An evidence based surgical algorithm for management of Odontogenic keratocyst

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Abstract

The effective management of odontogenic keratocyst (OKC) remains a subject of interest and confusion in the Oral and Maxillofacial surgery literature. Currently, there is a lack of consensus regarding the most appropriate treatment for patients with odontogenic keratocyst. Of the various treatment options available, no modality to date has been shown to demonstrate a zero-or near zero recurrence rates except wide resection with clear margins. With the prevailing dearth of evidence based surgical protocols for the management of patients with odontogenic keratocyst in the literature, this study aims to present a surgical algorithm, based on meta-analysis results, that hopefully will be beneficial in enhancing treatment of patients with this condition. Using parameters of; size, lesion type (primary or secondary), syndromic or solitary nature of the lesion, presence of cortical perforations, and locularity; we present a decision tree, to aid treatment planning and help attain the least chance of recurrence in the management of the odontogenic keratocyst.

Introduction

The Odontogenic keratocyst (OKC) (previously known as keratocystic odontogenic tumor) has remained a subject of interest in the Oral and Maxillofacial Surgery/Pathology specialties. Being one of the frequently disputed and categorized lesions, there has been a great deal of confusion as to whether to label it a cyst or a cystic neoplasm. The most recent World Health Organization (WHO) classification of Head and Neck tumors in 2017 has advised that as per not enough evidence exists to support a neoplastic origin for keratocystic odontogenic tumor and in view of the absence of further reviews, this condition be reinstated to being termed a keratinising cyst. In addition, the new classification documents the orthokeratinised histological variant as a separate entity, now referred to as orthokeratinised odontogenic cyst (OOC) [1]. The “ideal” treatment of OKC remains controversial for both surgeons and pathologists [2]. To date, there appears to be no consensus of opinion as to the most appropriate treatment for OKCs to minimize the recurrence rate. Certain factors influence the choice of appropriate treatment options and these vary with individual surgeons and in a variety of circumstances. They include, but are not limited to, patient’s general health status, age, size and location of the cyst, soft tissue involvement, cortical perforations, reliability for follow-up, lesion type (primary or secondary), and presence of an associated syndrome, for example, basal cell nevus syndrome [3–8].

According to a meta-analysis of 33 studies by Al-Moraissi et al [9] in 2017, enucleation with application of Carnoy’s solution, enucleation with cryotherapy and marsupialization followed by residual cystectomy were reported to have the lowest recurrence rates when compared to enucleation or marsupialization alone. On the other hand, an earlier meta-analysis of 14 studies indicated that initial cystectomy with or without adjuvant therapy (Carnoy’s solution, peripheral ostectomy, and cryotherapy in isolation or combination) has the least chance of recurrence when compared to marsupialization with or without secondary cystectomy [10]. A third systematic review with meta-analysis suggested that in addition to cyst enucleation (when indicated), excision of the overlying attached mucosa is mandatory to eliminate clusters of epithelial lining and micro-cysts [11]. Adjunctive application of chemical fixatives to reduce the

recurrence rate after enucleation of OKC is an age long practice. The use of Carnoy's solution, shown to decrease OKC's recurrence rate after enucleation, was discontinued because of chloroform's carcinogenicity, and replaced with modified Carnoy's Solution omitting the chloroform[12, 13]. The original Carnoy's solution is presently no longer available in the United States and some other countries because the FDA has prohibited its use since 2008. Another chemical fixative (Liquid nitrogen) applied after enucleation of the lesion resulted in recurrence rates of 11.5%, [14] similar to that reported with Carnoy's solution itself [15, 16]. The use of modified Carnoy's solution on the other hand has been associated with markedly higher recurrence rates than with the original Carnoy's Solution. [17] Aside from recurrence, peripheral nerve injury estimated at 18.2% [16] following direct application of the solution onto the nerve with the 3-minute protocol defined by Frerich et al [18] has also been reported with the use of Carnoy's solution.

More recently, a targeted approach to the treatment of OKC based on the current understanding of the molecular genetics of OKCs and its similarities to basal cell carcinoma (BCC), has been proposed [19, 20]. Rui et al [21] reported that smoothened (SMO) gene alterations are likely to play an important role in the development of OKC, thereby suggesting that sonic hedgehog (SHH) signaling pathway antagonism might be an efficient way to molecularly target OKCs through SMO inhibition and suppression of SHH transcription factors. [22] Orally administered Vismodegib (an SHH inhibitor), could help decrease the number and morbidity of multiple BCCs and OKCs (previously keratocystic ondontogenic tumors) in patients with nevoid basal cell carcinoma syndrome (NBCCS). [23] Also, the antimetabolite drug, 5-fluorouracil (5-FU), which was shown to induce apoptosis by inhibiting SHH in hepatocellular carcinoma cells [24] has been applied in the treatment of malignant diseases, including topical application to treat superficial BCCs. [25]

Owing to its molecular etiopathogenesis similarities with BCC, 5-FU has been applied in the adjunctive treatment of OKC, leading to a conclusion that 5-FU effectively treats OKC with less postoperative morbidity than conventional treatment. Topical 5-FU was then tagged a novel therapy for OKC which provides a targeted molecular approach to treatment. [26]. Thus, based on the aforementioned meta-analyses, we propose a surgical algorithm for management of patients with OKCs.

