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Current practice in the management of peripheral ameloblastoma: a structured review

[1]A Anpalagan, [2]A Tzortzis, J Twigg, [3]R Wotherspoon, P Chengot and A Kanatas

1. Abbiramy Anpalagan, Medical Student, University of Leeds
   um17a2a@leeds.ac.uk
2. Andrianos Tzortzis, Medical student, University of Athens.
   andtzortzis@gmail.com
3. Joshua Twigg, BDS (hons), PhD, Dental Core Trainee / Academic Clinical Fellow, Leeds Teaching Hospitals and Leeds Dental Institute.
   denjtw@leeds.ac.uk
4. Robert Wotherspoon, BChD, MBChB, FRCS (OMFS). Specialist Registrar Leeds Teaching Hospitals and Dental Institute
   robert.wotherspoon@nhs.net
5. Preetha Chengot, BDS, MFDS RCPS, FRCPath. Consultant Oral and Maxillofacial Pathologist and Associate Professor, Leeds Teaching Hospitals and St James Institute of Oncology preetha.chengot@nhs.net
6. Professor Anastasios Kanatas, MFDSRCS, FRCS (OMFS), MD, PGC, FHEA. Consultant Surgeon / Professor, Leeds Teaching Hospitals and St James Institute of Oncology and Leeds Dental Institute.

   a.kanatas@doctors.org.uk

Address for correspondence: Anastasios Kanatas, BSc (Hons), BDS, MBChB (Hons), MFDSRCS, MRCSRCS, FRCS (OMFS), MD, PGC, FHEA. Consultant Surgeon / Professor, Leeds Teaching Hospitals and St James Institute of Oncology, Leeds Dental Institute and Leeds General Infirmary, LS1 3EX.
Tel: 00447956603118 e-mail: a.kanatas@doctors.org.uk

Key words: Head and neck cancer, donor site morbidity, reconstruction, free tissue transfer

Abstract

Ameloblastoma is the most common benign, but locally destructive, epithelial odontogenic tumour. Peripheral ameloblastoma (PA) may involve soft tissues without invasion or involvement of bone. The aim of this review is to evaluate the literature on the optimal management of PA.

Three online databases were search for relevant studies and included Medline, EMBASE, Ovid Evidence Based Medicine. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for this structured review.

Forty-four papers were included. The majority were case reports with a limited number of case series and review articles. Conservative surgical excision was the treatment of choice. One study evaluated radiotherapy as primary treatment of peripheral ameloblastoma, with increased recurrence rates noted, compared to surgical management. There is no consensus in relation to the extend of the surgical margins required. Few studies report specific excision margin dimensions and follow-up protocols, with no rationale for such decisions. Further studies are required which include long term follow up to assess recurrence rates, to allow comparison of management options.

The management of soft tissue recurrent ameloblastoma appears to generally favour conservative excision with narrow margins of normal tissue. Follow up of at least 10 years is recommended to monitor for recurrence.

Introduction

Ameloblastomas account for 1% of all oral tumors and 11 % of odontogenic tumors (Bertossi et al. 2014). The majority of patients first present between 30-40 yrs, although individuals of African descent often present at an earlier age. Ameloblastomas have been reported to be more prevalent in Asian or Afro-Caribbean individuals (Reichart et al. 1995). The same report found an approximately 1:1 ratio of incidence between genders. While ameloblastomas rarely exhibit malignant change, locoregional recurrence of such lesions is a major clinical challenge and may occur many years after surgical intervention to excise the lesion (Philipsen et al. 2001).

