the jaw were uncommon. They reported an extremely rare B-Cell lymphoma associated with a dentigerous cyst of an impacted mandibular third molar. This was treated with surgery and radiotherapy and followed up for 18 years with no recurrence.

CHAPTER 3

Patients, Methods and Materials

This retrospective study was reviewed and approved by the University of Cape Town Department of Surgery Research Committee. This was PROJECT 2006/20 and approved on 13 April 2006.

All reports of the histological findings as well as the original patient records from the practice were available for analysis. The patients were not identified by means of theatre records etc and contemporaneous data of the patients was obtained from their actual files and subsequent histological diagnoses made.

(1) Patients.

All patients referred to the author's private practise between 1987 and 2007 were included in the study.

The practice is a referral practice for maxillofacial and oral surgery. Patients were referred from Cape Town and the surrounding area, from Namibia (South West Africa) and members of the South African National Defence Force, their dependants and retired members.

Only patients with symptoms attributed to third molar pathologies were included in the study and only symptomatic teeth were removed. All the patients had been seen by a dental surgeon prior to referral. All the patients presented with symptoms thought to be related to third molar teeth or some other pathology in the oral cavity. The symptoms were general or localised. General

symptoms included malaise, pain, lymphadenopathy in the head and neck areas, involvement of cranial nerves examined as well as temporomandibular joint clicking, crepitus or changes in mouth opening. One accepts that that these symptoms can be related to other pathologies or causes. Assymetry of the head and neck could also occur. Local symptoms included pericoronitis especially related to lower third molar teeth, pain and swelling, movement of the anterior teeth but sometimes involving other teeth, bleeding in relation to areas of pericoronitis often as a result of chemical burns, and rarely alteration in tongue function resulting from central lesions as well as alteration in the oral mucosa.

All patients underwent a thorough clinical examination of the head and neck area as well as the oral cavity and were referred on a selective basis for periapical radiographs, orthopantomograms (OPG), computerised tomography (CT), magnetic resonance image (MRI), and other maxillo-facial radiographs. The radiology was used to assist in the diagnosis, pre-operative planning, and treatment of the patients, as well as the actual operation.

(2) Methods and Surgical Procedures.

(i) Surgical removal of third molar teeth and protocol.

A standard protocol could not be found in the literature.

The protocol used in this practise was as follows:

Third molar teeth erupted and in function were not removed except when oral hygiene was below standard and a risk to the patient i.e. asymptomatic teeth were not removed. The recommendations of the South African Society of Maxillofacial and Oral Surgeons were generally followed. This included the following criteria:

- The root formation was ideally no more than 2/3 complete.
- That a high degree of probability of disease or pathology existed.
- When pericoronitis existed or was more likely.
- When the risk of caries was increased.
- When the procedure was performed under General Anaesthetic it was considered good practice to remove other remaining impacted third molars even if they were “pathology free”.
- The wishes of the patient were respected.
- In older patients the completely embedded third molar could be left in situ and reassessed at regular intervals to make sure no pathological processes were taking place.

A comprehensive pre operative History and Clinical Examination was performed.

A pre-operative radiograph showing vital structures associated with the third molars was taken.

This was often an orthopantomogram and had to be of an acceptable standard.

The surgery was undertaken as described in detail hereunder.

Post operatively the patient was prescribed an antibiotic in order to minimise sepsis, an analgesic and a mouth wash. At any time in the postoperative period if the patient experienced problems of any kind they were instructed to contact the surgeon immediately.

A post operative appointment to assess healing and review of the histological report was scheduled 10 days from the time of operation.

The removal of third molar teeth was performed mainly under general anaesthesia with a few cases under local anaesthesia or sedation. Standard surgical techniques were used. The procedure involved raising a mucoperiosteal flap, bone removal and dividing the tooth as necessary utilising surgical drills and burrs, removal of the tooth as well as the associated soft tissue using mainly elevators, thorough debridement and curettage of the area followed by suturing with resorbable sutures. All soft tissue together with the teeth was submitted for histological examination.

Only teeth which were giving symptoms pre operatively or had significant soft tissues associated at operation were submitted for histology. The histology reported only pertained to these teeth and hence no differences between symptomatic and non-symptomatic could be ascertained.

(ii) Other surgical procedures

Other surgical procedures involved taking biopsies under local anaesthetic intra orally by means of incision or excision biopsy, and open bone biopsy was usually undertaken under general anaesthesia. Fine needle and punch biopsies were seldom undertaken. All operations were performed using standardised techniques, and all tissue was subsequently submitted for histological examination.

(3) Histology.

All third molar teeth that were removed with soft tissues associated were sent for histological examination by Oral Pathologists. All histological specimens were examined by Oral Pathologists. One Oral Pathologist reviewed the majority of the lesions but on rare occasions two other Oral Pathologists were involved. If specimens were examined by General Pathologists these were always reviewed by one of the Oral Pathologists.

All specimens were initially fixed using Formalin (10%). This was followed by processing in buffered alcohol. The specimens were embedded in paraffin wax and cut into thin sections using a microtome. These were mounted onto microscope slides and stained using Haematoxylin and Eosin (H&E) routinely, and using special stains if required. Hard tissues were decalcified prior to processing.

(4) Review of patient records.

The records of all the patients included in the study were retrospectively reviewed and the following information obtained:

- Age
- Position of lesion
- Gender
- Histological diagnosis

(5) Statistical methods

The chi-square test was used in the statistical analysis employed in this study as described by Motulsky ^[145]. It was used to analyse a contingency table. This is appropriate when two groups are compared and the outcome variable is categorical. A statistician was used to compute the results.

The 3427 specimens belonged to 1682 individual patients. Some individuals contributed only one specimen while others had multiple specimens. The majorities of patients had up to four specimens and less than 1 % had more. The frequency distribution was studied in the Table below.

# of Specimens	Frequency Distribution	% Distribution
1	597	35.5%
2	668	39.7%
3	206	12.2%
4	196	11.7%
5	8	0.5%
6	2	0.1%
7	1	0.1%
8	4	0.2%
1682		

The patients who contributed
one to four specimens = 99,1%

Table (4). Frequency distribution of the number of specimens contributed.

The number of patients who contributed two or more specimens was 1085 (64.5% of the total of 1682 individuals in the study). Therefore, more than half of the patients (64.5%) were weighted according to the number of specimens originating from the 1085 patients.

The first method to estimate the prevalence rate of a certain phenomenon is calculated as follows:

- Count of specimens fulfilling the criteria of the diagnosis divided by count of specimens satisfying the definition.

The above formula was used to calculate the prevalence rate of a certain diagnosis.

The second method by which the prevalence rate of a certain phenomenon can be estimated, is calculated as follows:

- Count of individuals of whom any specimen fulfils the criteria of the diagnosis divided by count of individuals satisfying the definition.

The above calculation is preferable.

A third hybrid method to estimate the prevalence rate of a certain phenomenon is calculated as follows:

- Count of specimens fulfilling the criteria of the diagnosis divided by count of individuals satisfying the definition.

(6) Material.

All of the 5659 specimens from the third molar area and rest of the oral cavity were divided into two large groups. These consisted of 3427 specimens from the third molar area and a further 2232 from the rest of the oral cavity.

The 3427 from the third molar area were divided into the most commonly occurring and significant lesions under the guidance of the Oral Pathologist. These included the following:

- Hyperplastic follicular tissue.
- Early dentigerous cyst formation.
- Dentigerous cyst formation.
- Paradental cyst formation.
- Odontogenic keratocyst (Keratocystic Odontogenic Tumour).
- Odontogenic fibroma.
- Odontomata.
- Ameloblastoma.
- Lymphoma.

Each of these entities was analysed as previously described

There were 2232 reports found in the rest of the mouth. These were identified but not included in this study.

CHAPTER 4

Results.

(1) General.

During the 20 year period between 1987 and 2007, 3427 patients were referred for removal of symptomatic third molar teeth. Some of the patients had more than one pathology in the submitted specimens, ie there might have been a hyperplastic follicle in one specimen and a dentigerous cyst in another.

The relationship of various pathologies related to third molar teeth and to the age of the patient is summarized in Table (5). A large majority of the patients were in the second and third decades for all the pathologies.

	AGE	
	RANGE	PEAK
Hyperplastic Follicular Tissue	14 - 26 years	17 years
Early Dentigerous Cyst	14 - 36 years	19 years
Dentigerous Cyst	16 - 35 years	21 years
Paradental Cyst	15 - 38 years	19 years

Table (5). Age distribution and pathological changes in the third molar area.

Of the patients referred for removal of symptomatic third molar teeth (n=1682), 36.8% (n=619) were male and 63.2% (n=1063) were female. The age range was from 12 – 77 years. The majority of the patients were female (p<0.001).

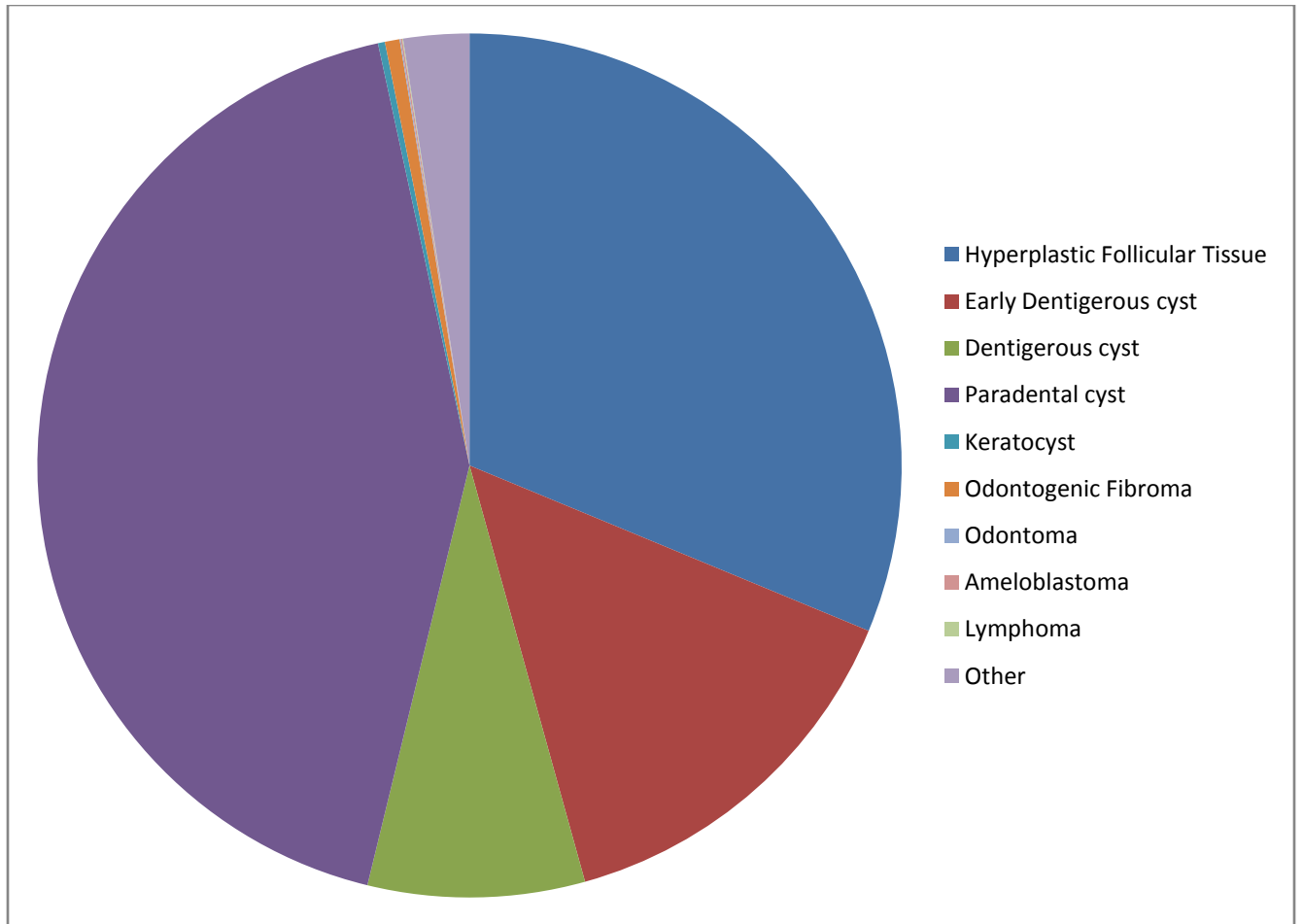
The relationship of the various pathologies in the third molar area is related to the gender of the patients and is summarized in Table (6).

	Number		Proportion	
	n=1259	n=1834		
	Male	Female	Male	Female
Hyperplastic Follicular Tissue	361	710	28.67%	38.71%
Early Dentigerous Cyst	196	299	15.56%	16.30%
Dentigerous Cyst	128	150	10.16%	8.18%
Paradental Cyst	574	675	45.59%	36.80%

Table (6). Gender distribution of patients with pathological changes of the third molar area.

Of the 3427 third molar teeth removed, 2548 were from the mandible and 879 were from the maxilla. The number of third molar teeth removed from positions 38 and 48 were similar (1284 and 1263; $p>0.10$) which is not statistically significant, and the number removed from 18 and 28 were similar (449 and 430; $p>0.10$) which is also not statistically significant. However the numbers of third molars removed from positions 38 and 48 were significantly higher than the numbers in the 18 and 28 positions.

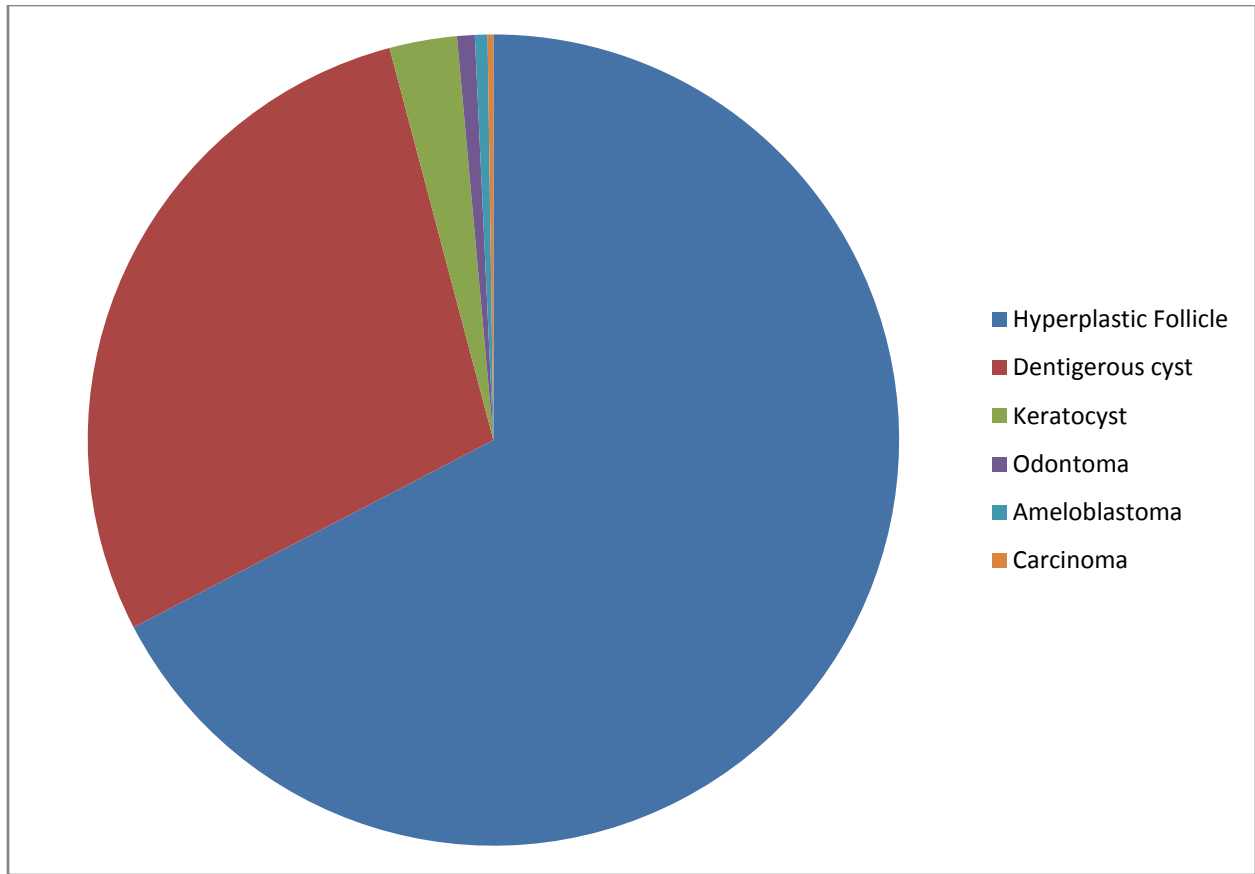
The results of this study showed that 31.25% of the lesions consisted of hyperplastic follicular tissue, 14.4% were early dentigerous cyst and 8.1% dentigerous cysts. These lesions represented a total of 53.75% of the total. Paradental cysts contributed 42.8% alone which constituted a large number of the cases. These two groups together amounted to 96.55% of the lesions in the third molar area. The rest consisted of small numbers of odontogenic keratocysts (0.26%), odontogenic fibromas (0.55%), odontomata (0.06%), ameloblastoma (0.06%) and lymphomas (0.03%). Excluding Hyperplastic Follicles which were not in themselves pathological entities, a total of 68.75% pathoses were found. This was higher than in the the extensive Curran et al study ^[26] in which 32.9% pathoses were reported. They did not, however, include paradental cysts in their study.



Pathologies in this study of the 3rd molar area (n = 3427 cases)

Pathologies	%
Hyperplastic Follicular Tissue	31.25
Early Dentigerous cyst	14.44
Dentigerous cyst	8.11
Parodontal cyst	42.80
Keratocyst	0.26
Odontogenic Fibroma	0.55
Odontoma	0.04
Ameloblastoma	0.06
Lymphoma	0.03
Other	2.46
Total Pathology (Excluding Hyperplastic Follicular Tissue)	68.75%

Graph (1). Pathoses found in the 3rd molar area in this study.



Curran Study (n = 2646)	
Pathologies	%
Hyperplastic Follicle	67.10
Dentigerous cyst	28.40
Keratocyst	2.68
Odontoma	0.70
Ameloblastoma	0.50
Carcinoma	0.23
 Total pathology (excluding hyperplastic follicle)	 32.90%

Graph (2). Comparison between present study and Curran et al study (2002) ^[26]

(2) Pathological lesions in the third molar area.

Of the 3427 symptomatic third molar teeth removed and the soft tissue sent for histological examination 0.3% was reported as normal i.e. normal dental follicular tissue.

Hyperplastic follicular tissue was reported in 31.35 % of specimens. The dental follicular tissue enlarges as a result of stimulation and results in a thicker than normal layer of fibrous tissue around the crown of the tooth and is lined with reduced enamel epithelium. The fibrous tissue contains numerous islands of odontogenic epithelium and shows a mild chronic inflammatory cell infiltrate.

Early dentigerous cysts were found in 14.4% of the specimens. An early dentigerous cyst is a developmental odontogenic cyst that has soft tissues similar to the hyperplastic follicle. The reduced enamel epithelium undergoes squamous metaplasia and a cystic cavity develops between the enamel of the tooth and the epithelial lining that increases in size due to fluid accumulation within the cyst.

Dentigerous cysts were found in 8.1% of the specimens. The dentigerous cyst is one which encloses the crown of an unerupted tooth by expansion of its follicle, and is attached to the neck of the tooth.

Paradental cysts were found in 42.8% of the specimens. The paradental cyst is an odontogenic cyst that develops from the inflamed dental follicle around a partially erupted third molar tooth and is situated distal to the crown of the tooth and results in destruction of the adjacent bone. Rare pathological lesions included odontogenic keratocysts (0.26%), odontogenic fibroma (0.55%), odontoma (0.04%), ameloblastoma (0.06%) and lymphoma (0.03%).