Materials And Methods

This study was conducted according to the PRISMA guidelines for meta-analyses studies [27].

Search strategies:

We performed an electronic literature search using the terms "odontogenic keratocyst treatment/management" and "keratocystic odontogenic tumor treatment/management" to identify articles published on management of odontogenic keratocyst and erstwhile keratocystic odontogenic tumor with various surgical modalities between 1970 and 2018.

Inclusion and Exclusion criteria

The management modalities considered included; enucleation alone, enucleation with curettage, enucleation with adjunctive therapy (Carnoy's solution (with or without chloroform), 5-FU, cryotherapy, and peripheral ostectomy), marsupialization or decompression with or without secondary cystectomy/adjunctive therapy, and resection with regard to recurrence rate at an adequate follow-up period (for at least 1 year). The choice of one year was predicated on the pattern reported commonly in the literature.

All clinical studies (either prospective or retrospective and case series) that assessed and compared the various surgical management modalities (stated above) for management of OKCs were included. We found a total of 41 studies and 3 systematic reviews with meta-analysis. For this review, the orthokeranitised odontogenic cyst was considered a separate entity in accordance with WHO's latest classification [1].

Study selection

The electronic search was conducted on MEDLINE, Embase and Cochrane Central library using "PICOS" criteria (population, intervention, comparisons, outcomes and study design) as shown in online supplementary File 1.

Three of the authors; EA, FO and OO went through the identified studies to ensure they met the inclusion criteria.

Data extraction

For the selected studies; one of the authors (FO) pulled out necessary information using a personally designed form. Parameters entered included; authors' name, year of publication, study design, number of patients, number of lesions, demographic information, surgical treatment given, follow-up period and recurrence rate. The other authors reviewed this information and they were entered into different tables as online supplementary File 2.

Results

The results derived from 41 studies including 3 systematic reviews and meta-analyses [6, 8, 9] are summarized and presented using a narrative structure/framework. Since majority of the studies included in this analysis are retrospective, we acknowledge that a low level of evidence is derived from such studies and that constitute an unavoidable limitation of this work. The proposed surgical algorithm includes diagnosis and treatments of OKCs (Figs. 1, 2 and 3).

Pathogenesis

The pathologists have been encumbered with the task of confirming OKCs alleged nature in order to appropriately label it and this informed the choice of treatment modality that will result in low prospect of

recurrence. The surgeons, in addition, have explored various treatment modalities in a bid to discover the most suitable approach to preventing its persistently high recurrence rate [2].

The neoplastic nature of OKC was largely attributed to both its association with patched (PTCH) gene alterations and its destructive growth pattern. The PTCH gene which is a tumor suppressor gene is an important molecule in the SHH signaling pathway as it normally forms a receptor complex with the oncogene SMO [28–32]. The binding of SHH to PTCH releases the inhibition of growth signal transduction seen in PTCH binding to SMO. Mutation in PTCH gene mapped to chromosome 9 q22.3–q31 ultimately results in its inactivity and an eventual exaggeration of the proliferating–stimulating effect of SMO [33]. Despite the fact that loss of heterozygosity (LOH) in the 9q22.3 region, a presumed tumorigenic feature, has been documented in most cases of OKCs studied, these changes are non-specific because some other odontogenic cysts also have been reported to exhibit LOH in this region [34–38]. Furthermore, reports that OKC has been successfully treated by marsupialization with reduction in rate of recurrences has also augmented the argument for its reinstatement as a cyst [39, 40].

Clinical features

OKC is generally more common in males than females. The mandible is by far the more frequently affected site, with the angle-ramus region being the predominant site. The cyst has a wide age of distribution spanning the first to ninth decades of life but with a peak in the second and third decades [41].

OKC characteristically grows rapidly within the medullary cavity in an anteroposterior direction such that clinically obvious swelling of the jaw bones appears late [41]. Thus, patients are usually not symptomatic until the lesion grows to a large size to cause an obvious swelling. Other features of OKC include; pain (usually when infected), cystic content discharge and pathological fracture. Otherwise, early cases of this condition are discovered fortuitously with routine dental radiographs [1, 41].