Ameloblastomas can be classified according to histological features. According to the most recent World Health Organisation classification system (El-Naggar et al. 2017), there are four types of ameloblastoma: conventional (solid/multicystic), unicystic, metastasizing and peripheral (extraosseous). Peripheral ameloblastomas (PAs) are a rare subtype, comprising only 1-5% of all ameloblastomas (Goda et al. 2015). PAs feature more benign behavior than other ameloblastomas, with minimal bone involvement. This makes diagnosis of the peripheral subtype an important finding, as treatment may consequently be much more conservative in nature. Peripheral ameloblastomas occur primarily in the mandible (70.9% vs. 29.1% in the maxilla) (On et al. 2019). They most frequently present in the gingival tissues (Goda et al. 2015). Potential sources of PAs include odontogenic remnants of vestibular lamina, pluripotent cells in the basal cell layer of the mucosal epithelium and pluripotent cells of minor salivary glands (Yamanishi et al. 2007). PAs tend to present later than most ameloblastomas, with the maximum incidence reported to be in the sixth decade of life (Bertossi et al. 2014). This may indicate that PAs are genuine neoplasms rather than embryologic hamartomas (On et al. 2019). In contrast to other ameloblastomas, the lesion is more common in males with a male to female ratio of 1.9:1 (On et al. 2019).

The most common presentation of peripheral ameloblastoma is a painless and gradually growing mass (Zhang et al. 2018). Typically, such lesions are noted as an incidental finding during routine dental examination or in radiographs (McClary et al. 2015). The deep margin of PAs does not tend to invade bone extensively but may be seen to result in a scalloped lesion radiographically. Consequently, 3-dimensional imaging modalities such as CT or MRI are useful to accurately demarcate the lesions (Zhang et al. 2018). Despite this fairly characteristic appearance, formal diagnosis requires histological examination (Pictures 1 and 2) to exclude other peripheral odontogenic tumours (Manor et al. 2004).

The historical rationale for management of peripheral ameloblastomas has been increasingly challenged in recent years. In many cases, the traditional approach using extensive resection is increasingly avoided in favour of more conservative techniques in current practice. However,

due to its rarity, there is no strong consensus on the management of PAs. Although PAs are less aggressive than other ameloblastoma types, excision using a local conservative approach (Borrello et al. 2016), or more extensive resective treatment (Yanamoto et al. 2005) have both been advocated. There is a dearth of high quality, robust research evaluating the outcomes of either approach in this rare form of ameloblastoma. The aim of this review is to evaluate the available evidence and determine best practice in the management of peripheral ameloblastoma.

Materials and Methods

We searched three online databases: Medline, EMBASE, Ovid Evidence Based Medicine for relevant studies. Library staff at both Leeds and Athens assisted with the formulation of search strategies. Search terms used included 'peripheral ameloblastoma', OR 'peripheral ameloblastoma' OR 'extraosseous ameloblastoma'; AND (ameloblastoma management OR ameloblastoma treatment OR ameloblastoma outcomes). Studies were included if they were conducted on adult human subjects, available in full text and written in English language. Review articles were included if the focus of the review was recurrent ameloblastoma. Studies were excluded if they focussed on paediatric populations, conference abstracts, opinion papers, or not available in English. The research team comprised six authors. Literature searches and abstract screening were conducted independently by four individuals (AA, AT, JT, RW). Each paper examined was classified as included, excluded, or 'unsure' if the information from the title and abstract was insufficient to decide. Where the abstract was insufficient, the full-text was requested and reviewed by PJ and AK. When there were disagreements regarding whether a paper should be included or excluded papers, the two senior author adjudicated to achieve consensus. After de-duplication of results, information was inputed into a preformulated data collection form in Excel and collated data used to perform the descriptive analysis. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for this structured review **(reference).**

Results

A total of 520 papers were identified initially. We included 44 papers, most of which were case report studies (Table 1). Surgical excision was the treatment of choice in many studies. This ranged from conservative supra-periosteal resection to en-bloc bony resection. One study utilised primary radiotherapy as first-line treatment (Atkinson et al. 1984). The overall recurrence rate ranged from 9 (Buchner and Sciubba 1987) - 20% (Philipsen et al. 2001) for supra-periosteal excision. Recurrence was more frequent (30%) in the one study utilising primary radiotherapy (Atkinson et al. 1984). Recurrence presentation time was noted to vary

from 2months to 7years with the quicker recurrences considered more likely to be related to incomplete excision. No studies evaluated the benefit of larger resection margins on recurrence rates as numbers of lesions treated in this way appear low. Follow-up duration was highly variable, ranging from a few months to 10y, with most presented cases discharging around 2y.