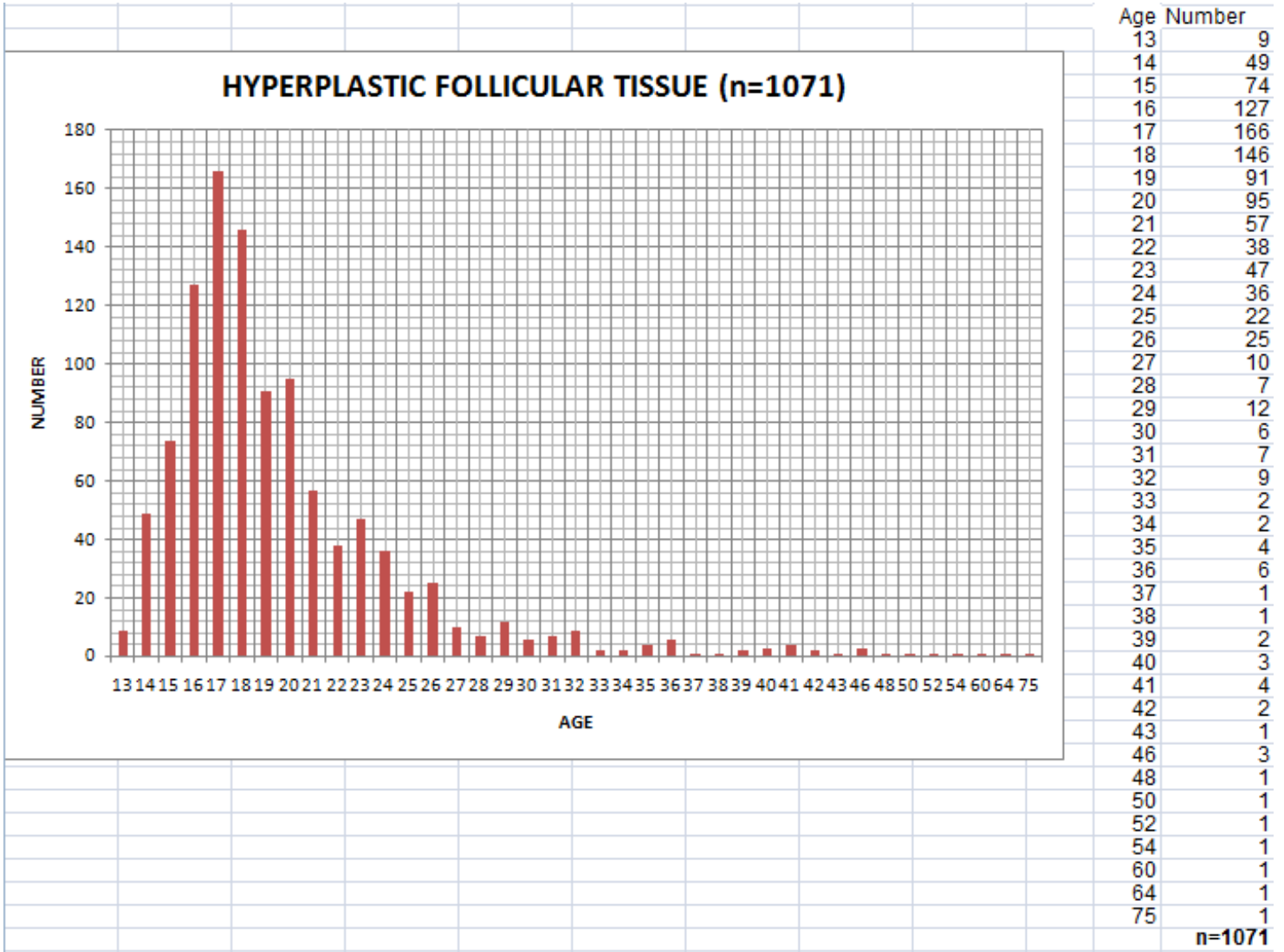
(3) Pathological lesions.

(i) Hyperplastic follicular tissue.

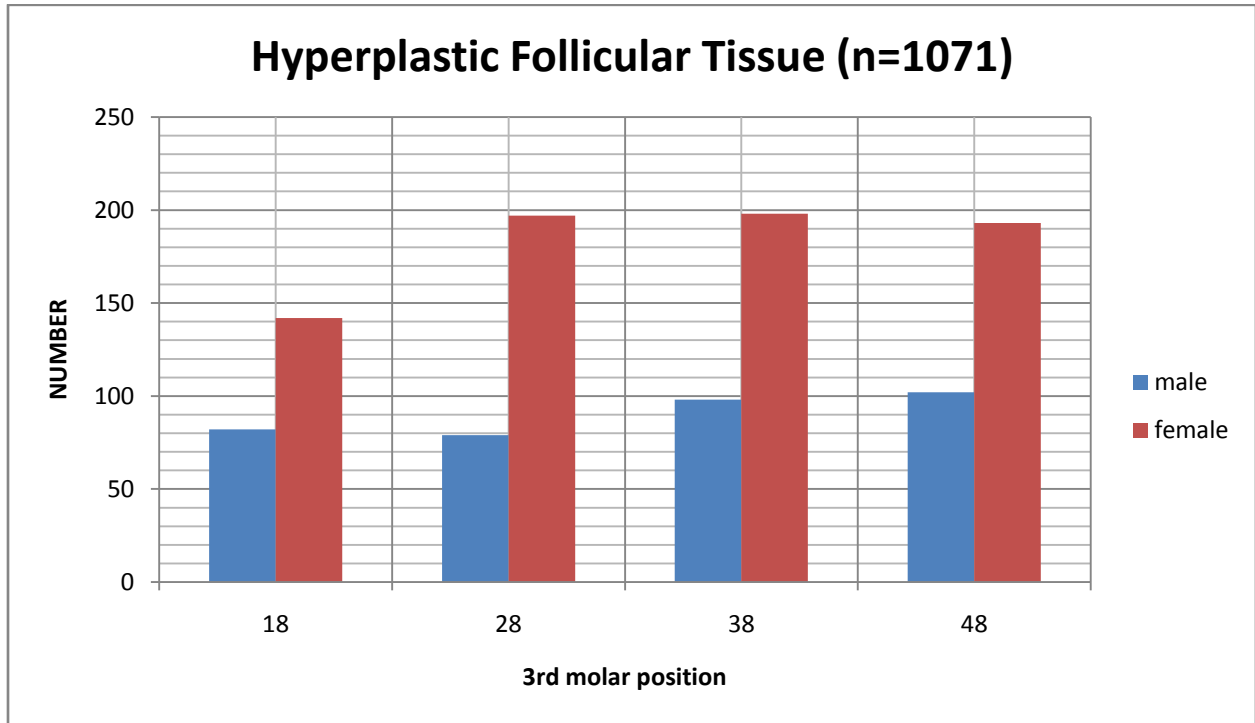
The total number of cases of purely hyperplastic follicular tissue was 1071 out of a total of 3427 seen exclusively in the third molar area. This was 31.25 % of the total number of specimens seen in the third molar area. The age distribution of the patients with hyperplastic follicular tissue is shown in Graph (3). Almost all of the patients (91.1%) were between 14 and 26 years old. Numbers seen at 14 years was 49 cases (4.60%) with a maximum of 166 cases (15.4%) at 17 years of age. There were 146 cases (13.6%) at 18 years and 91 cases (8.5%) and 95 cases (8.9%) at 19 and 20 years respectively. There were very few cases in the older age groups.

There were more female than male patients with hyperplastic follicular tissue in the third molar area, (710 versus 361; $p = 0.0918$) which is not quite statistically significant. However the proportion of female and males with hyperplastic follicular tissue in the third molar area were similar (66.29% versus 33.71%; $p = 0.0918$) which is also not quite statistically significant.

Of the specimens with hyperplastic follicular tissue, a significantly greater number were from positions 38 and 48 (mandible) compared to positions 18 and 28 (maxilla) (591 versus 480; $p = 0.0106$) which is statistically significant. However the proportion of third molars in position 38 and 48 with hyperplastic follicular tissue were similar to positions 18 and 28 (55.18% versus 44.82%; $p = 0.0106$) which is statistically significant. The male to female ratios at each of the four positions were similar.



Graph (3). Number of hyperplastic follicular tissue vs age.



Graph (4). Number of hyperplastic follicular tissue vs position and gender.

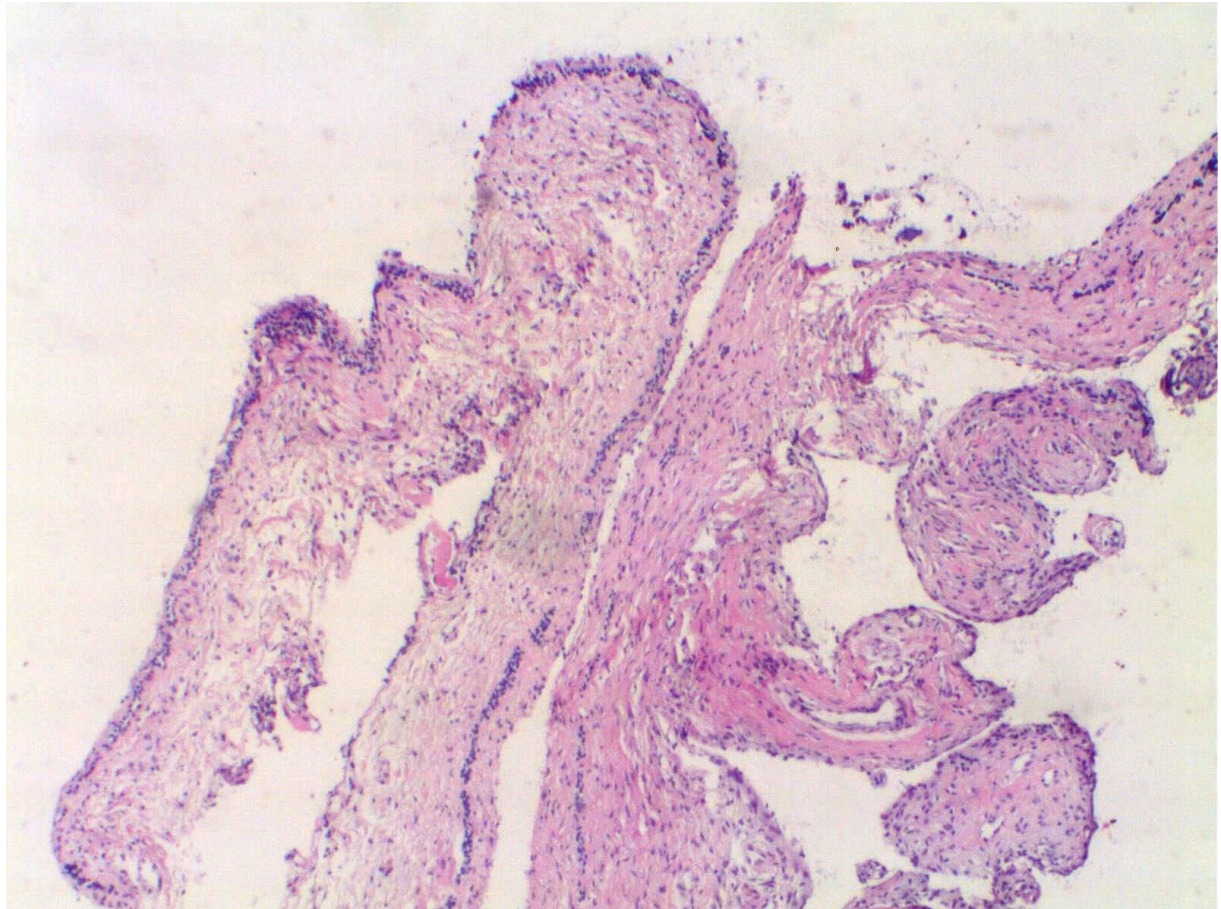


Figure (3). Hyperplastic follicular tissue (H&E x 40). This shows the dental follicle lined with reduced enamel epithelium and containing islands of odontogenic epithelium.

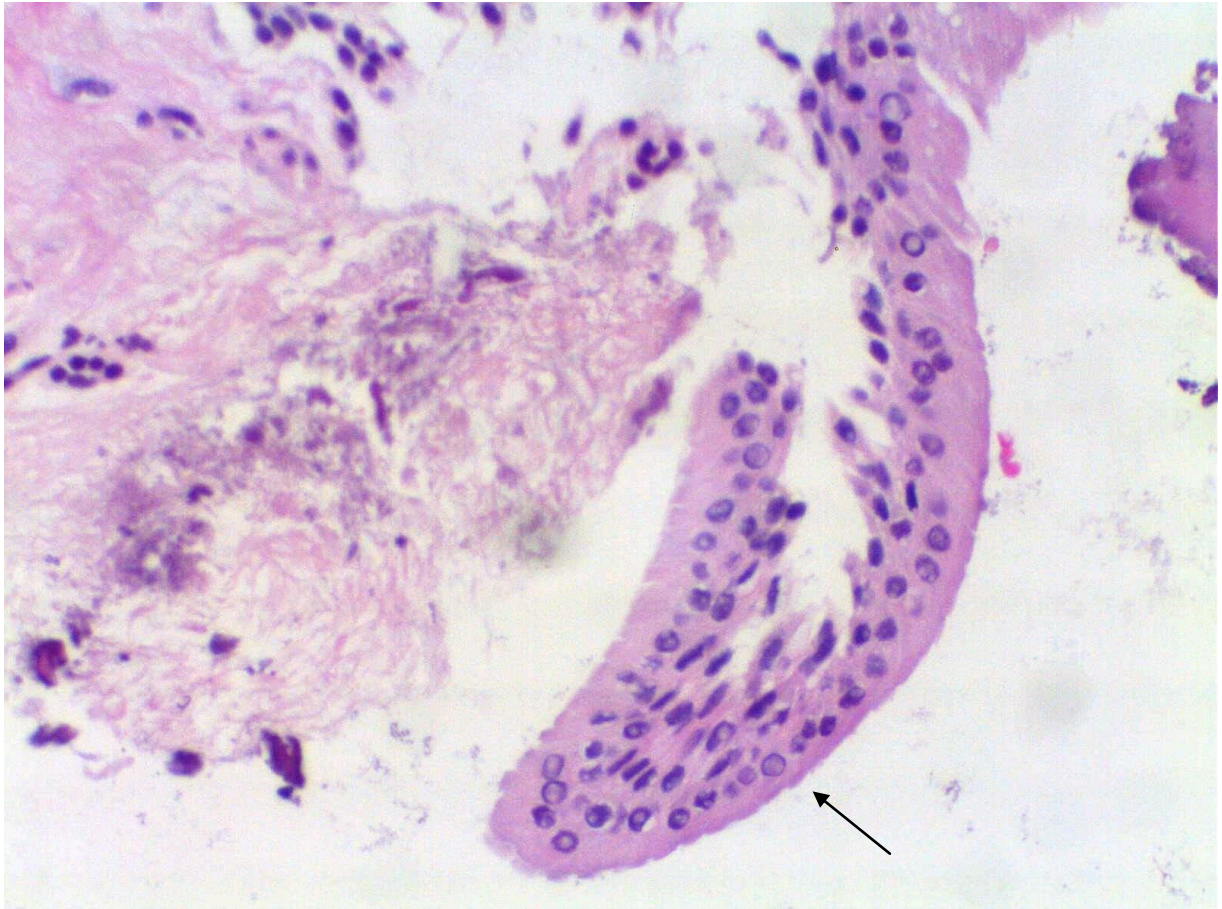


Figure (4). Reduced enamel epithelium from the dental follicle (H&E x 320).

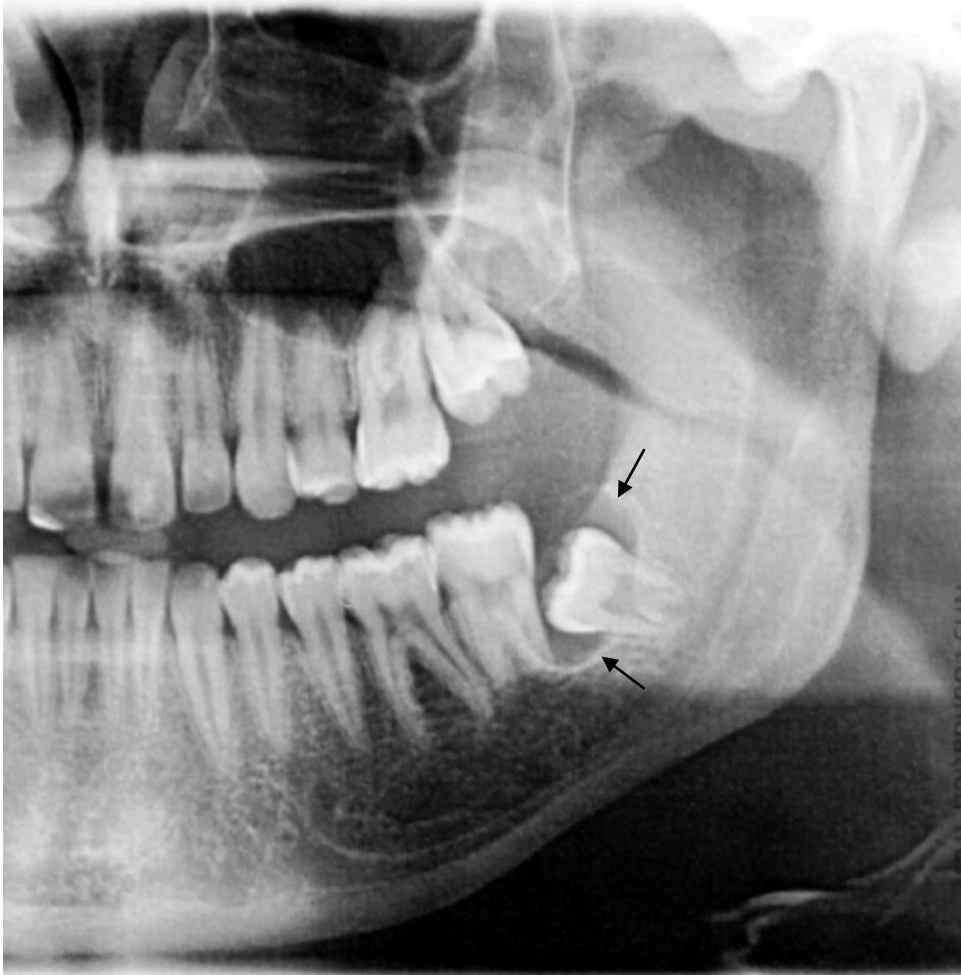


Figure (5). Hyperplastic follicular tissue with early dentigerous cyst formation at the angle of the mandible associated with an impacted 3rd molar.

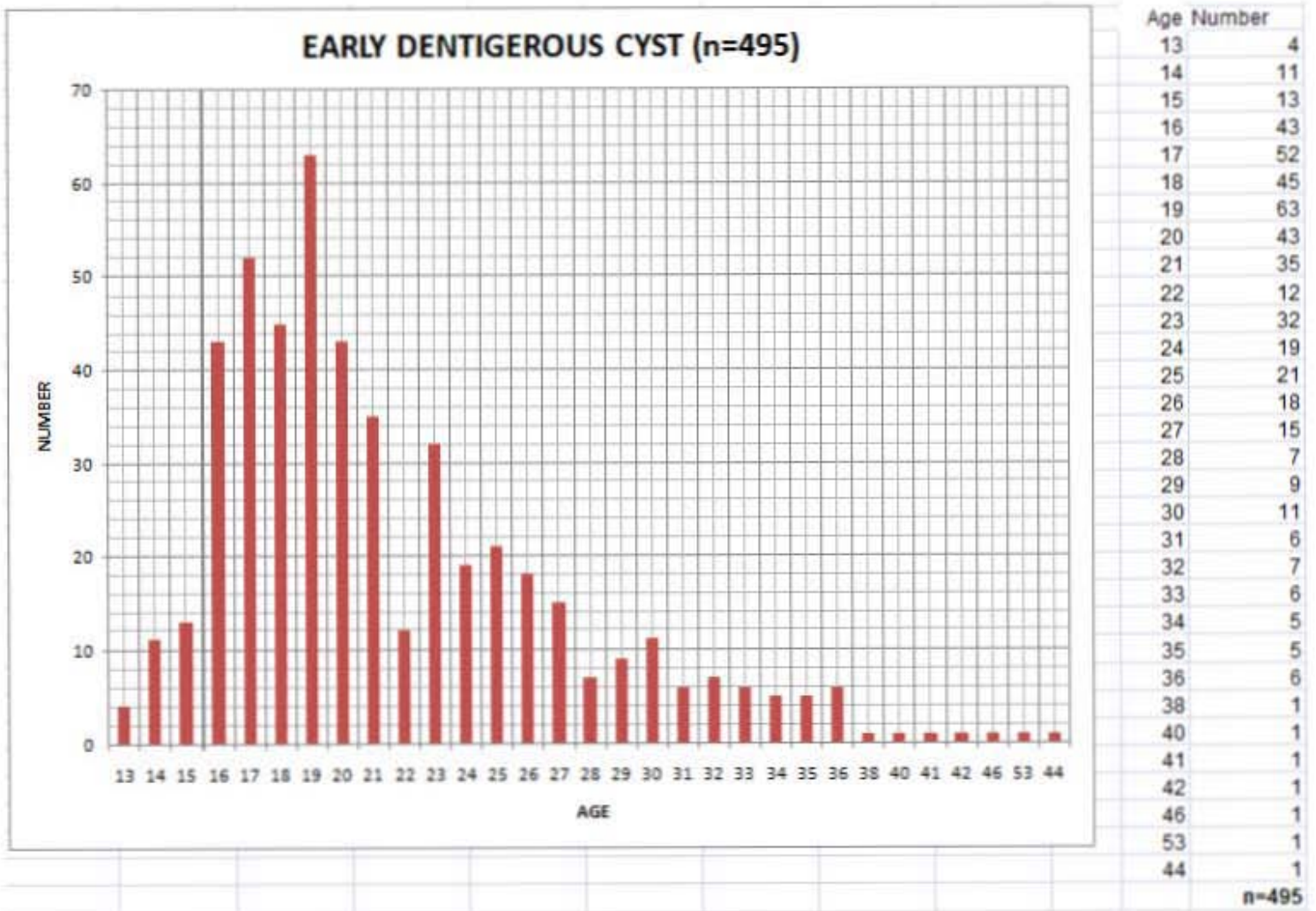
(ii) Early dentigerous cysts.