Radiological studies

It is paramount to outline the preoperative diagnostic differences between OKC and other odontogenic cysts or the cystic subset of ameloblastoma as this definitely has an impact on subsequent treatment planning and definitive management. In other words, working around the effective differential diagnoses of cystic jaw conditions can help surgeons better plan their final treatment, which tends to differ according to lesion.

Radiographically, OKC may present with displacement of the roots of adjacent teeth but root resorption is not common. Some cases may be associated with an unerupted tooth, thus mimicking a dentigerous cyst [1, 41].

With the use of conventional radiograph and computerized tomography (CT), it is not possible to differentiate between ordinary odontogenic cysts and ameloblastoma. Besides this, radiographic presentation of OKC (unilocular or multilocular radiolucency) is often similar to those of other

odontogenic lesions such as; dentigerous cysts, calcifying odontogenic cysts, calcifying epithelial odontogenic tumors and cystic ameloblastomas [3–5, 7]. However, CT and magnetic resonance image (MRI) have been reported to aid accurate localization of OKCs particularly in the maxillary sinus and small crevices at the rim of the lesion [6–10]. In particular, conventional magnetic resonance imaging sequences (T1 and T2-weighted images) with or without fat suppressed or contrast enhanced (i.e. Gadolinium chelate) and MRI have the potential to differentiate these lesions [6–10]. OKCs present as heterogeneous signals intensity of cystic contents (non-enhancing lesions) with intermediate or high signal intensity on T1-weighted images, intermediate signal intensity on T2-weighted images and thin rim enhancement on contrast enhanced T1-weighted images lesion [6, 8–10]. Ameloblastoma on the other hand appears as low signals intensity on T1-wieghted images, high signals intensity on T2-wieghted images and relatively thick rim enhancement on contrast enhanced T1-weighted images. While odontogenic cysts present as homogeneous low signal intensity on T1-weighted images and homogeneous high signal intensity on T2-weighted images [9–10]. In addition, it has recently been reported that diffusion-weighted MRI may help to differentiate odontogenic cysts from odontogenic tumors using the measurement of Brownian motion of molecules technique in the attempt of tissue characterization [8, 11, 42–43]. Thus, estimation of apparent diffusion coefficient for non-enhancing lesions (cystic contents) can help to differentiate between OKCs and other odontogenic cysts. OKCs have been reported to have lower values of apparent diffusion coefficient of non-enhancing lesions when compared to ameloblastomas [11, 42–43].

Histopathology

Aspiration and analysis of cystic content to identify amount of total protein (which is usually less than 4g/100 mL), albumin, pre-albumin, and detection of epithelial squames may be used as a reliable preoperative diagnosis of OKC [44–46]. However, for non-expansile lesions where aspiration is relatively difficult to perform, incisional biopsy through an open technique will provide adequate tissue sample to obtain a definitive histologic diagnosis prior to undertaking treatment.

Pindborg and Hansen in 1962 were the first to propose necessary histological criteria for the diagnosis of OKC as; uniformly thin lining of stratified squamous epithelium devoid of rete ridges, above which is an equally thin parakeratinized surface layer, intracellular oedema present within a 4–8 celled spinous layer and a relatively thin fibrous connective tissue capsule that lacks inflammatory cells but may contain daughter cysts [47]. The friable and thin lining coupled with absence of rete ridges usually makes it easy for the epithelial cells to detach from the connective tissue capsule during treatment, leaving remnants of cyst epithelium behind and forming foci for recurrence [41]. In previously inflamed OKC, the epithelial lining appears thicker and becomes orthokeratinized; masking the actual pathology [48–51]. In such instances, it is advisable to obtain multiple incisional biopsy specimens from sites adjudged to be uninflamed for histologic assessment [52]. Hopefully, a small area of these several cuts should give the diagnosis.

Recent reports have supported the intraoperative use of frozen section in the diagnosis and management of OKC. This technique can either be employed without a prior incisional biopsy in “the one stage

method" or it is used intraoperatively to determine if the entire cystic lining has been removed from the surgical site [52]. Later use of frozen section biopsy will help decide which further adjunctive treatment option is appropriate [52–54].

Immunochemistry

Immuno-staining with p53 has been reported to reveal significantly higher levels of abnormal p53 in OKC than other epithelial cysts and oral mucosa. Thus, the locally invasive behavior and high recurrence rate of OKC can be attributed to the presence of mutant or otherwise inactive p53 protein [55]. Higher Ki-67 positive cells with increased proliferation rates have been reported in epithelium of OKC as compared to other developmental cysts. In addition, when compared with non-recurrent type, the recurrent OKC had a higher median LI for Ki-67. These findings have been proposed to contribute to the clinical aggressiveness of OKC [56]. Immune-staining with α-SMA has been found to be significantly highest in OKC than other destructive jaw lesions, indicating the presence of a higher mean number of myofibroblasts in OKC compared with other tumours that behave aggressively [57].