Discussion

Primary treatment of ameloblastoma is a current area of controversy. It has historically been based on the aggressiveness and recurrence potential of each subtype. The use of extensive surgical resection has been challenged in recent years with a transition to a more conservative algorithm (Kamil 2015). In addition, the choice of treatment depends not only on the histopathological features seen in biopsy samples, but also on the tumour location, size of the lesion, age of the patient, and presumed adherence of the patient to long-term follow up appointments (Borrello et al. 2016). Alternative management strategies including segmental resection (Califano et al. 1996) and enucleation (Cadavid et al. 2019) have been advocated in appropriate clinical situations. Management of ameloblastoma recurrence in both hard and soft tissues is a significant clinical challenge. Intraosseous recurrences are most frequently managed with further surgical resection, which may be conservative or radical. PAs, although rare, harbor a high potential for recurrence, although this is less frequent than intraosseous ameloblastomas (Bertossi et al. 2014). Tumour depth, local invasion and marginal boundaries are challenging to accurately assess clinically or radiographically. The decision to include healthy surrounding tissue in the margin is guided partly by tumour location (e.g. proximity to important anatomical structures) and patient factors. Peripheral ameloblastoma must be differentiated clinically and histologically from alternate pathologies including squamous cell carcinomas and pyogenic granulomas. It is also of importance to distinguish histologically between PA and intraosseous ameloblastoma; the latter distinguished by penetration through the jaw bone and invasion of the mucosal connective tissue (Patrikiou et al. 1983). A clear diagnosis of isolated PA must be achieved to establish the optimal treatment modality.

To date, there are no interventional trials evaluating different management options for PAs. This is unsurprising given the low prevalence of the lesions. Retrospective observational studies and case reports make up the available data. The variability of duration and frequency of follow up renders accurate assessment of recurrence rates unreliable.

On review of the current literature we recommend management of PAs as follows:

1) Primary surgical excision of PA and any recurrent lesions. This should involve the lesion in entirety down to periosteum, including 5 mm of normal tissue, generally without the removal of teeth.

2) Long term follow-up (at least 10 y) of both primary and recurrent lesions.

3) Where surgical excision of PA is not possible, for instance due to close proximity to important anatomical structures or medical comorbidities which preclude surgery, radiotherapy should be considered as a primary treatment modality.

Long-term follow up is standard as part of primary amelobalstoma management. Following initial surgical management of intraosseous ameloblastomas, potential for recurrence remains high. Late recurrences, up to 10 y, have been noted necessitating a long term periodic follow up protocol. The high variability in time to recurrence of PA points to the necessity of long-term review. Recurrence may be a true feature of the disease or a manifestation of incomplete excision but may take many months or years to become clinically apparent. Regardless of the aetiology of recurrent lesions, repeat surgery comprises the best modality where possible. (Gardner 1977; El-Mofty et al. 1991). Although infrequent, the possibility of recurrences associated with, or progressing to dysplasia and malignancy cannot be overlooked (Martelli-Júnior et al. 2005). This information should form part of the patient counselling and the importance for close, long-term surveillance. Although the role of radiation therapy in the treatment of ameloblastomas has been investigated, the low incidence and non-aggressive behaviour of PA, coupled with the potential for malignant transformation as a result of radiotherapy render this treatment option unfavourable. In certain cases where complete surgical excision would be technically difficult because of bulk and/or local invasion, or where other medical factors, would make surgery impossible, radiotherapy could be considered as a primary modality. It is not believed that ameloblastoma is an inherently radioresistant tumour (Atkinson et al. 1985).

Peripheral ameloblastoma is a rare but clinically significant diagnosis to consider for exophytic gingival lesions. This lesion features limited, if any, bone invasion, but may carry a high risk of recurrence following excision. While there is insufficient evidence to either support or refute particular techniques in the management of peripheral ameloblastoma, we recommend complete surgical excision. However, in contrast to intraosseous ameloblastomas, where a 15 mm margin of normal tissue is frequently advocated, a more conservative approach can be employed. Significant bone resection or the removal of teeth is rarely necessary and should be avoided where possible to reduce surgical morbidity. Long term follow-up is critical both to monitor for recurrence and potential malignancy. Further research is required to gain insight into the pathophysiology and epidemiology of PA, and to inform contemporary management.