For the purposes of this study an early dentigerous cyst was defined as a developmental odontogenic cyst that has similar soft tissues to the hyperplastic dental follicle. The reduced enamel epithelium undergoes squamous metaplasia and a cystic cavity develops between the enamel of the tooth and the epithelial lining that increases in size due to fluid accumulation within the cyst. This is a pathological diagnosis made by specific Oral Pathologists. In this study the total number of cases of early dentigerous cysts was 495 of a total of 3427 specimens seen in the third molar area. This is 14.44% of the total number of specimens seen in the third molar area exclusively.

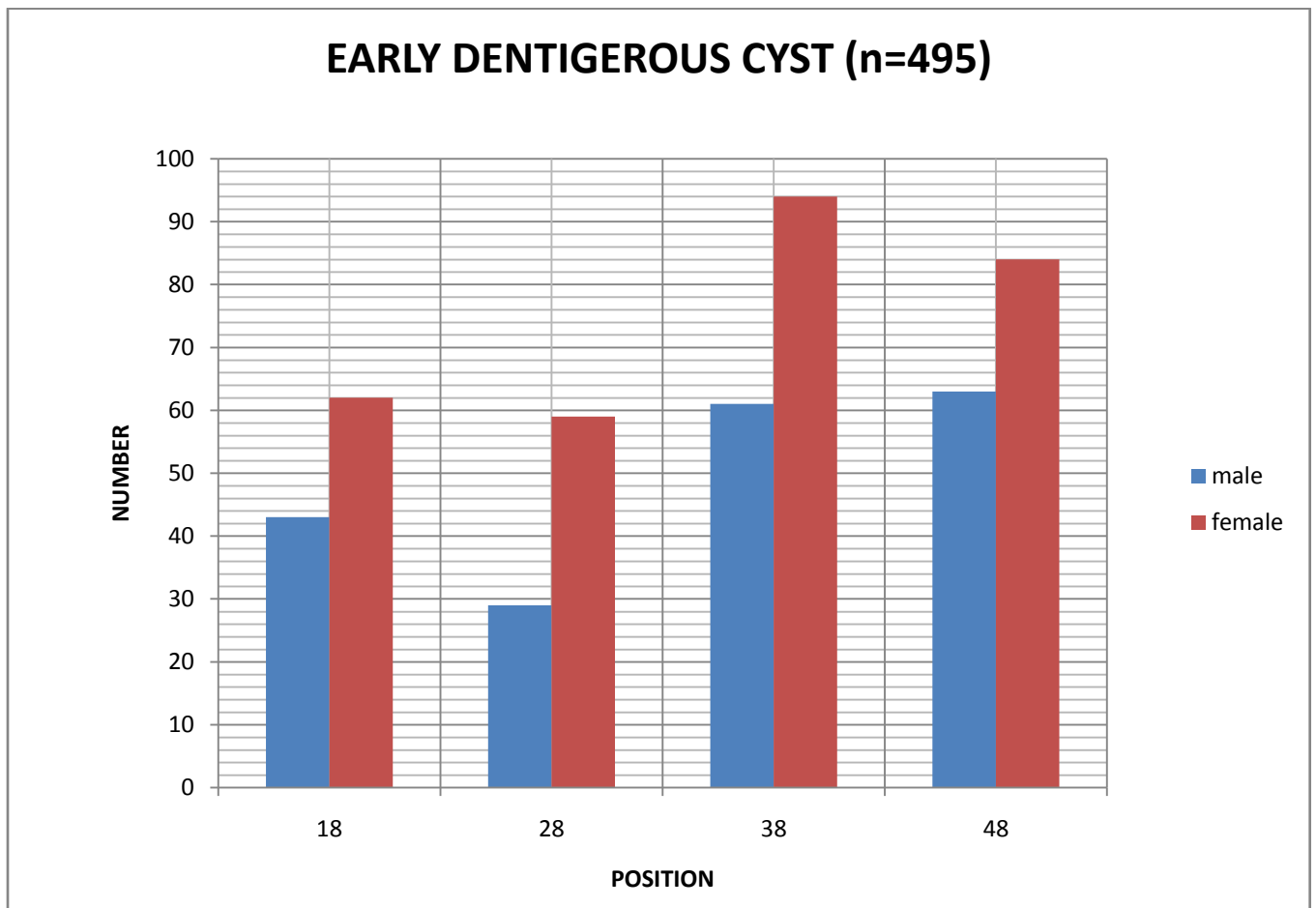
The age range was 13 to 44 years with the majority of the cases in the age range of 16 to 27 years. There were a number of cases in patients between 28 and 36 years of age and thereafter very small numbers of cases to 44 years. There were significantly more females than males with early dentigerous cysts, 299 versus 196. The rates within females and males of early dentigerous cysts was 14.9% and 14.0% respectively ($p>0.10$).

With regard to the individual third molar positions, the number of cysts in position 38 and 48 were similar, 11.8% and the numbers in position 18 and 28 were similar, 22.8% ($p<0.001$). The male to female ratios at each position were similar.

This is regarded as a new entity and requires subsequent investigation and publication.



Graph (5). Number of early dentigerous cysts vs age.



Graph (6). Number of early dentigerous cysts vs position and gender.

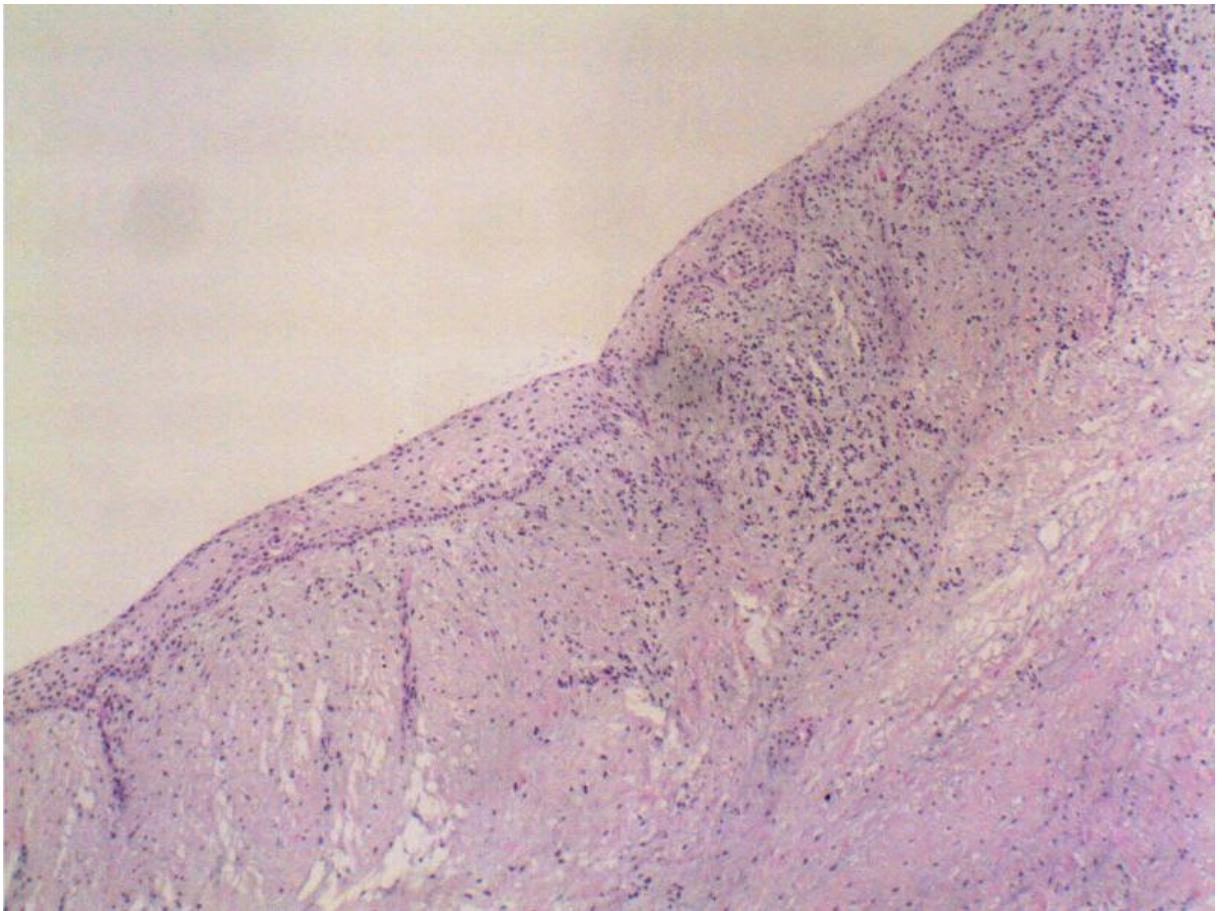


Figure (6). Early Dentigerous cyst showing variation in the thickness of the epithelial lining (H&E x 100).



Figure (7). Early dentigerous cyst showing the variation in thickness of the epithelial lining (H&E x 40).

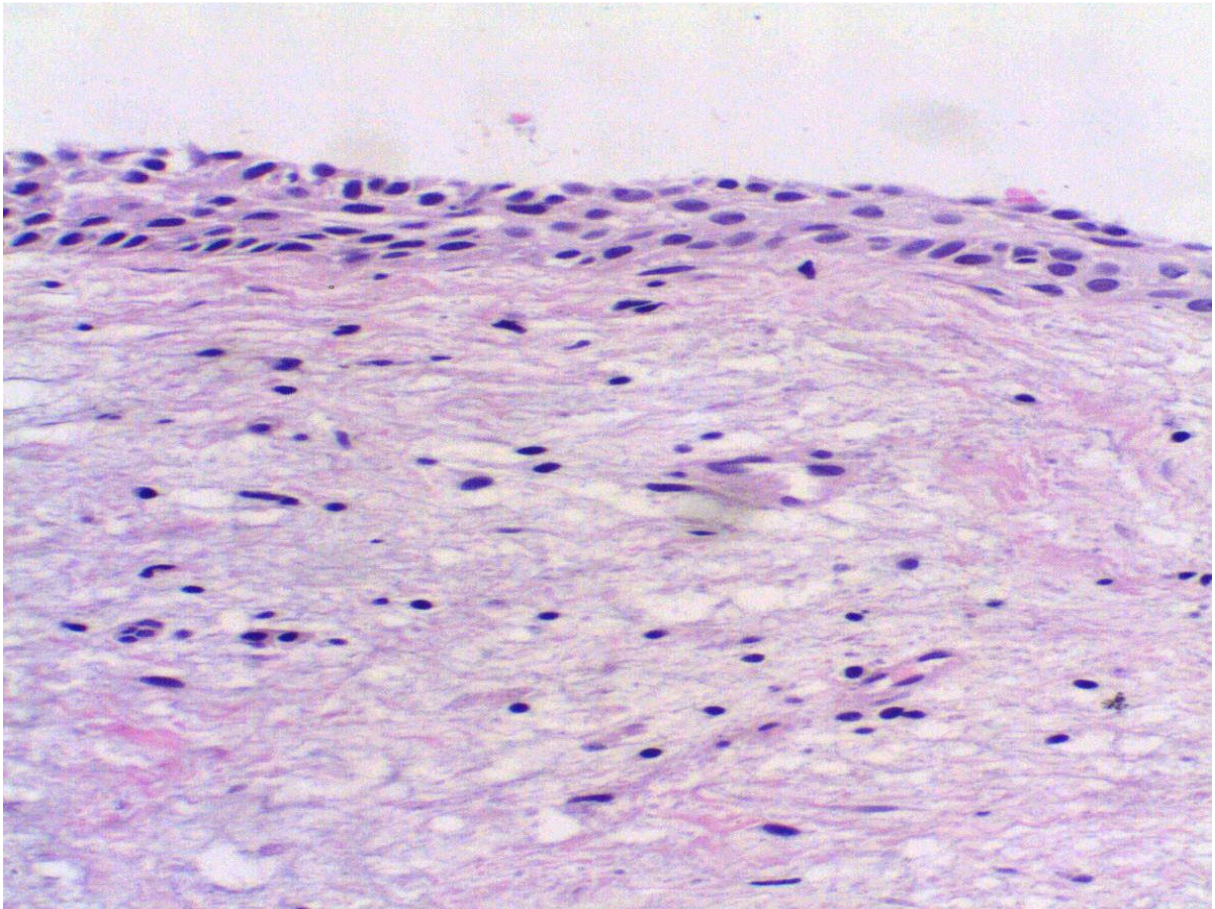


Figure (8). Early dentigerous cyst. The reduced enamel epithelium is undergoing squamous metaplasia, (H&E x 320).

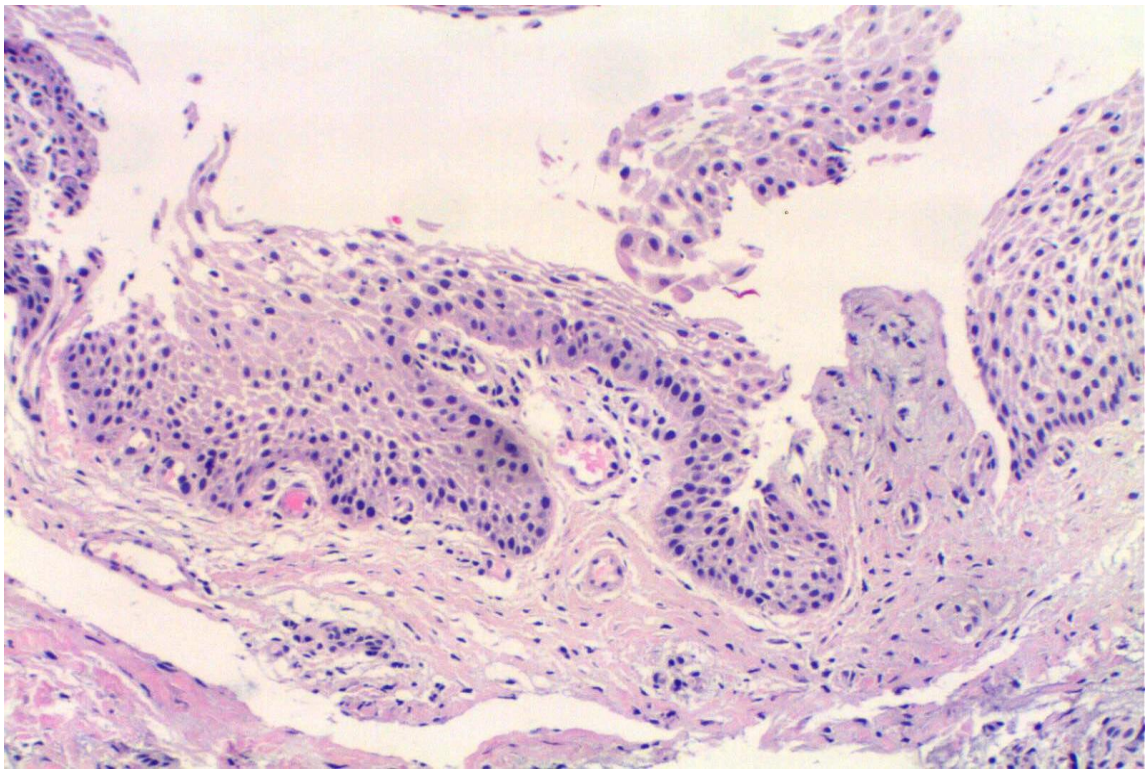


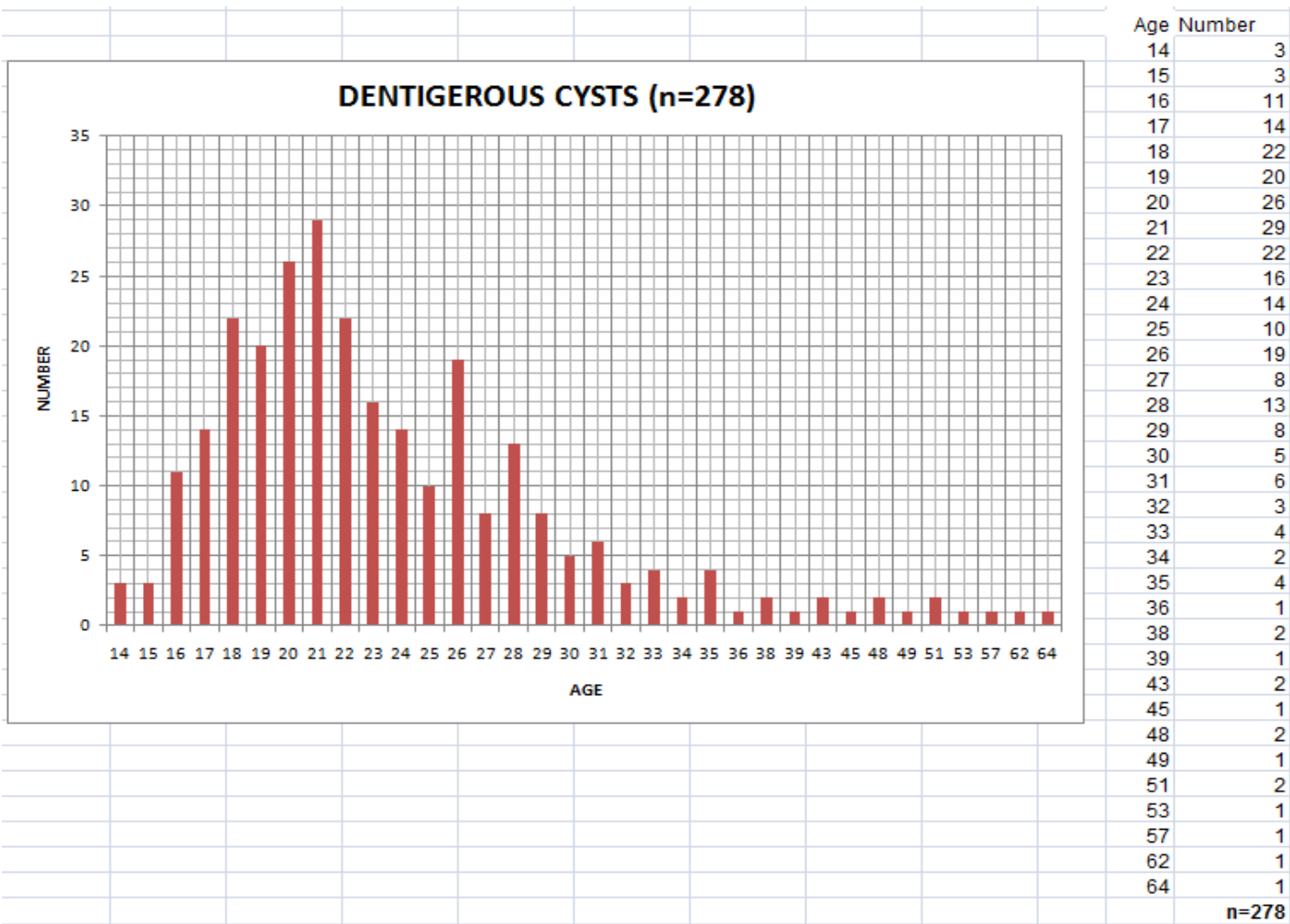
Figure (9). Early dentigerous cyst showing squamous metaplasia of the reduced enamel epithelium (H&E x 100).

(iii) Dentigerous Cysts.

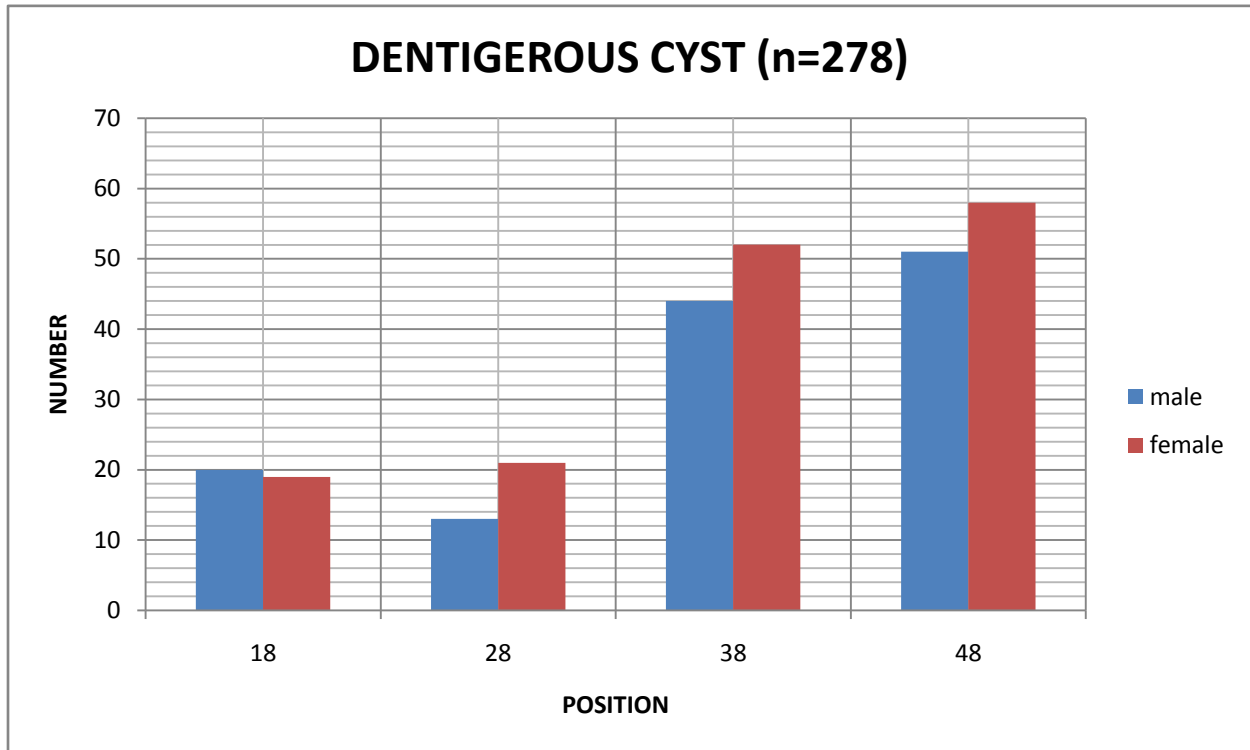
The number of cases of dentigerous cysts in this study was 278 out of a total number of 3427 specimens (8.11%) found exclusively in the third molar area.

The majority of the cases of dentigerous cysts were seen in the 16 to 31 years age group with the largest group at 21 years comprising 29 cases (10.43%) (Graph 7). There were smaller peak incidences at 26 and 28 years with a gradual decrease thereafter in numbers to 64 years. The numbers of female and male patients with dentigerous cysts were similar, 150 versus 128 respectively. However the proportion of females with dentigerous cysts was lower than males, 7.5% versus 9.2%; $p > 0.05$ but this is not statistically significant.

There were a greater number of third molars with dentigerous cysts removed from the mandible compared to the maxilla, 205 versus 73.



Graph (7). Age distribution vs number of cases of dentigerous cysts.



Graph(8) . Gender distribution and position vs number of cases of dentigerous cysts.

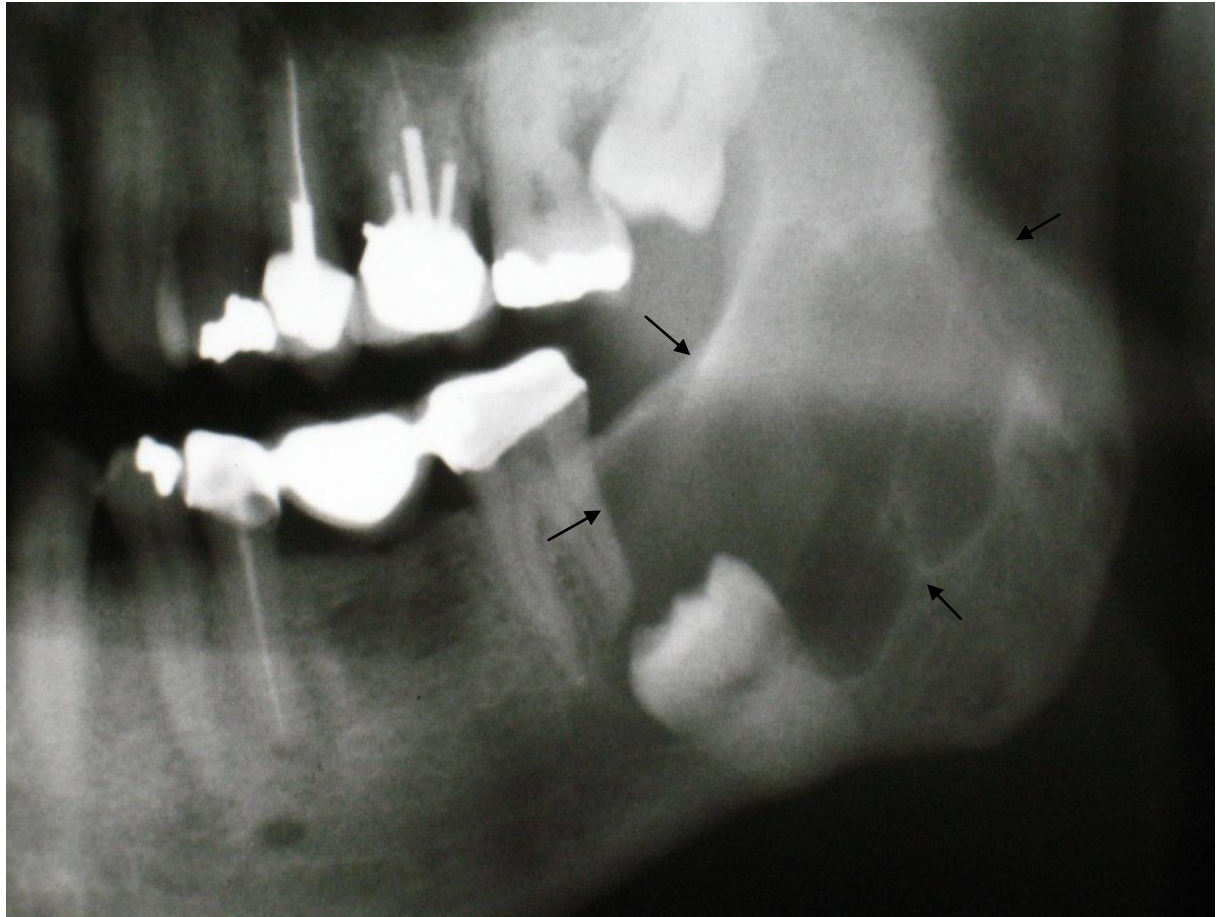


Figure (10). Dentigerous cyst at the angle of the mandible displacing the 3rd molar to the lower border. This developed from a radiographic report of hyperplastic follicular tissue 15 years previously.



Figure (11). Example of typical unilocular dentigerous cyst originating from the third molar area in the dentate mandible eroding the angle as well as part of the body and mainly situated in the ramus of the left mandible. The outline of the lesion is smooth and not loculated as in figure 10.

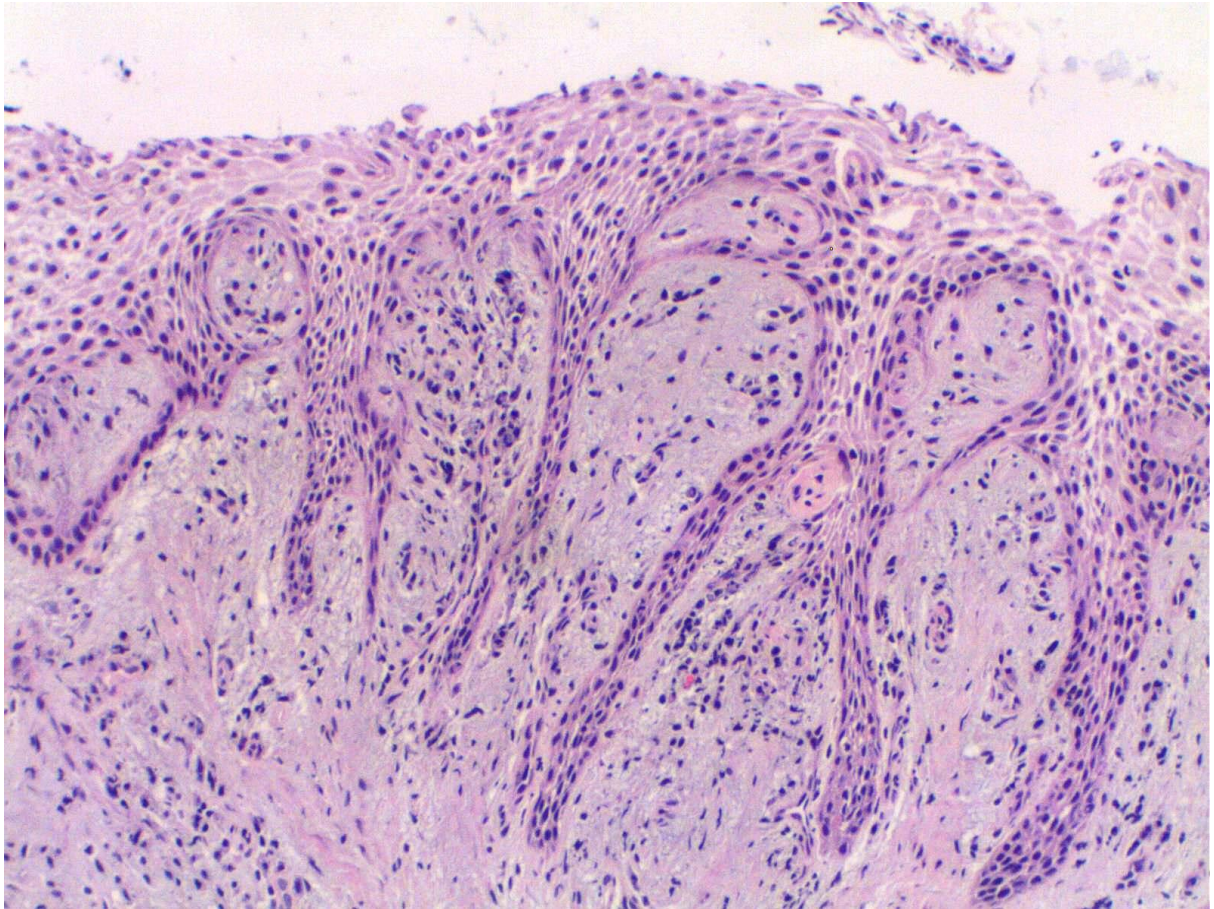


Figure (12). Inflamed dentigerous cyst showing squamous epithelium with elongation of the rete pegs and chronic inflammatory cells in the surrounding fibro-vascular connective tissue (H&E x 100).

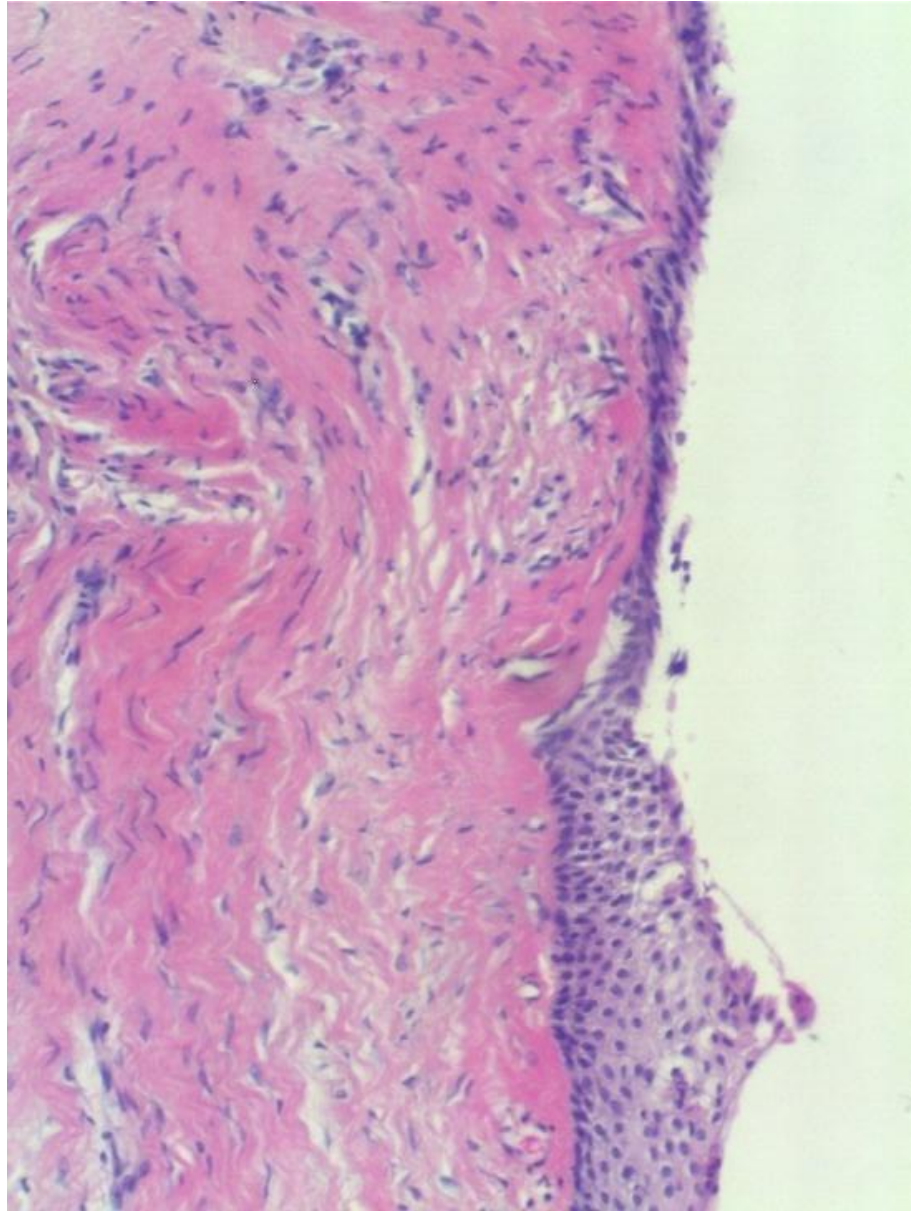


Figure (13). The stratified epithelium of the dentigerous cyst can vary in thickness from a unicellular layer to a thick multicellular epithelium (H&E x 40).

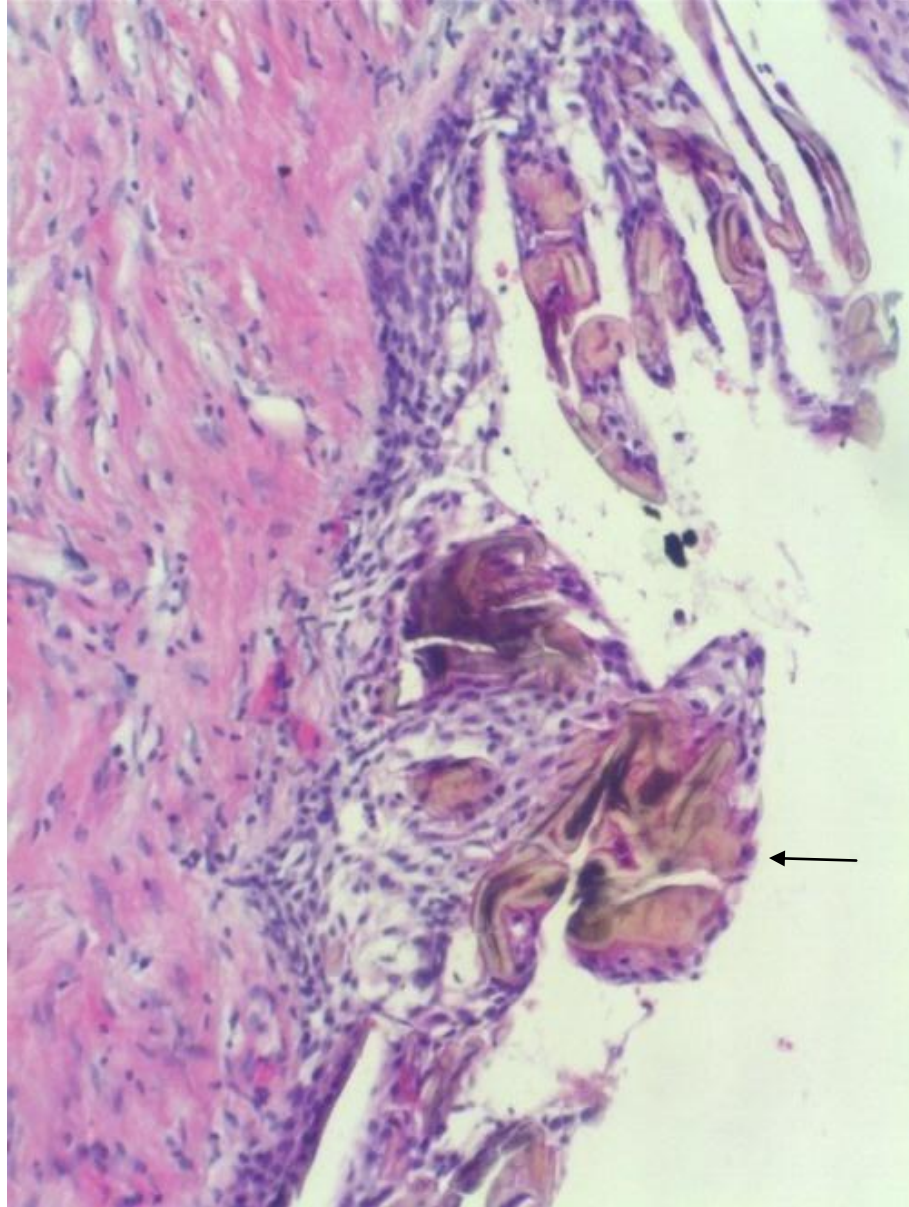


Figure (14). Rushton bodies (arrow) can be seen in the epithelium of the inflamed dentigerous cyst in areas of inflammation. (H&E x 40).

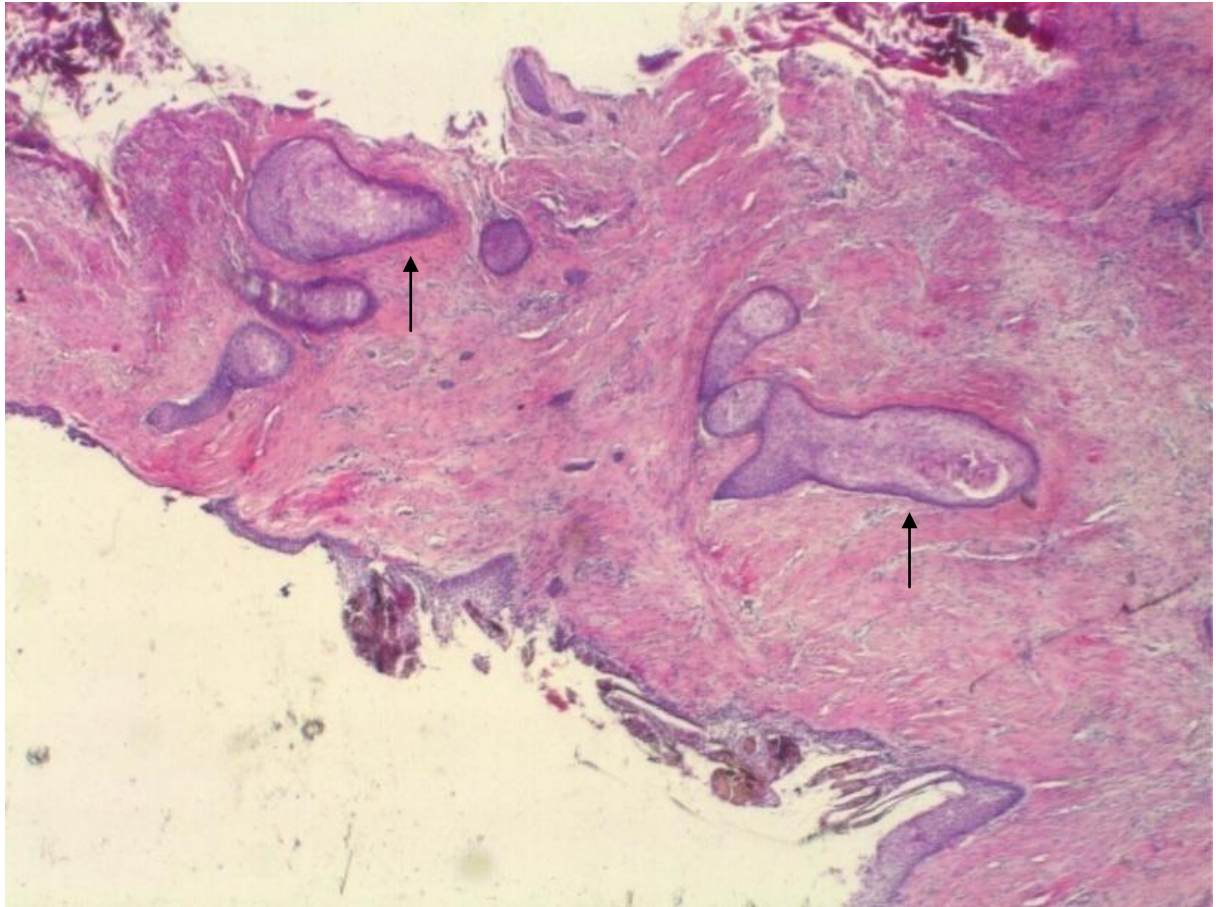


Figure (15). Islands of odontogenic epithelium in the surrounding connective tissue of a dentigerous cyst from the third molar area (H&E x 40).