Conflict of interest: The authors have no conflict of interest to report

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Figure 1: PRISMA statement for included/excluded studies (Moher et al. 2009)

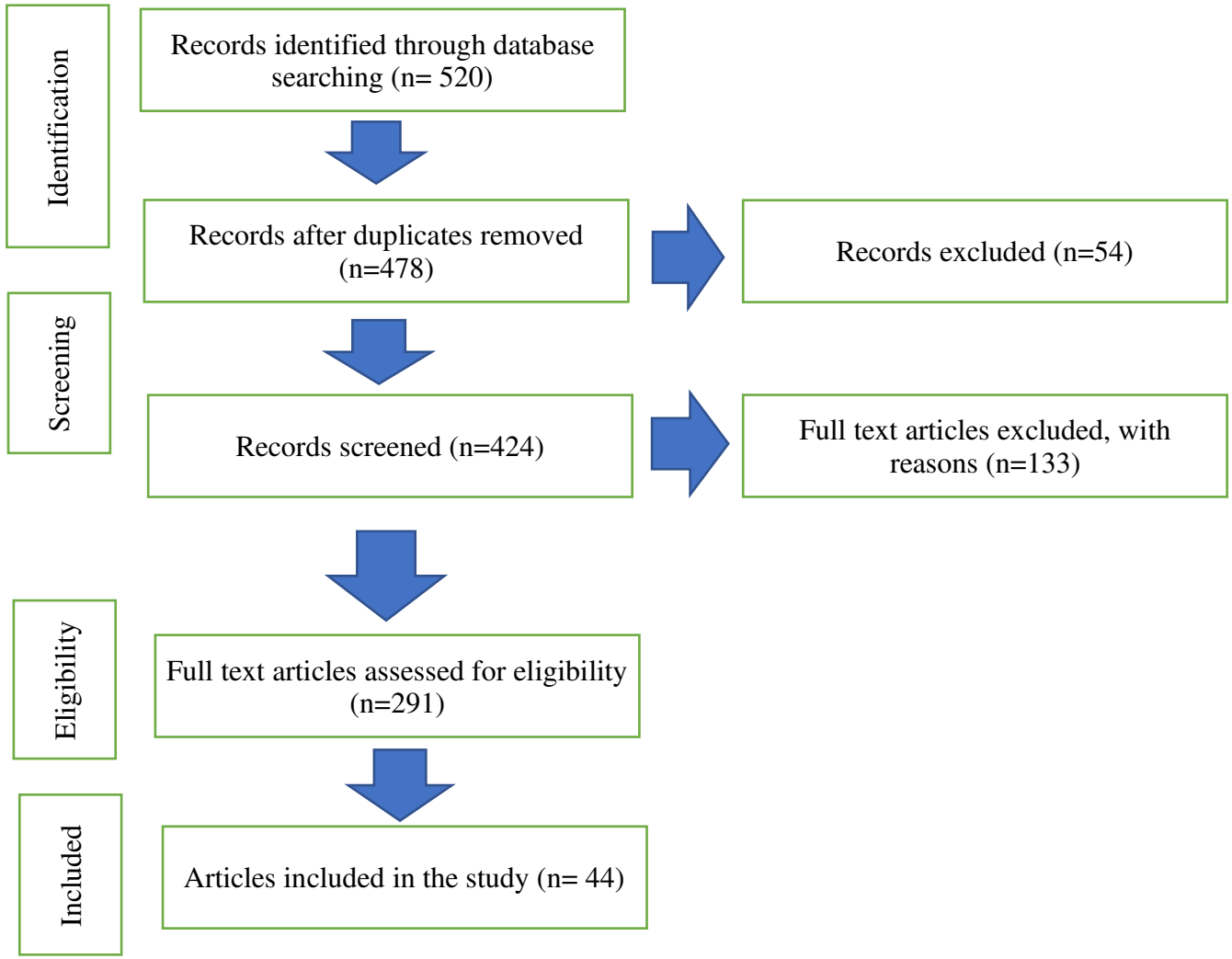


Table 1: Details of the papers included in this study

Authors	Type of study	No. of patients	Follow up	Outcome	Treatment	Recurrence
Atkinson et al. 1984	Case report	10	Not reported	Not reported	Megavoltage radiotherapy (4500 rads in 4 weeks); 3 cases received adjuvant surgery	1
Baden et al. 1993	Case report	1	5 y	Not reported	Excision	2 ameloblastic carcinomas originating from site of primary lesion
Beena et al. 2012	Case report	1	Not reported	Not reported	Excisional biopsy of soft tissue lesion only	Not reported
Bertossi et al. 2014	Case report	1	2 y	Discharged	Resection of lesion with surrounding bone, extraction of the second molar, flap for closure	No
Bhat et al. 2014	Case report	1	1 y	Discharged	Excised with a 5 mm margin using diathermy under general anesthesia	No

Borrello et al. 2016	Case report	1	1 y	Discharged	Excisional biopsy (2 lesions)	No
Braunstein 1949	Case report	1	4 m	Discharged	Excision of soft tissue lesion only (blunt dissection)	No
Buchner et al. 2006	Case series	13	Not reported	Not reported	Excision (initially incomplete in 4 cases but repeat excision performed)	1 peripheral ameloblastic carcinoma from recurrent lesion
Cadavid et al. 2019	Case report	2	10 y	Discharged	Treated conservatively with enucleation plus curettage or cryotherapy	No
Califano et al. 1996	Case report	1	12 m	Discharged	Surgical resection of the left maxilla with excision of the bone surrounding the tumour	No
Curtis et al. 2006	Case report	1	3 y	Discharged	Resection of the lesion, buccal pad of fat and a mucosal flap for reconstruction	No
El-Mofty et al. 1991	Retrospective case review	11	Long term follow up recommended	Not reported	Excision of the lesion down to the periosteum with small amount of normal tissue	1 (further details not specified)

Ficarra and Hansen 1987	Case report	1	5 y	Discharged	Excision	No
Gardner 1977	Case study	21	11 m - 5 y (8 cases) No follow up information available (9 cases) 4 cases with recurrence or complications , no follow up duration documented	Discharged	Excision (13 cases), electrocautery, extraction of teeth, removal of small amounts of bone, wide resection of the mandible with retention of the inferior border (1 case)	Minor local recurrences (3 cases). Fistulous tract leading to the maxillary sinus. (1 case)
Gardner et al. 1980	Review	-	-	-	Excision with a small margin of normal tissue down to the periosteum, but no removal of bone or teeth necessary	Periodic follow up recommended but duration unspecified
Goda et al. 2015	Case report	1	2.5 y	Discharged	Complete surgical excision by intraoral approach (blunt dissection)	No

Gomes et al. 2007	Case report	1	9m	Discharged	Excisional biopsy	No
Gurol and Burkes 1995	Case report	8	3 cases with no follow up reported, 2 cases- 6 m, 1 case-2 y, 1 case-9 y, 1 case-10 y	Discharged	Complete excision through the periosteum without removing bone or teeth	No
Hernandez et al. 1992	Case report	1	2 y	Not reported	Excision down to level of bone (2 lesions)	1 recurrence at site of primary lesion
Ide et al. 2009	Case report	1	1 y	Discharged	Excision	No
Kamil 2015	Systematic review		-	-	Conservative excision with a margin of normal tissue	9-20%
Kandagal et al. 2016	Case report	1	2 y	Discharged	Complete surgical excision of soft tissue lesion only	No

Klinar et al. 1969	Case report	1	2-3-5 m	Discharged	Surgical excision by extraoral approach, wide margins	No
Lascane et al. 2014	Case report	1	1 y	Discharged	Excisional biopsy under local anaesthesia	No
LeCorn et al. 2006	Case report	1	4 m	Discharged	Excision under local anaesthesia	No
Lopez-Jornet et al. 2005	Case report	1	2 y	Discharged	Excisional biopsy with curettage of the affected mandibular bone	No
Martelli-Júnior et al. 2005	Case report	1	1y	Discharged	Excision with narrow margin including underlying periosteum under local anaesthesia	No
Marucci et al. 2004	Case report	1	Not reported	Not reported	Radical surgical excision	Not reported