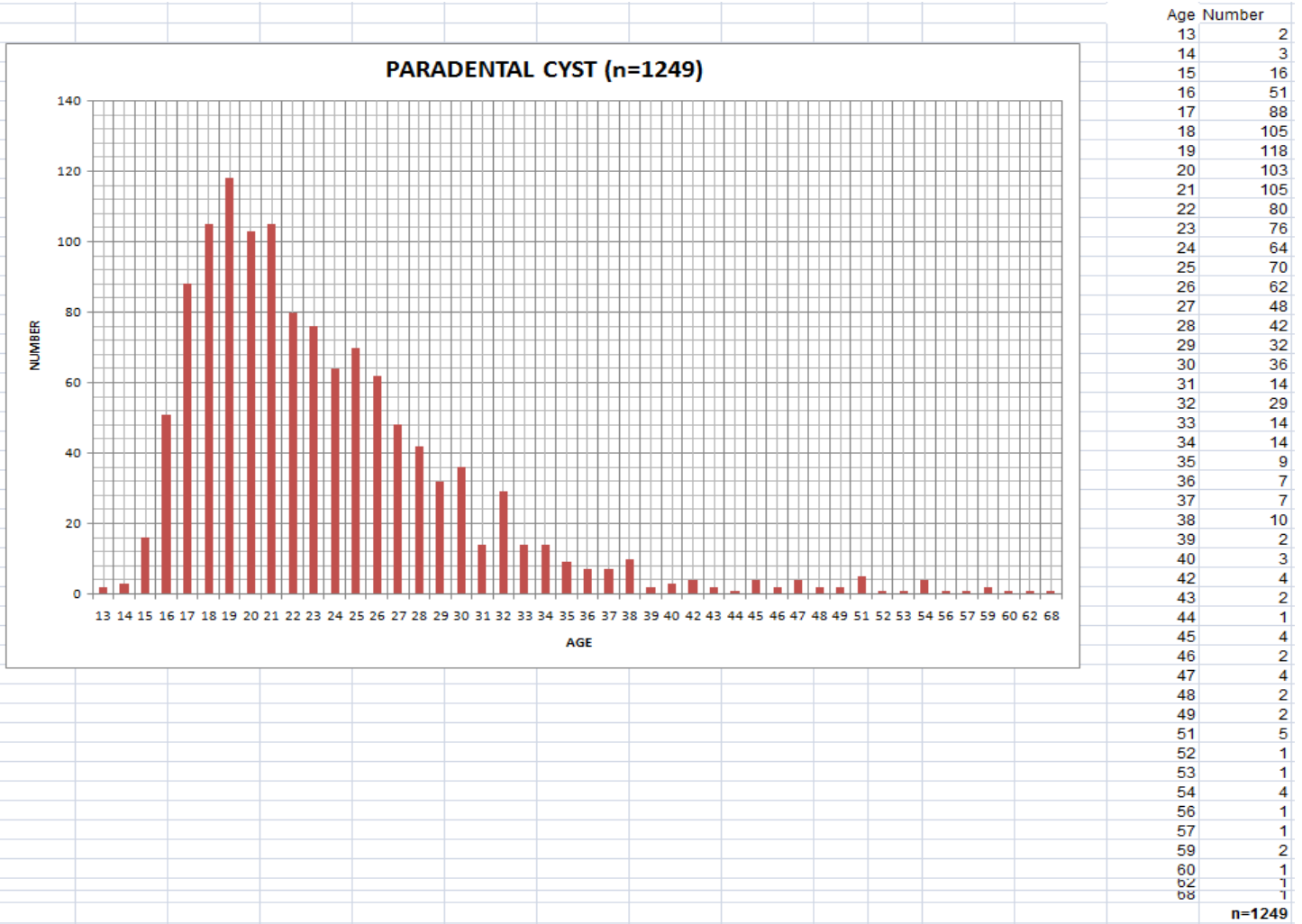
(iv) Paradental cysts.

The total number of cases of paradental cysts was 1249 out of a total of 3427 cases seen exclusively in the third molar area and accounted for 42.8% of the specimens seen in this position.

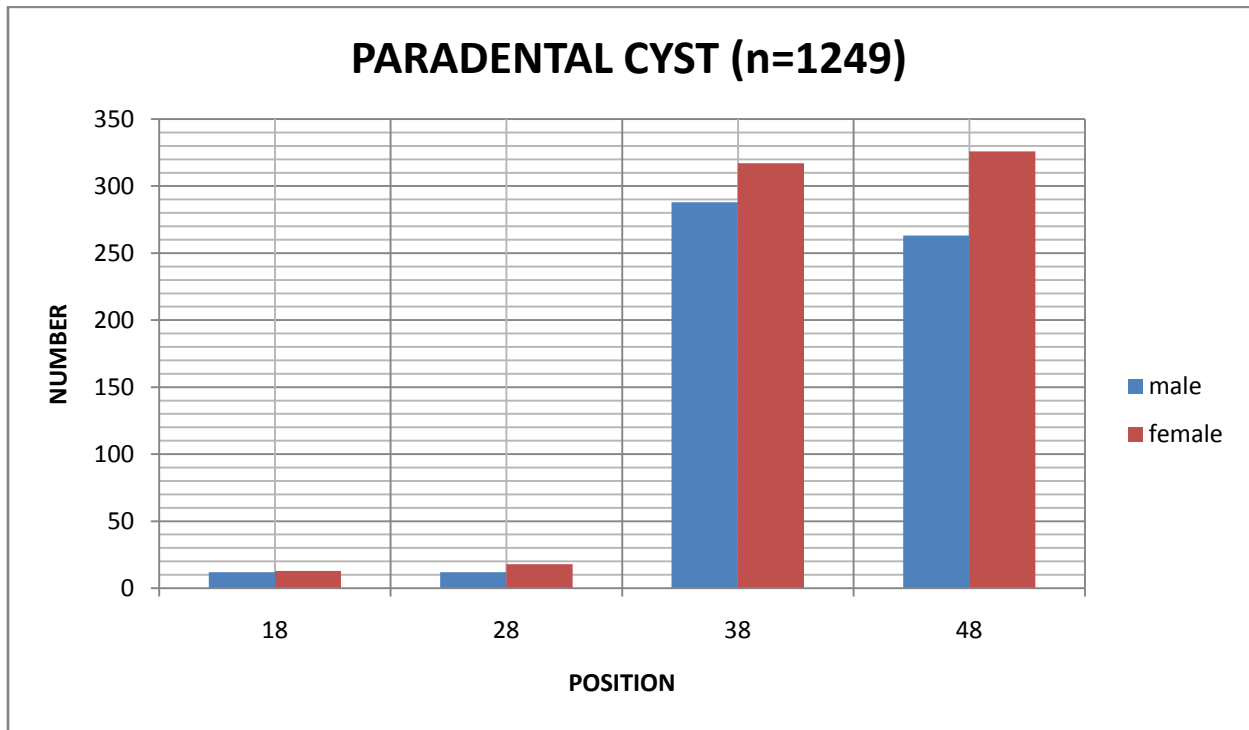
The age distribution of the cases of paradental cysts in the third molar area is shown in Graph (8). The majority of cases were between 15 and 38 years of age. The largest number of paradental cysts was found at 19 years and consisted of 188 cases that corresponded to 9.44% of the total number of cysts. The bulk of the cases were seen in the second and third decades.

The numbers of female and male patients with paradental cysts were similar 675 versus 574. However the paradental cyst rate for male patients was 41.1% and for female patients 33.6% ($p < 0.001$). Almost all the specimens containing a paradental cyst (95.6%) were from the mandible. The gender distribution of cases with paradental cysts was equal in all four quadrants of the jaws.

The number of third molar areas containing paradental cysts was similar in positions 38 and 48 and in positions 18 and 28 respectively. There was a significantly greater number of third molars with paradental cysts removed from positions 38 and 48 (1198) ie. 89.1%, compared to 18 and 28 (53), 6.6% $p < 0.001$. From the rates in the mandible and maxilla it is clear that there is a highly significant difference (Graph 10).



Graph (9). Age distribution vs number of cases of paradental cyst



Graph (10). Gender distribution and position vs number of cases of paradental cysts.

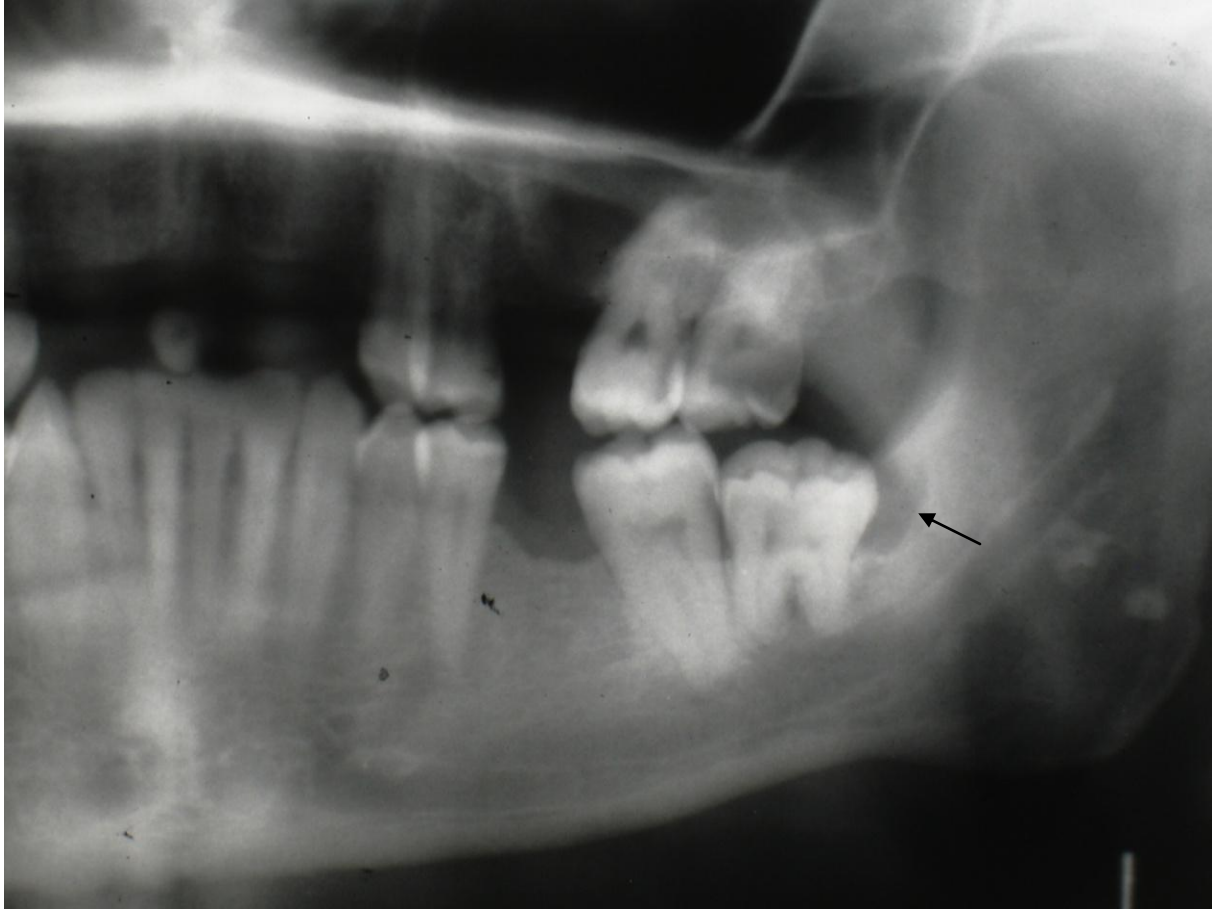


Figure (16). Parodontal cyst associated with an infected and impacted wisdom tooth at the angle of the mandible. The lesion caused systemic symptoms of submandibular lymphadenopathy and sore throat as well as local symptoms of severe pericoronitis, retromandibular swelling and trismus.

Hyperplastic crevicular epithelium

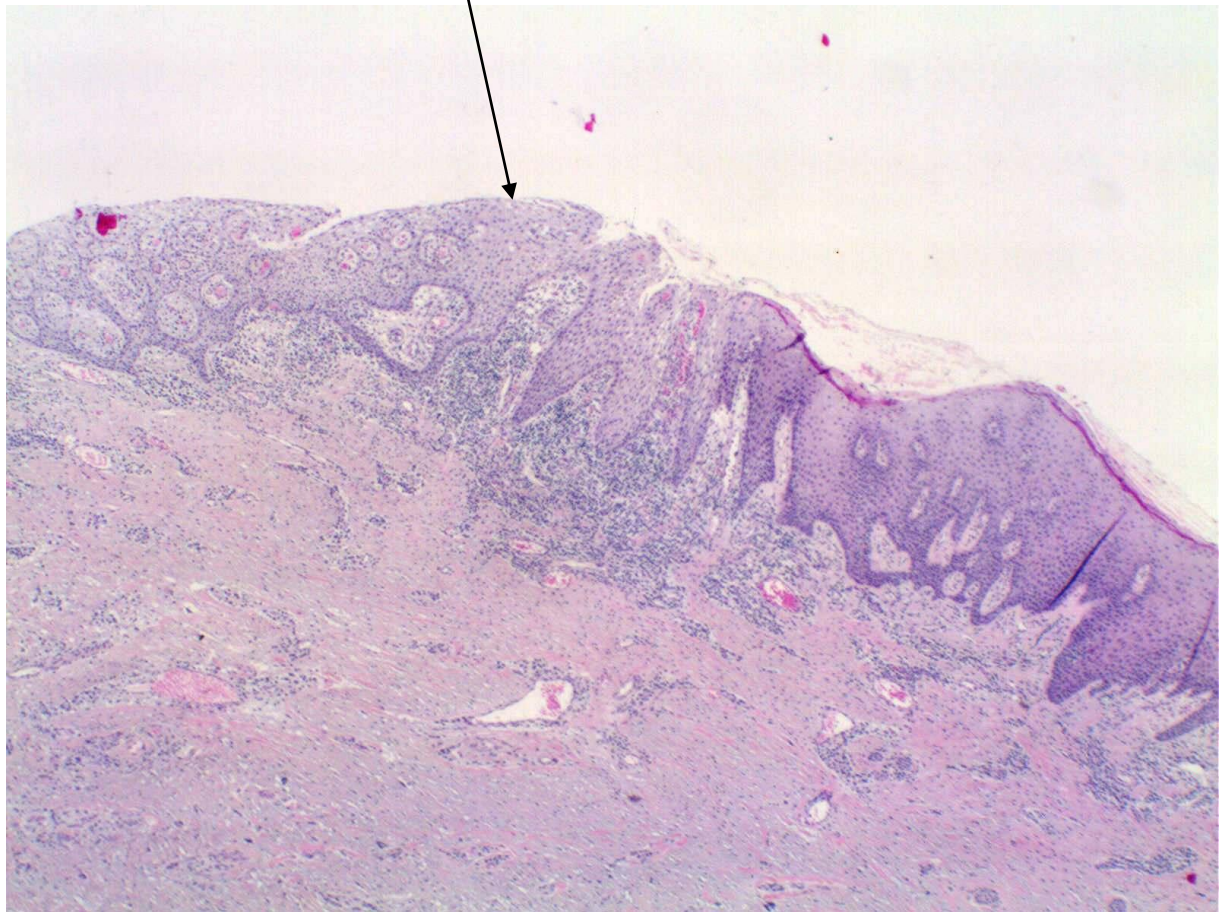


Figure (17). Oral mucosal epithelium (H&E x 40). The junction between the oral mucosal epithelium and the hyperplastic crevicular epithelium of a paradental cyst.

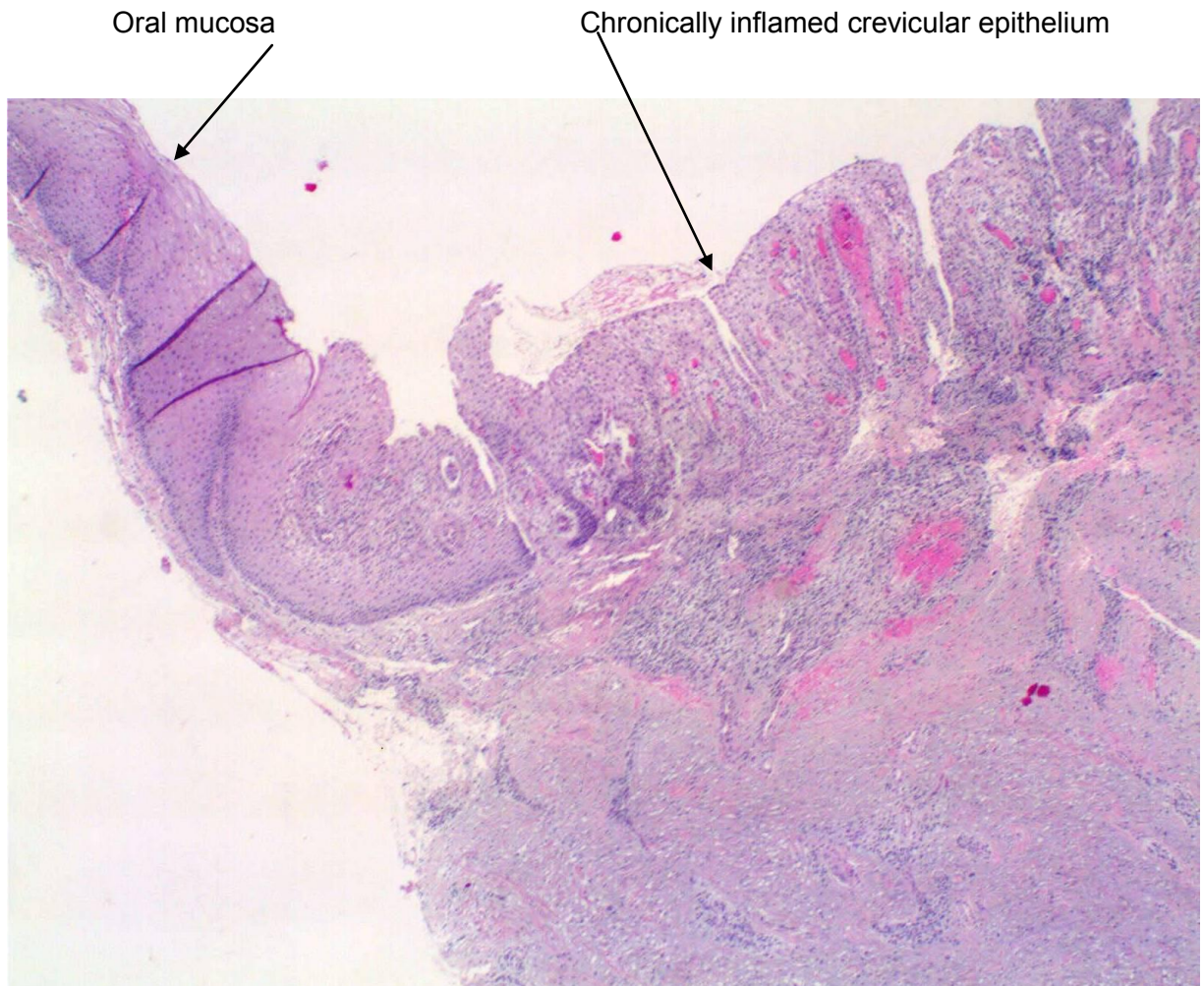


Figure (18). Chronically inflamed crevicular epithelium showing the junction between oral mucosal epithelium and the inflamed epithelium of the residual enamel organ (H&E x 40).