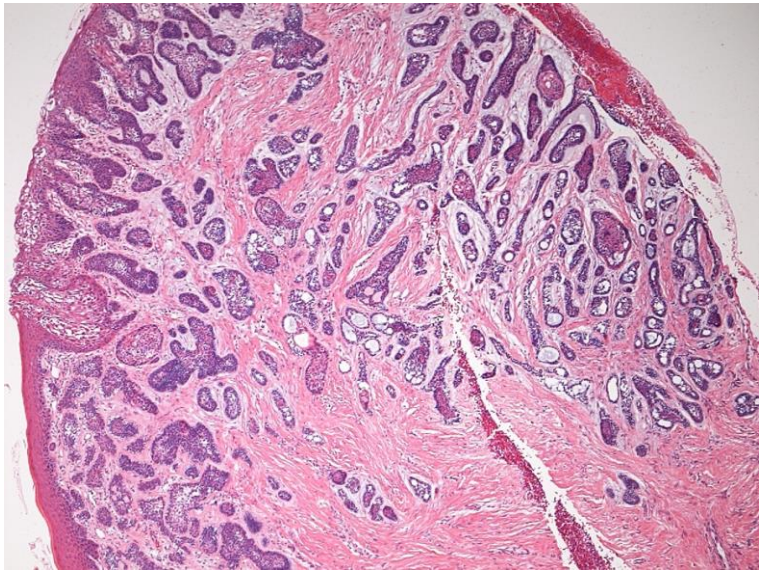
McClary et al. 2015	Review	-	-	-	Excision with 1 cm soft tissue margins and a cuff of the uninvolved alveolar bone (marginal mandibulectomy) to ensure a proper deep margin	-
Nauta et al. 1992	Case report	1	1 y	Lost to follow up	Excision	No
Nurkic et al. 2018	Case report	1	Not reported	Not reported	Complete surgical excision	Not reported
On et al. 2019	Case report	1	Not reported	Disturbance of lingual nerve, recovered within 2 m, no other complication after the surgery	Excisional biopsy of the lesion after the 5 cm incision and dissection of lateral wall of oropharynx by intraoral approach under general anaesthesia	Not reported
Patrikiou et al. 1983	Case report	1	8 m	Discharged	Excision under general anaesthesia with curettage of underlying bone	No

Philipsen et al. 2001	Review	160	-	-	Conservative supraperiosteal surgical excision with a margin of normal tissue	16-19%
Pogrel et al. 2009	Review	-	-	-	Local excision only	-
Schaberg 1985	Case report	1	3.5 y	Discharged	Excision with small margin of normal tissue, subsequent re-excision with larger margin of normal tissue	No recurrence but incomplete excision noted on histology report
Shetty et al. 2018	Review	-	-	-	Conservative approach with supraperiosteal incision	-
Vanoven et al. 2008	Case report	1	Not reported	Not reported	En bloc resection of the maxilla and lateral nasal wall up to the level of the middle turbinate through a standard left lateral rhinotomy with lip split incision; split-thickness skin graft harvested from the anterior thigh	Not reported

Wettan et al. 2001	Case report	1	3 y	Not reported	Excision	2 recurrences with evidence of dysplastic change
Woo et al. 1987	Case report	1	9 m	Discharged	Excision by intraoral approach	No
Yamanishi et al. 2007	Case report	1	7 m	Discharged	Complete surgical excision by intraoral approach (blunt dissection)	No
Yanamoto et al. 2005	Case report	1	15 y	Discharged	En bloc excision together with the maxillary canine and underlying alveolar bone, under local anaesthesia; layer of exposed bone surface shaved with a round bur	No

Zhang et al. 2018	Case series	25	3 to 180 m (mean of 61 m).	Discharged	Complete surgical removal of the lesions small lesions - conservative supra periosteal surgical excision with adequate disease-free margins. Partial bone resection if cuplike or saucerized bone involvement was detected during the operation	1 recurrence speculated to be due to incomplete removal of primary lesion
Zhu et al. 1995	Case report	1	3 y	Discharged	Excision including overlying gingiva and thin lingual alveolar bone.	No

Picture 1: x5(Low power) histologic picture of PA



Picture 2: x20(High power) histologic picture of PA