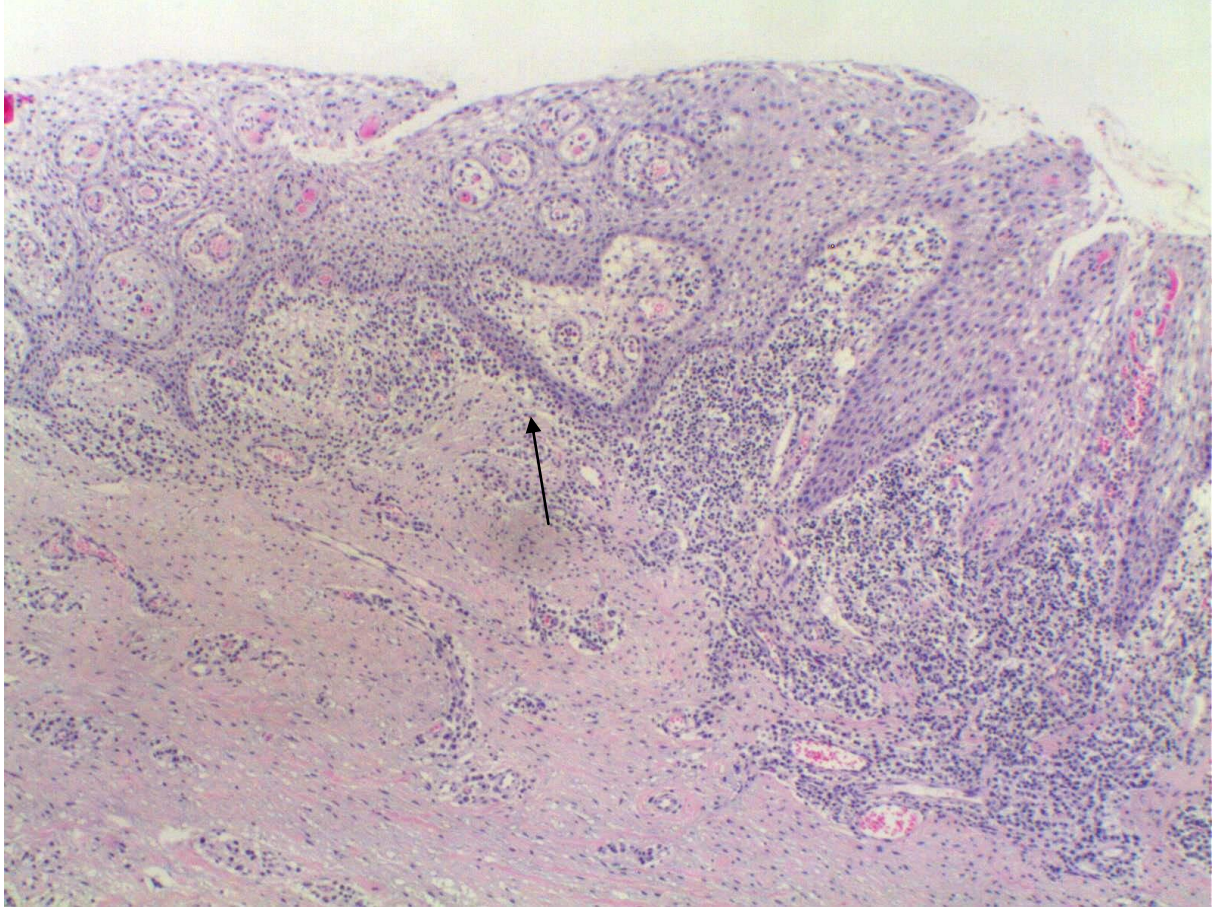


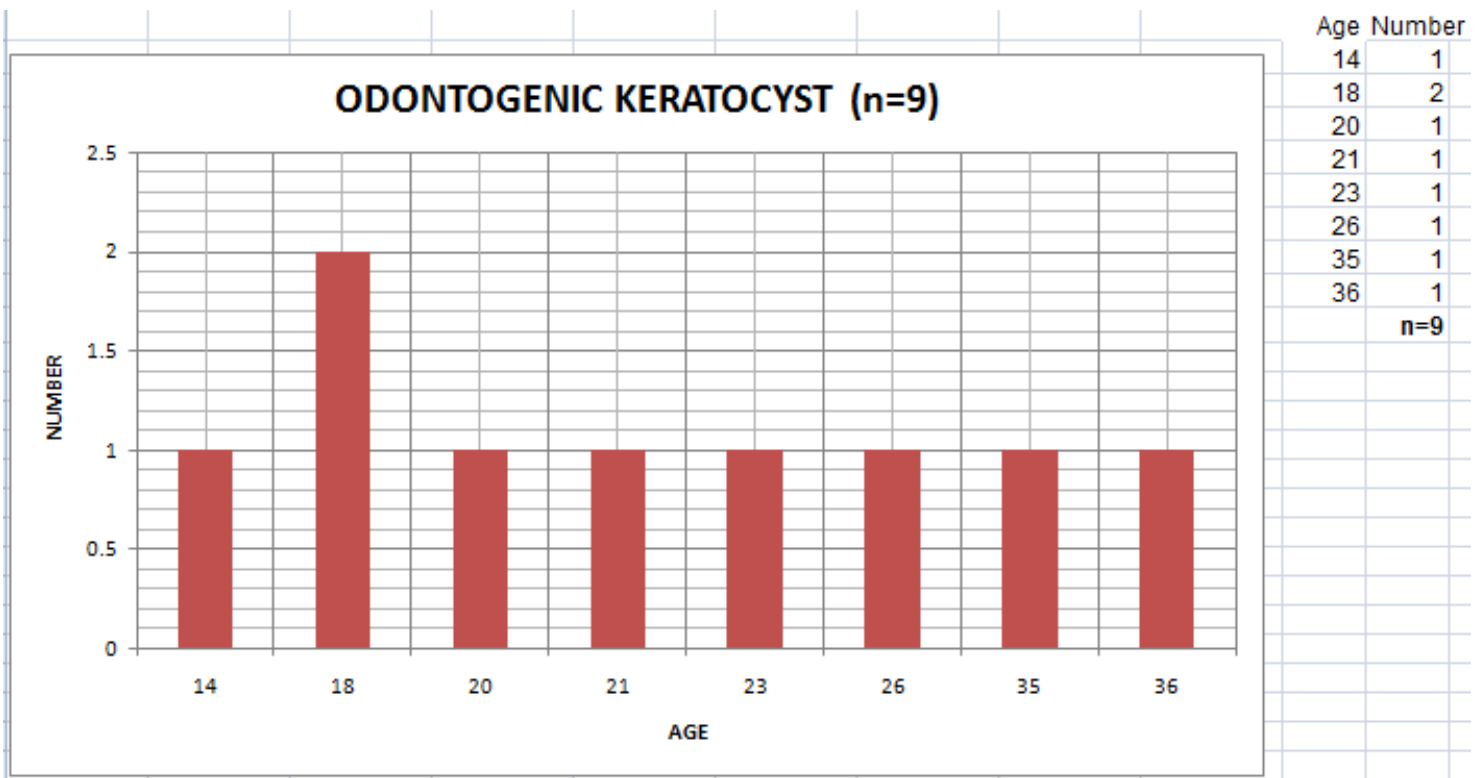
Figure (19). Proliferation of the crevicular epithelium due to the chronic inflammatory cell Infiltrate in the lamina propria. The rete pegs of the epithelium fuse and form arcades. This epithelium resembles that of a radicular cyst (H&E x 40).

(v) The Odontogenic Keratocyst.

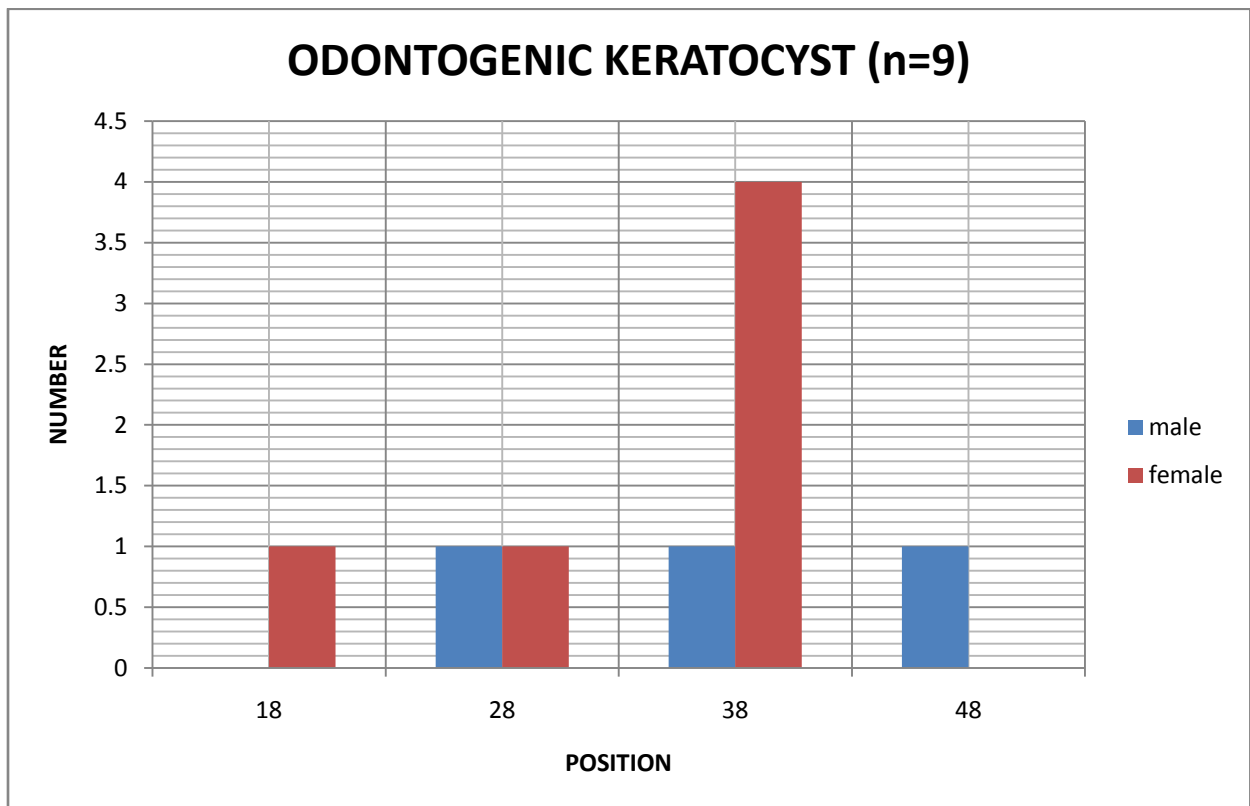
The total number of cases of odontogenic keratocyst found in the 3rd molar area exclusively was small, being only 9 of the total of 3427 lesions (0.26%). The 9 cases were equally distributed the second, third and fourth decades (Graph10).

The numbers of males and female patients with odontogenic keratocysts were similar. Furthermore there was no predeliction for any particular third molar position.

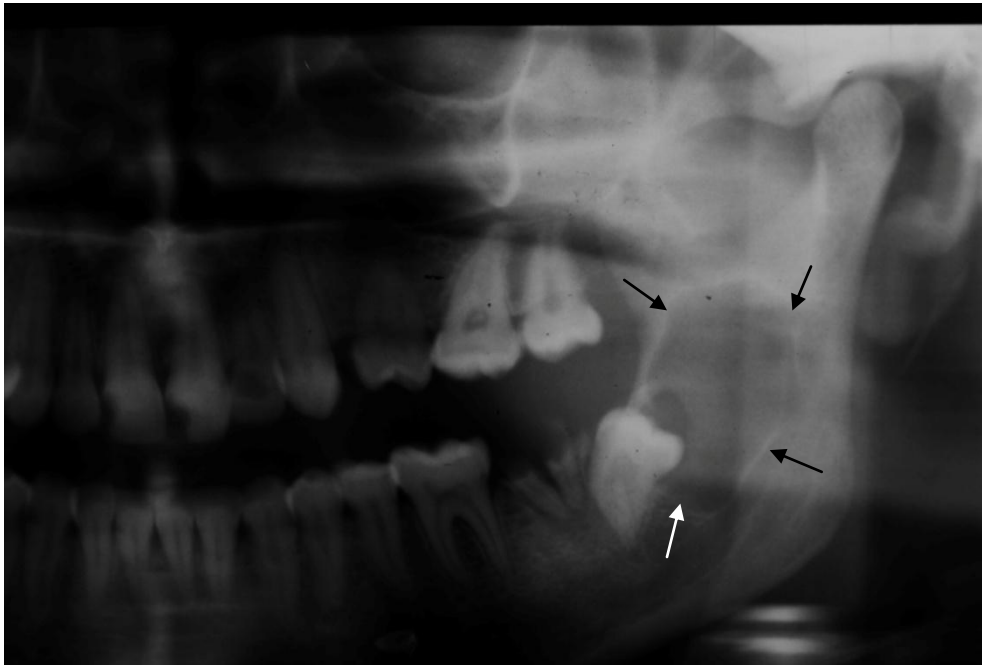
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Graph(11). Age distribution vs number of cases of odontogenic keratocyst.



Graph(12). Gender distribution and location vs number of cases of odontogenic keratocyst.



Figure(20). Odontogenic keratocyst at the angle of the mandible eroding the ramus and associated with an impacted wisdom tooth. The lesion was symptomless and pain was found in the retained root rests and impacted third molar. Subsequent histology revealed the lesion.



Figure (21). Odontogenic keratocyst from the left third molar extending from the angle of the mandible and including part of the body of the left mandible extending to the lower border which has been resorbed.

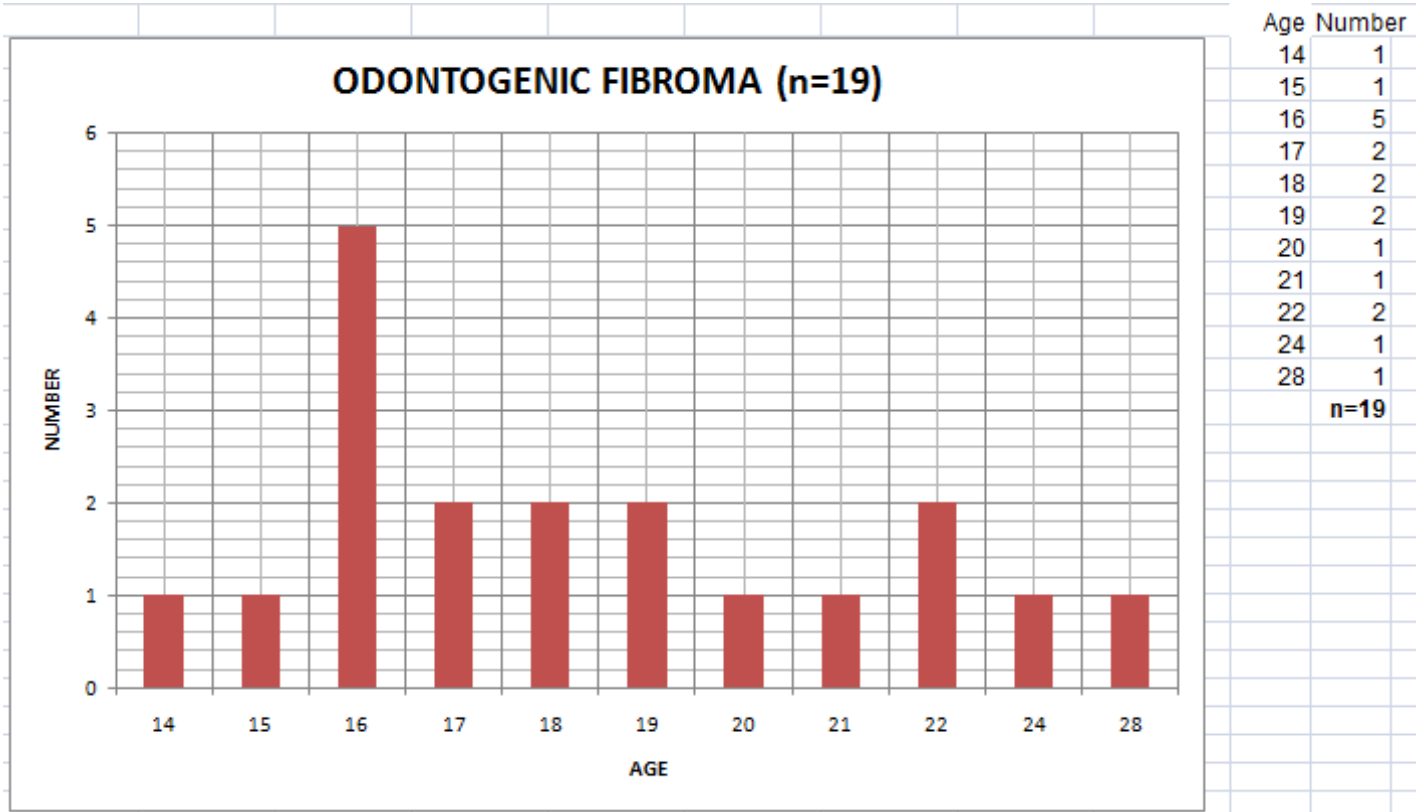
(vi) Odontogenic fibroma.

The total number of cases of odontogenic fibromas occurring in the 3rd molar area was 19 of the total number of cases of 3427. This accounted for 0.55% in this study.

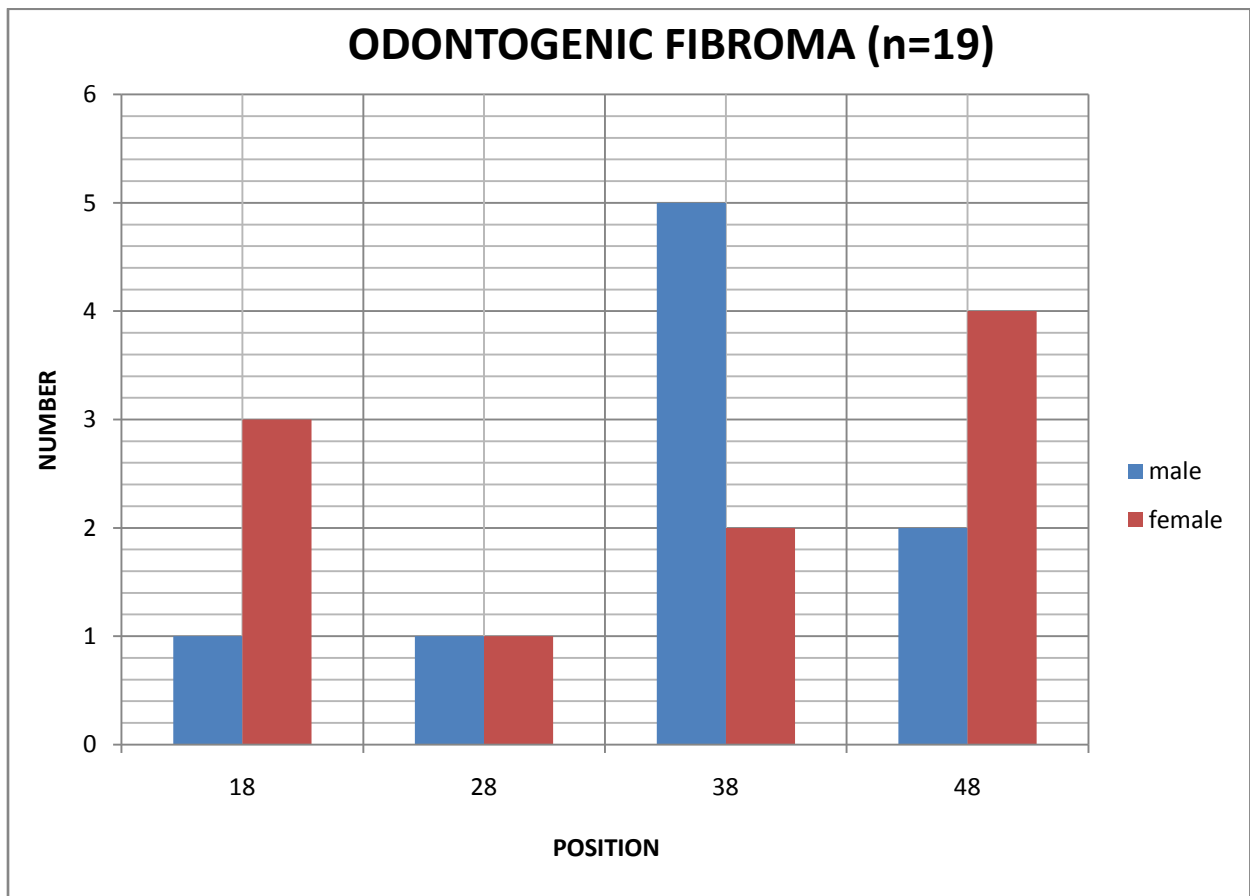
The lesion was seen in the second decade predominantly with a few cases in the 3rd decade of life.

The odontogenic fibromas were equally distributed between the genders and the various third molar positions.

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Graph (13). Age distribution vs number of cases of odontogenic fibroma.



Graph (14). Gender distribution and position vs number of cases of odontogenic fibroma.

(vii) Odontomata.

There were only two cases of odontomata out of a total of 3427 lesions found in the third molar area. Both lesions occurred in the fourth quadrant in the 48 position. One occurred in the female patient of 29 years and was diagnosed as a compound odontoma. The other was a male patient of 51 years and diagnosed as a complex odontoma.

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Figure (22). Compound odontome at the angle of the mandible resorbing the root of tooth 47. Symptoms included vague discomfort in the area of the impacted third molar. The lesion was only discovered on subsequent radiology.

(viii) Ameloblastoma.

Only two ameloblastomas out of the total of 3427 cases were seen in the study (0.06%). Both occurred in the 48 area. One occurred in a 70 year old female whilst the other was in a 51 year old male patient.

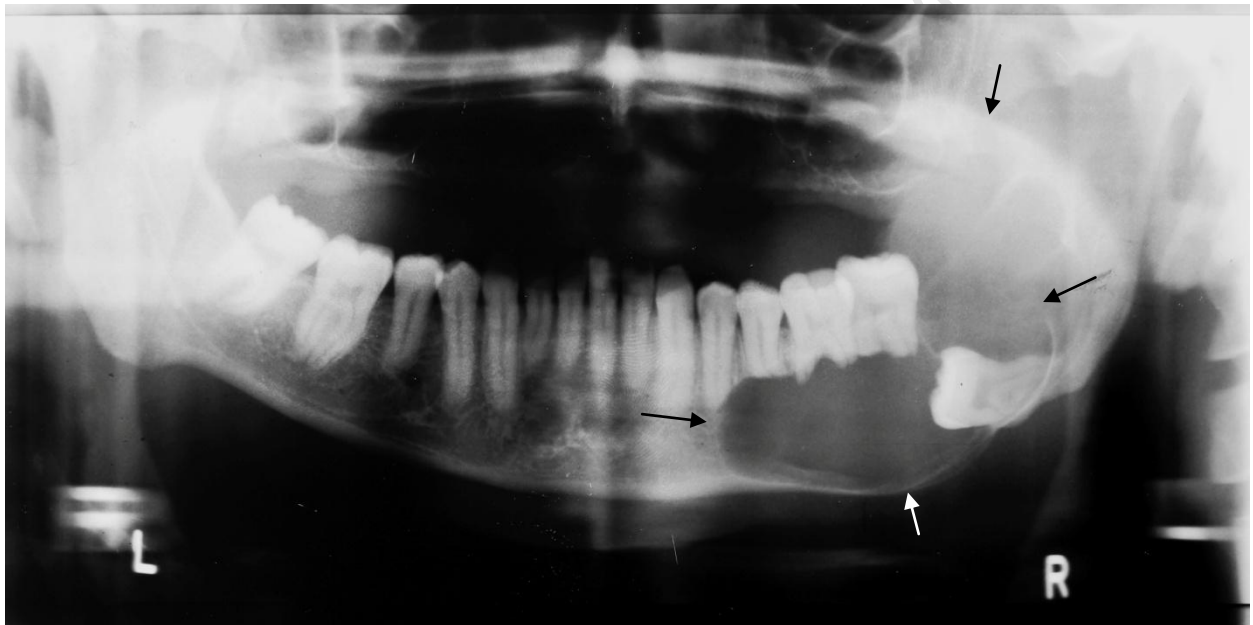


Figure (23). Ameloblastoma involving the angle of the mandible originating from an impacted third molar tooth and resorbing the roots of the adjacent teeth which would result in radical resection and reconstruction by means of a radial forearm or fibula free flap followed ideally by the placement of osseointegrated dental implants and subsequent prosthesis.



Figure (24). Multicystic ameloblastoma at the angle of the mandible. Tooth 36 is missing and the third molar is a mesio-angular impaction which has been displaced due to the underlying lesion.



Figure (25). Ameloblastoma involving the angle of the mandible resorbing the ramus and associated with a displaced third molar tooth.



Figure (26). Computerized tomography of an ameloblastoma of the mandible (L) demonstrating gross destruction of the ramus and angle areas and massive soft tissue swelling.

(ix) Lymphoma.

B Cell Lymphoma Formation

Only one case of lymphoma was reported in this study of 3 427 cases (0.029%). This occurred in a 28 year old female patient in conjunction with dentigerous cyst formation in the 48 region. The lesion was discovered incidentally on histology post operatively by an Oral Pathologist.

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CHAPTER 5

Discussion

(1) General

In this study over a 20 year period, between 1987 and 2007, the pathological reports of all the tissue removed from symptomatic third molar teeth removed in a private practice, as well as other tissue from the oral cavity, was retrospectively reviewed. In this Maxillofacial and Oral Surgery practice, all tissues from removed third molars were routinely sent to an Oral Pathologist for histological assessment.

A total 3427 specimens of tissue from symptomatic third molar teeth were included in this study. This represented the largest study of the pathological assessment of third molar tissue investigated to date. Previously Curran et al ^[26] reported on 2646 specimens from third molar teeth. The rest of the literature of pathological changes associated with third molar teeth consisted of case reports, case series and cohorts of a few hundred patients.

In this study, only 10 patients (0.3 %) had tissue removed from symptomatic third molar teeth reported as normal, i.e. no pathology was found. Therefore in this study 99.7% of third molar teeth removed contained some sort of pathological lesion. Curran et al ^[26] found pathology in 32.9 % of their cases. Their study differed in that early dentigerous cysts, paradental cysts, odontogenic fibromas, lymphomas and small numbers of other lesions were not included. These entities constitute 58.09% of the present study. If added to the results of lesions cited by Curran et al ^[26] this brings the total to 90.99% which is similar.

In comparison with the literature reviewed including the largest single available study of Curran et al ^[26] conditions from the third molar area including follicles, hyperplastic follicles, dentigerous cysts and paradental cysts, have been found to be underestimated and under investigated in the literature. If these tissues were left behind at surgery they might develop into odontogenic tumours, not necessarily cysts. In the NICE guidelines ^[16] no mention is made of soft tissue removal after the removal of third molars, except if there was disease of the follicles or cystic tumour formation prior to removal of the lesions. One wonders how such a statement could be made without histological investigation. Most of the indications for removal of the teeth according to the NICE guidelines were tooth related. Some of the literature from the United States advocated submitting specimens of soft tissues to Oral Pathologists for examination post operatively. (Assel ^[24], Curran et al ^[26], Kim et al ^[60], Glosser et al ^[62], Yildirim et al ^[48]). Numerous papers advocated the early removal of third molars to decrease the incidence and risk of development of pathoses related to third molar impactions (AAOMS white paper ^[21], Bagheri ^[23], NIH Consensus Conference ^[27], South African Association of Maxillofacial and Oral Surgeons ^[30], Mercier et al ^[31], Blondeu et al ^[29], Saravanna et al ^[52]). Other unexpected and unusual pathologies were found in this study eg. lymphoma, when tissues were referred to Oral Pathologists after removal of impacted third molars. From these findings it seems mandatory that soft tissues removed from the third molar area are submitted to Oral Pathologists for examination. This indicates that the patient has been treated comprehensively and not just the signs and symptoms.

It is prudent to note that some Dentists remove third molars without adequate pre-operative radiographs and do not submit the soft tissues obtained after surgery for examination. This was emphasised by Franklin et al ^[63] in which numerous cysts and benign tumours were found in specimens submitted by General Dental Practitioners. If these tissues are left they may lead to post-operative odontogenic lesions forming in that area.

(2) Incidences of various pathologies.

(a) Hyperplastic Follicle.

In this study 31.25% of the specimens contained hyperplastic follicular tissue. In all positions female patients showed a greater frequency of hyperplastic follicular tissue than male patients. The 38 and 48 areas were similar in both male and female patients. Curran et al ^[26] found hyperplastic follicular tissue in 67.1% of their cases. The treatment of all lesions of hyperplastic follicular tissue consisted of enucleation followed by curettage. No recurrences are expected with this entity.

(b) Early dentigerous cysts.

We found early dentigerous cysts in 14.4% of the cases. Curran et al ^[26] does not mention this lesion at all. This included the mandible (11.8%) and the maxilla (22.8%). In this study the incidence of hyperplastic follicular tissue formation and early dentigerous cyst formation were similar. Both entities occurred in the young with a maximum occurring at 17 and 19 years respectively. Treatment of all lesions diagnosed histologically as early dentigerous cysts consisted of enucleation followed by thorough curettage. No recurrences are expected.

(c) Dentigerous cyst.

In the present study 8.1 % of cases were dentigerous cysts. Curran et al ^[26] found an incidence of 28.4%. This may be because they grouped early dentigerous cysts with dentigerous cysts and then the incidence becomes 22.5% versus 28.4% which is similar. Shear et al ^[44] has an incidence of 51.1% dentigerous cyst formation in impacted third molars.

The peak incidence of dentigerous cysts was 21 years. The data showed a female predominance for hyperplastic follicular tissue, early dentigerous cyst formation and dentigerous cyst formation. It also showed that the 38 and 48 areas were more prone to these lesions than the 18 and 28 areas. There was an increase in the peak age incidences occurring from 17 years in the case of hyperplastic tissue to 19 years for early dentigerous cyst formation and 21 years for dentigerous cyst formation, an increase of about two years between each of these entities.

The literature reviewed did not contain specific information related to the development of dentigerous cysts. However articles relating to the removal of wisdom teeth alluded to the fact that they should be removed early. (Stevens et al ^[32], Haung et al ^[34] , Baykul et al ^[55] , Mesgarzadeh et al ^[47]). They did not state whether this was prophylactic or if the patients actually had symptoms.

In our study, it was clearly shown by studying follicles, hyperplastic follicles, early dentigerous cyst formation as well as dentigerous cyst formation that there was a gradual progression in age between these entities. There was no data available for follicular tissue.

In hyperplastic follicular tissue, the peak incidence was found at 17 years of age. This accounted for 170 out of 1115 cases (15.24%). In early dentigerous cyst formation the peak was at 19 years in 63 cases of 495 diagnosed (12.72%) and had increased by 2 years. Dentigerous cysts peaked 2 years later at 21 years of age (8.1%).

There was therefore a change in the peak incidence between hyperplastic follicular tissue, early dentigerous cyst formation and dentigerous cyst formation of approximately two years between each entity. There were a relatively high number of cases associated with the peak incidences

in each case. The graph moved to the right which indicated an increase in age (Graph numbers 3, 5 and 7).

This vindicated the recommendation in many publications that symptomatic impacted third molars should be removed early as there appeared to be an increasing chance of pathology with an increase in age. Dentigerous cysts diagnosed on histology from impacted third molars were treated by surgical removal and thorough curettage.

(d) Paradental cyst.

In the current study paradental cysts were found in 42.8% of the cases. Curran et al ^[26] did not mention this entity at all. The reason for this is unknown. In our study paradental cyst formation showed a peak incidence at 19 years with 118 out of 1249 cases (9.44%). Substantial numbers were seen from 18 years to 21 years. In all positions female patients showed a greater propensity for the lesion than male patients. An overwhelming majority of lesions occurred in the 38 and 48 areas.

The incidence pattern of paradental cyst formation and early dentigerous cyst formation was similar. This indicated that paradental cysts were often associated with lesions causing symptoms in the third molar area and hence also required removal. However in the literature reviewed, the incidence of paradental cyst was reported as low. Philipson et al ^[96] reported 0.19% to 4.7% of their cases as paradental cysts while Magnussen et al ^[92] reported 0.9%. The incidence in our study of 1249 out of 3427 cases (36.44%) was closer to the 25% found by Colan et al ^[94] but still higher than previously reported. The treatment of paradental cysts consisted of enucleation of the soft tissue with removal of the offending tooth followed by thorough curettage of the area. No recurrences are expected.

(e) Odontogenic keratocysts.

Although the number of odontogenic keratocysts in this study was small, the numbers did not agree with Shear et al ^[44]. Almost half of the lesions occurred at the angle of the mandible. They showed that the cases were seen predominantly in the second and third decade although they were seen over a wide age spectrum according to Shear et al ^[44]. Their paper was from the records of a teaching institute. Most odontogenic keratocysts are seen in these institutions and few seen in private practice and could account for the difference between Shear's paper (11.2%) and this study where only 0.62% was seen. The Conservative Management of Large Odontogenic Keratocysts was suggested by Eyre et al ^[146] while several studies suggested radical treatment (Hassan et al ^[147], Gonzalez Alva ^[148] and Chkoura et al ^[149]). The treatment of the odontogenic keratocyst varied from enucleation with thorough bone debridement and peripheral ostectomy, enucleation followed by placement of Carnoy's solution or enucleation followed by placement of BIPP (Bismuth Iodoform Parafin Paste), to resection of the mandible. The treatment depended on the severity of the lesion as well as the preference of the operator. All treatments were thorough however, as recurrences were common and widely reported.

Hassan et al ^[147] suggested decompression followed by enucleation with the use of Carnoy's solution to obviate the need for more radical surgery. In their ten cases, new bone formation was reported with thickening of the cyst wall and no recurrences after five years. No specific treatment was mentioned in the paper by Gonzalez-Alva ^[148] but they noted the need to formulate appropriate treatment of recurrences and stressed the need to avoid a misdiagnosis. In their review of 183 cases of keratocystic odontogenic tumour they reported a tendency for recurrence rather than the risk of malignant transformation. Furthermore they reported daughter cysts in 6% of their series. They concluded maxillary lesions had a higher recurrence rate.

Chkoura et al ^[149] considered most treatments performed and classified these as conservative or aggressive. They postulated that epithelial remnants or residual tissue were the prime source of recurrence. They recommended peripheral ostectomy with or without the use of Carnoy's solution instead of enucleation only. Furthermore they recommended removal in one piece, if at all possible and found cryosurgery ineffective. They also suggested follow up by orthopantomogram or CT scan every six months until complete ossification of the post operative bony cavity had occurred.

The efficiency of Carnoy's solution in conjunction with enucleation was investigated by Gosau et al ^[150] where they found a definite decrease in the recurrence rate from 50% to 14% with the use of Carnoy's solution. No reason for this was given.

(f) Odontogenic Fibroma.

The literature mentioned very few cases of odontogenic fibroma in the third molar area specifically. The literature agreed with our findings that the lesion was benign but rare. However the average age of our patients was far below the average of 40 years as quoted by Khan ^[109], occurring predominantly in the second decade with a few cases occurring in the third. These occurred predominantly in the maxilla.' These lesions were treated exclusively by thorough curettage and no recurrences were found.

(g) Odontomata.

This study showed the incidence of odontomata occurring in the third molar area was very small. This agreed with the literature in which Owens et al ^[117] said that odontomata occurring in

the third molar area was small and occurred in older patients. In our cases one was a compound odontome the other a complex. Treatment of odontomata consisted of local excision. The chance of recurrence is small.

(h) Ameloblastoma.

The importance of ameloblastoma is the early detection and treatment of the lesion. The lesion is generally locally invasive and in the vast majority of cases benign. Treatment can be curative and according to the extent of the lesion almost always results in resection of the area involved. Only 2 cases were seen in this study. They occurred in the 6th and 8th decades and both in the third molar area. This agreed with Neville et al ^[75]. However it was older than found by Kim et al ^[126] where they found the mean age of the patients to be 30.4 years. The younger age was also found by Ord et al ^[128]. They reported a mean age of 15.5 years with 45% at the angle of the mandible and almost 50% occurring in black patients.

In the multicystic ameloblastoma an acceptable clinical practise in treatment includes initial marsupialization with BIPP (Bismuth Iodoform Parafin Paste) in larger lesions in order to shrink the tumour and prepare for eventual resection of the affected area. The resected area results in contour deficiencies. If this is performed in the mandible it can result in both a cosmetic deficiency as well as a shift of the occlusion to the affected side. Traditionally these defects were corrected using Kirschner wires and autologous free bone grafts. More recently use has been made of reconstruction plates with or without the use of free bone grafting. This was reported by Bueno et al ^[130]. Excellent results have also been obtained utilizing vascularised bone grafts obtained mainly as radial forearm or fibular flaps. The treatment of unicystic ameloblastoma remains controversial but simple enucleation has been employed followed by

long term follow up. This lesion occurs predominantly in younger patients according to Ord et al ^[128].

Posterior maxillary ameloblastomas are particularly difficult to treat as wide resection borders are difficult to obtain. This can lead to subsequent local recurrence and involvement of the base of skull. It can kill the patient by erosion of vital structures. High recurrence rate was noted as well as wide resection advocated by Motamedi ^[127].

Radiotherapy is contraindicated as this may lead to malignant transformation. Final reconstruction can employ the use of dental implants in order to reconstruct the deranged occlusion or act as an anchor for ocular prosthesis in the case of maxillary ameloblastomas.

(i) Lymphoma.

Lymphoma is extremely rare in the oral cavity but even one case in a lifetime with a successful outcome supports the practice that all lesions removed at operation must be submitted for histological examination. The findings of the Yasouka et al ^[56] were that carcinomas were rare in the first molar areas, and that formation of the lymphoma was even rarer. Reports by Bertolotto et al ^[135], Sarde et al ^[137], Robbins et al ^[134] and Steinbacher et al ^[142] said that the condition was very rare. Single case reports were sighted in the previously mentioned papers.

The rarity of the lymphoma was again confirmed in the paper published by Berezowski et al ^[132]. In this case, a B-Cell lymphoma was diagnosed and treated successfully with an 18 year follow up with no recurrence. This again stressed the value of submitting third molar tissue removed at operation for histological examination by Oral Pathologists. This practice averted grave consequences for this patient.

(j) Other pathologies.

The other pathologies were uncommonly found in both the present study and in the reports of Curran et al ^[26]. In the Curran study hyperplastic follicular tissue and dentigerous cysts make up 95% of their cases. In their study if the paradental cysts are included, then hyperplastic follicles, early dentigerous cysts and dentigerous cysts also make up about 95% of the cases.

(3) Age distribution.

The peak in the age distribution curve were 17 years, 19 years and 21 years for the patients with hyperplastic follicular tissue, early dentigerous cysts and dentigerous cysts respectively.

The relatively young age at which pathological changes can be found in this study would support the recommendation that third molars be removed early, possibly at the start of the third decade. (Stevens et al ^[32] , Huang et al ^[34] , Baykul at al ^[55] , Mesgardeh et al ^[47]).

(4) Gender distribution.

Overall, the majority of the patients in this study were females (1063 Females: 619 males).

The reason for this has not been investigated, but it is well known that female patients in general seek medical advice and intervention if needed earlier than male patients.

There were greater numbers of females patients with hyperplastic follicles, early dentigerous cysts, dentigerous cysts, and paradental cysts. However the proportions of males and females with each of the above pathologies were similar. No specific studies with regard to gender distribution were found in the literature.

(5) Position of tissue from third molar teeth.

Hyperplastic follicular tissue and early dentigerous cysts were found in all four third molar positions with a slight proponderance in the mandible (Positions 38 and 48) compared to the maxilla (positions 18 and 28). Dentigerous cysts were also found in all four third molar positions, but there was a significantly greater number in the mandible compared to the maxilla. Paradental cysts were found almost exclusively in the mandible (position 38 and 48 equally), with only a few cases in the maxilla (positions 18 and 28). No specific references in regard to tooth position could be found in the literature.

(6) The progression of hyperplastic follicular tissue to dentigerous cysts.

Findings of this study were that the peak incidence in the age distribution of hyperplastic follicular tissue was two years younger than that of early dentigerous cysts, which in turn were two years younger than that of dentigerous cysts. This observation supports the progression of hyperplastic follicular tissue to early dentigerous and then on to dentigerous cysts. This would also support the recommendation that third molar teeth be removed at an early age, in order to prevent the progression from hyperplastic follicular tissue to dentigerous cysts (Assael ^[24], Curran et al ^[26], NIH Consensus Development Conference for Third Molars ^[27], Blondeau et al ^[29]). Thus the early removal of third molars at the hyperplastic follicular stage would be associated with lesser morbidity.

(7) Pathology and the management of third molar teeth.

The management of third molar teeth remains controversial and to a large extent unresolved. The arguments both in favour of routine removal of all third molar teeth and in favour of relative removal are both convincing. It would therefore be helpful to see if the pathological findings reported in this study could be used in support or refute the recommended treatment options.

Approximately two-thirds (68.75%), of third molar teeth removed were found to have some pathological changes, including early dentigerous cysts, dentigerous cysts, paradental cysts and other lesions but excluding hyperplastic follicular tissue. If hyperplastic follicular tissue is added then the number is close to 100%, as only 0.3% was normal follicular tissue. One could appreciate that these teeth needed to be removed because of the pathology. Furthermore, pathology was probably a cause of the symptoms and therefore to relieve the symptoms one has to remove pathology.

(8) Importance of routine histological assessment.

It is generally not standard practice to send the tissue following third molar tooth removal for routine histological examination, but significant pathological lesions may be missed if they are not examined by an Oral Pathologist. In some of the literature the use of radiographs alone are not recommended and a histological diagnosis as well is recommended (Shear et al^[44], Farah et al^[46], deOliviera et al^[69], Fukuta et al^[72], Meric et al^[74], Saravana et al^[80]).

(9) Radiological assessment of cystic lesions.

The importance of differentiation between hyperplastic follicular tissue and dentigerous cysts was discussed by Shear et al ^[44] both radiologically and histologically. Their recommendation was that if a lesion around the crown of an impacted tooth was less than 3 – 4 mm then it was considered to be hyperplastic follicular tissue and a lesion bigger than this was a dentigerous cyst. Shear et al ^[44] stated that "trabeculations may be seen and may give the erroneous impression of multilocularity". Multilocularity of dentigerous cysts on radiographs may be due to extension of the cyst into adjacent marrow spaces. The radiological interpretation of follicles was discussed by Farah et al ^[66] and de Oliveira et al ^[69] and both concluded that there was little correlation between radiological and histological results. The interpretation of hyperplastic follicular tissue and the formation of subsequent cysts were also investigated by Fakuta et al ^[72], Shear et al ^[44], Meric et al ^[74] and Saravana et al ^[80]. All these authors suggested that there should be histological as well as radiological investigation of these lesions as purely radiological interpretation often leads to misdiagnosis.

CHAPTER 6

Conclusion.

This study took into account all histological reports from symptomatic third molars in a Private Maxillofacial and Oral Surgery Practice in Cape Town and not from institutions such as dental hospitals or general hospitals with dental departments.

The third molar data analysed in this study studied the development from the dental follicle to the formation of dentigerous cysts.

It also examined the formation of paradental cysts in the area and was used in addition to analyse the formation of other entities that have clinical significance in the third molar area. The analysis gave accurate details as to the age of the patients and when third molars should ideally be removed.

It showed the histological transformation from dental follicular tissue and hyperplastic follicular tissue to the formation of an early dentigerous cyst and then to a fully formed dentigerous cyst. Paradental cyst formation was also investigated as this formed a large percentage of the lesions found. This occurred predominantly in the late second and third decades and corroborates the statements of numerous authors that symptomatic third molars should be removed at an early age. However these papers do not state a definite age and this study shows this to be ideally before 24 years of age to minimise the risk of developing other pathoses later in life. This was correlated to clinical significance.

The third aim of the study was to try to analyse the conflicting opinions whether impacted third molars should be removed or not. After extensive review of the literature considering both points of view, one is left to conclude there is no definite answer to this age old question. Both the advocates for the removal of third molars and their retention have definite views on the subject and give quite strong arguments in their articles. This study has shown that symptomatic third molars have a large amount of pathological material associated and should be removed. It has also shown that dentigerous cysts form predominantly early in life. Removal of symptomatic third molars that are impacted at that stage seems wise, in order to prevent other possible pathoses developing later in life.

A further and important conclusion of this study is that it is necessary, if not mandatory, to submit all soft tissues removed with symptomatic impacted third molars to an Oral Pathologist for histological analysis. This is highlighted by the latest classifications of both cysts and tumours where the expertise of the Oral Pathologist can be utilised to the maximum so that the correct and definitive treatment can be given to the patient.

CHAPTER 7

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CHAPTER 8

ADDENDUM

PAPER 1

PRIMARY B CELL LYMPHOMA OF THE MANDIBLE.

University of Cape Town

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Author's names

Brian M Berezowski^{a, *}, Vincent M Phillips^b.

Contact information:

Dr B M Berezowski

Address: 8 Mount Pleasant Road, Newlands. Cape Town 7700

E-mail address: berezbc@mweb.co.za

Fax No. 27 21 6868052

Affiliations:

Dr Brian M Berezowski (main author)

Part time consultant Department of Maxillofacial and Oral Surgery University of the Western Cape and Private Practice ,Cape, South Africa.

Prof Vincent M Phillips (contributing author)

Department of Oral Pathology. Dental Faculty University of the Western Cape, South Africa

Corresponding author:

Corresponding author: Dr B M Berezowski

Address: 8 Mount Pleasant Road, Newlands. Cape Town 7700

E-mail address: berezbc@mweb.co.za

Fax No. 27 21 7977252

PRIMARY B – CELL LYMPHOMA OF THE MANDIBLE

Abstract

Primary lymphomas of the jaws are uncommon and only 2% of extra-nodal lymphomas arise in the oral region. A case of a primary B-cell lymphoma is reported that was associated with an impacted third molar in the mandible. A dentigerous cyst was associated with the impacted tooth. The neoplastic tissue was removed together with the molar tooth and diagnosed immunocytologically as a B-cell lymphoma. The patient was treated with radiotherapy and followed up for 17 years with no signs of recurrence.

Keywords: Lymphoma, mandible

Introduction

Lymphomas are malignant lesions of cells derived from lymphoid tissue.¹ Lymphoid proliferation is divided into Hodgkin's disease in which Reed Sternberg giant cells are present and non-Hodgkin's lymphoma that account for all other neoplastic lymphoid proliferations.¹ It has been determined that only 2% of extra nodal lymphomas arise primarily in the jaws or the oral cavity.^{1,2} Most lymphomas are exclusively of B-cell lineage (98%), with 58% of these sub-typed as diffuse large B-cell lymphomas.¹

Classification systems have been modified and changed throughout the years. In the 1990's the Working Formation of non Hodgkin's lymphomas was used for clinical evaluation and treatment

(Table 1).⁶ Prior to this the Kiel classification, updated in 1992, was used extensively especially in Europe.⁵ This was supplemented by the Anne-Arbor staging system (Table 2) which is currently used in clinics in Cape Town.⁶ The WHO Real Classification of non Hodgkin's lymphomas according to the clinical aggressiveness is also used (Table 3).^{1,2,8} Non Hodgkin's lymphomas have been reported in the oral soft tissues, but there have been few reported cases of primary lymphoma in the jaws^{1,7,9}. A case of a primary B-cell lymphoma of the mandible is reported in an adult female with a 17 year non-recurrence follow up.

Case Report

A 27 year old female was referred to a Maxillofacial and Oral Surgeon in April 1992 for the removal of her wisdom teeth. She had no systemic symptoms; however, she reported a numb feeling over the whole of her mouth in the recent past which had recovered. Her past medical history indicated that she had a heart murmur which was insignificant and she did not take prophylactic antibiotics. Her general health was good. She had past operations with no general anaesthetic problems. She did have low blood pressure and was anaemic. Extra-oral examination of the head and neck revealed that there was lymphadenopathy of the submandibular group of lymph nodes on the right side. Her temporo-mandibular joint functioned well and there were no cranial nerve problems. Intra oral examination showed limited space for the wisdom teeth. Apart from slight crowding, she was in Class 1 bite on both sides. Her tongue function was normal, her glossopharyngeal and vagal nerve function were normal and the mucosae intact. The orthopantomograph showed that the 38 tooth had a mesio-angular inclination and was close to the inferior alveolar nerve (Figure.1). The 48 tooth had a disto-angular inclination in the ramus of the mandible and showed some radiolucency around its crown in the distal aspect (Figure.2). Its root was also near the inferior alveolar nerve. It was

decided that both lower wisdom teeth should be removed under general anaesthetic. The intra-bony soft tissue distal to the crown of the 48 was removed and placed in 10% formalin solution and sent for histological examination. The patient was given the normal post operation regime of antibiotics, analgesics and a mouth rinse. She was examined again one week later at which time the pathology report was discussed with her.

Pathology Report

The tissue received from the right mandibular third molar region (tooth 48) was reviewed by an Oral Pathologist. The specimen consisted of a molar tooth with soft tissue attached to the amelo-cemental junction. There was also a separate mass of soft rubbery tissue measuring 25 x 20 x 15 mm in size. The soft tissues were sectioned and those associated with the crown of the tooth were processed separately from the other soft tissue mass. Microscopic examination of the tissues from around the crown of the tooth showed features in keeping with that of a dentigerous cyst. The histological picture of the other mass of soft tissue showed a mass of lymphoid tissue containing numerous diffuse areas of lymphocytes with no germinal centre formation. The lymphocytic population showed numerous immunoblasts with prominent nucleoli (Figure. 3). Numerous mitotic figures were also evident in the lymphoid tissue.

The immunocytochemistry staining of these tissues at this stage consisted of B-cell and T-cell markers: L26-positive, UCHL1-positive, MB2-positive, CD21-negative and CD3-negative. This therefore indicated that the lymphoid tissue was reactive; containing both B- and T-cells, and a mixed cell lymphoma was present. An initial diagnosis of dentigerous cyst and mixed cell lymphoma was made.

Due to the nature of the lymphoid tissue and the extra nodal location of the tissue within the bone, it was decided that a lymph node from the submandibular area be removed to establish whether there was a neoplastic change in other lymph nodes.

A right submandibular lymph node was subsequently removed and measured 12mm in cross section. The surgeon reported that there was no sign of lymphadenopathy in the area of the operation, either in the submandibular or of the deep cervical group of lymph nodes. The histological picture of the submandibular node showed scattered germinal centres with reactive follicles in the cortical area and sinus histiocytosis of the medulla. There were no signs of any granulomatous inflammation and no evidence of malignancy. The lymph node therefore showed reactive changes probably as a result of the recent wisdom tooth removal.

The histological sections together with the processed tissue was referred and reviewed by another pathologist in the lymphoma clinic. She reported that the atypical lymphoid follicles had poorly formed mantles, showed no polarization and contained predominantly large non-cleaved cells which spilled out from the follicles into the inter-follicular areas where they infiltrated the fat and blood vessel walls. There was no evidence of epithelial structures associated with these lymphoid aggregates and the infiltrating cells were predominantly intermediate to large in size and showed plasmacytoid differentiation. The immunophenotypic staining profile of the large cells was interpreted as follows: L26-positive; LCA-positive; L26-positive; MB2-positive; T (UCHL)1-negative; CD21-negative; BerH2-negative; CD3-negative; CAM 5,2- negative. This profile was in keeping with a B-cell lineage. Immunohistochemical staining for immunoglobulins showed Lambda light chain restriction with expression of IgM heavy chain. In view of the morphological features and the demonstration of light chain restriction a diagnosis of Non-Hodgkin's malignant lymphoma was made with centroblastic and centrocytic features consisting of follicular large cells which were becoming diffuse and of intermediate grade (Category D of the Working Formulation).

The opinion of the oncologist at the lymphoma clinic was that the patient should be treated with radical radiotherapy in the area of the neoplasm to reduce possible mobility from the original lymphoma. She received 36Gy to the right mandible in the area of the lesion. Treatment was completed in 1992 and she was discharged from the lymphoma clinic in 2000. The patient returned at regular intervals to the original maxillofacial surgeon for monitoring. Clinical examinations and orthopantomographic radiographs up to 2009 showed no sign of recurrent disease.

Discussion

Lymphoma is the second most common neoplasm after carcinoma in the head and neck areas, but occurrence within the oral cavity is uncommon and within the jaws rare. This reported case, firstly diagnosed in 1992, was diagnosed and classified using the original Working Formulation (Table 1).⁶ This stated that it was a non-Hodgkin malignant lymphoma with a centroblastic and centrocytic growth pattern consisting of a follicular large cell lymphoma going onto intermediate grade. The lymphoma was placed into category D of the Working Formulation.

Today, using the Anne-Arbor staging system, this would be classified as stage IE.

The early diagnosis of this primary B-cell lymphoma and the subsequent radiotherapy was successful in eradicating this neoplasm. The long term follow up of this patient over 17 years was undertaken with subsequent orthopantomographs. There has been no recurrence of the neoplasm.

It is stressed that all tissue removed at operation by the Oral and Maxillo-Facial Surgeons should not be discarded, but sent for histological investigation by an Oral Pathologist. If the surgeon in this case discarded the tissue from the third molar area, thinking that it was probably hyperplastic follicular tissue, the diagnosis of a primary lymphoma would have been lost and possibly resulted in serious complications for the patient at a later stage.

Table 1: A working formulation of non-Hodgkin's lymphomas for clinical usage ¹

Low Grade
 Small lymphocytic
 Follicular, predominantly small cleaved cell
 Follicular, mixed small cleaved and large cell

Intermediate Grade
 Follicular, predominantly large cell
 Diffuse, small cleaved cell
 Diffuse, mixed small and large cell
 Diffuse, large cells

High-Grade
 Large cell immunoblastic
 Lymphoblastic
 Small non-cleaved cell

Miscellaneous

Table 2: Ann-Arbour staging system ⁶

Stage	Defining System
Stage I	Restricted to single lymph node region (I) or a single extranodal site (I-E)
Stage II	Two or more areas of nodal involvement on same side of the diaphragm (II) or one or more lymph nodes regions with an extranodal site (II-E)
Stage III	Lymphatic involvement on both sides of the diaphragm (III), possibly with an extranodal site (III-E), the spleen (III-S) or both (III-SE)
Stage IV	Liver, marrow, or other extensive extranodal disease
Sub stages	
Substage E	Localised, extranodal disease
Substage A	Absence of systemic signs
Substage B	Presence of unexplained weight loss ($\geq 10\%$ in 6 months) and or unexplained fever, and or night sweats

* The spleen is considered nodal.

Table 3: WHO REAL classification of non-Hodgkin's lymphomas according to clinical aggressiveness⁷

Indolent lymphomas

B-cell neoplasms

Small lymphocytic lymphoma B-cell chronic lymphocytic leukaemia
Lymphoplasmocytic lymphoma (\pm Waldenstroms macroglobulinaemia)
Plasma cell myeloma/plasmacytoma
Hairy cell leukaemia
Follicular lymphoma (grades 1 and 11)
Marginal zone B-cell lymphoma
Mantle cell lymphoma

T-cell neoplasms

T-cell large granular lymphocytic leukaemia
Mycosis fungoides
T-cell prolymphocytic leukaemia

Natural killer cell neoplasms

Natural killer cell large granular lymphocytic leukaemia

Aggressive lymphomas

Follicular lymphoma (grade 111)
Diffuse large B-cell lymphomas
Peripheral T-cell lymphomas
Anaplastic large cell lymphoma
T-null cells

Highly aggressive lymphomas

Burkitt's lymphoma
Precursor B lymphoblastic leukaemia/ lymphoma
Adult T-cell lymphoma/leukaemia
Precursor T lymphoblastic leukaemia/ lymphoma

Special group of localised indolent lymphomas

Extranodal marginal zone B-cell lymphoma of MALT type*
Primary cutaneous anaplastic large cell lymphoma

* MALT = mucosa-associated lymphoid tissue



Figure. 1. Pre-operative Pantomographic radiograph showing the impacted mandibular 3rd molars 38 and 48.

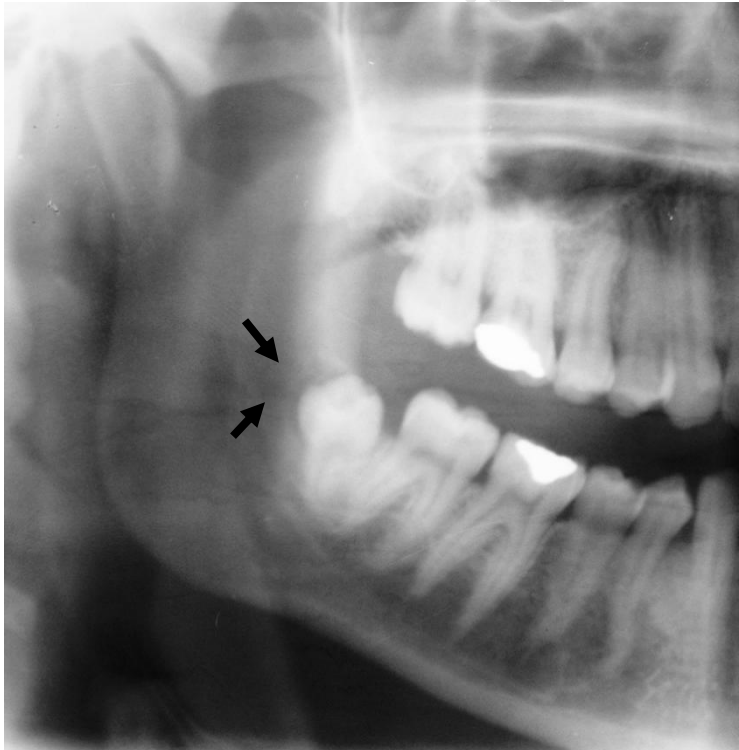


Figure. 2. The right Mandibular 3rd molar (48) with a Radio-lucent area distal to the crown (arrow)

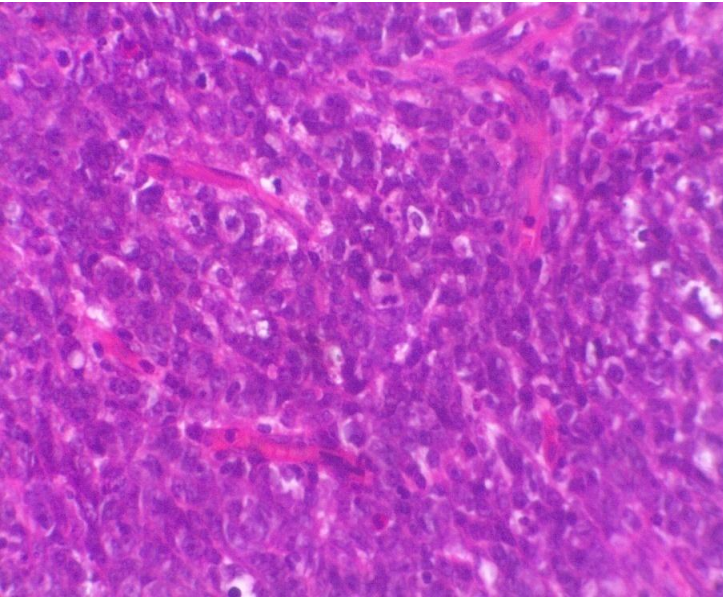


Figure. 3. The photomicrograph of the soft tissue adjacent to the right mandibular 3rd molar. The atypical lymphoid cells extend into blood vessel walls; numerous mitotic figures are visible. (Haematoxylin & Eosin X 400)

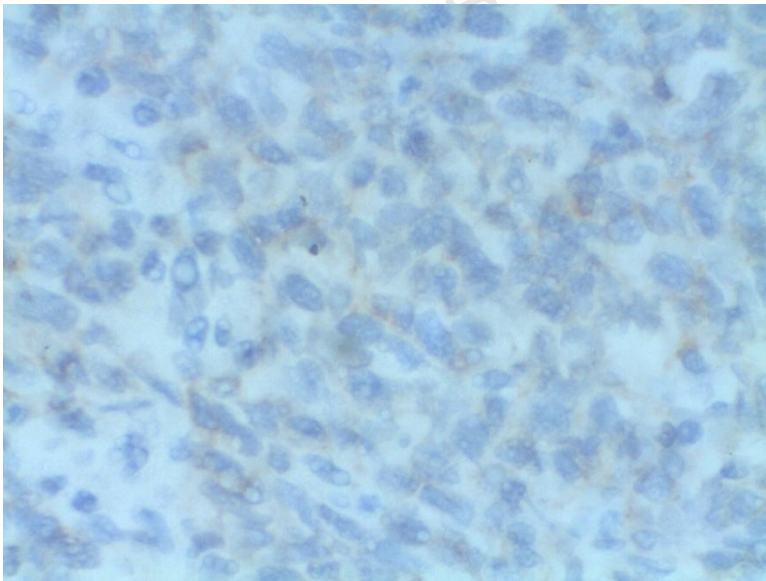


Figure. 4. Immunocytochemical staining for T (UCHL) 1 (T-cells) is negative (X 400)

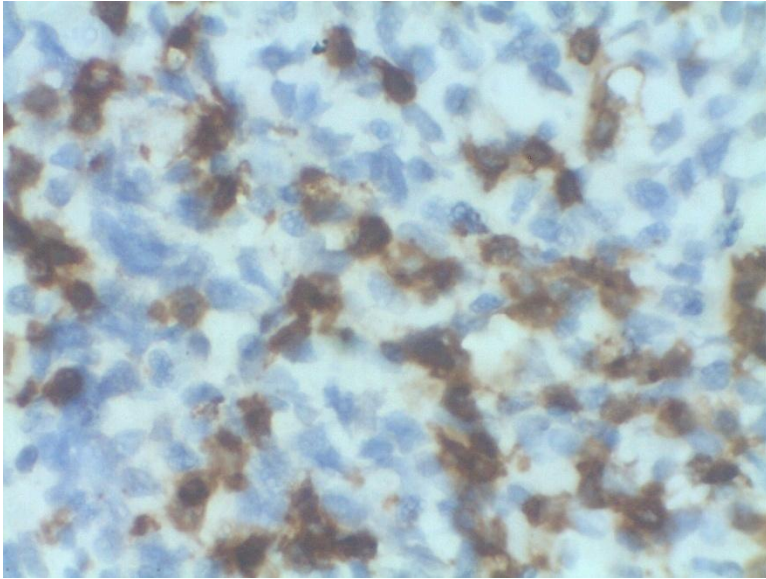


Figure. 5. Immunocytochemical staining for L26 (B-cells) is positive (X 400)

University of Cape Town

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