In view of the peculiar nature of OKC especially its high recurrence potential (placed at 20–60%) [ ] which can be ascribed to the nature of its cystic lining, it has become necessary to proffer a unified treatment modality that will help attain the least chance of recurrence in its management.

Suggested treatments

Unilocular lesions

We recommend that treatment for confirmed cases of OKCs presenting as small unilocular radiolucencies be careful enucleation without as much as possible violating the cyst integrity (although this is almost impossible given the friable nature of the lining). Extraction of adjacent involved teeth is then done. This treatment should be followed by selective management of the bone walls by use of either Carnoy's solution (with or without chloroform) or liquid nitrogen or 5-FU. In areas where cortical perforation has occurred, the overlying attached oral mucosa should also be excised. Studies on recurrence of OKCs have reported secondary lesions in close proximity to retained adjacent teeth [58]. This is the rationale for extraction of adjacent involved teeth in dentate patients.

A long-term follow-up period of up to twenty-five years is advised as such variants have been reported to recur several years later [59].

When large unilocular radiolucent lesions located in the posterior mandible or maxilla is encountered, the OKCs might often have perforated the thin cortex of the maxilla with possible invasion into the pterygopalatine space. The recommended and best treatment for such cases, aside enucleation followed by peripheral ostectomy is the excision of the overlying attached soft tissue. In large posterior maxillary cysts in particular, where the invasion of ptrygomaxillary space is imminent but undesirable, decompression prior to definitive treatment is recommended. Additionally, selective cauterization using

Carnoy's solution (with or without chloroform) or liquid nitrogen or 5-FU can be applied [17, 26, 41, 50, 60–64].

Multilocular lesions

For multilocular lesions, aspiration and incisional biopsies are usually easily performed because of bone expansion. While tissue biopsy remains the gold standard in diagnosis of OKC, MRI sequencing images is able to help in differenting between tumors and others cystic lesions [3, 5–11, 42–43] and, in localizing perforations, fenestrations and daughter's cysts specifically in maxillary lesions [7]. The treatment of choice for multilocular OKCs smaller than 3 cm is cyst enucleation and the bony defect are managed using Carnoy's solutions (with or without chloroform) or liquid nitrogen or 5-FU. Extraction of any adjacent involved teeth for dentate patients is carried out.

Where the lesion has perforated the bony confines, excision of the overlying attached gingiva should be performed. In addition, for those lesions located in suspected areas (posterior mandible and maxilla), more attention is required because of the presence of bony fenestration in the ascending ramus and thin perforated buccal cortex in the posterior maxilla respectively. Thus, excision of the overlying attached mucosa should be performed with cyst enucleation, followed by treatment of bone defect to destroy and fix any remnant of epithelial cells and daughter cyst using Carnoy's solution (with or without chloroform), or Liquid nitrogen or 5-FU. Selective cauterization of the bony defect should be performed in the maxilla to avoid injury to the sinus lining. Peripheral ostectomy of the surrounding bone defect should be done before chemical cauterization of alveolar process and tuberosity [17, 26, 41, 50, 60–64]. In cases where multilocular lucent lesions less than 3 cm radiographically are situated in close proximity to vital structures, either enucleation or marsupialization followed by residual cystectomy is recommended [65].

Multilocular lesion larger than 3 cm

Initial OKCs greater than 3 cm that are located in the tooth bearing areas should be treated using a conservative approach, specifically for pediatric, elderly and compromised patients or lesions that are approximate to vital structures. A recent meta-analysis showed 12% recurrence of KCOTs (now OKCs) after decompression followed by residual cystectomy [10]. Consequently, the recommended treatment is marsupialization, simultaneously with incisional biopsy of the cyst lining. The overlying attached oral mucosa should be examined closely to identify aspects with fenestrations or bone perforation. To decompress the cyst, excision of the overlying oral mucosa that has attached cyst lining (through fenestration or perforation) is strongly recommended. By so doing, possible presence of epithelial islands clusters and microcysts that could contribute to the development of new cysts if left behind (recurrence) would be eliminated. Twice daily cystic cavity irrigations (with 0.12% chlorhexidine gluconate and saline) through the inserted secured tube should be performed. Clinical and radiographic follow up for 1 year (every 2 months) should be carried out or until further treatment is engaged. After radiographic confirmation of considerable decrease in size of the lesion and obvious bone formation, the tube is remove and residual cystectomy performed with emphasis on excising overlying mucosa to completely eliminate remnant clusters of epithelial islands and microcysts that might be present between mucosa

and cystic lining. This should be followed by peripheral ostectomy and treatment of bone defect using Carnoy's solution (with or without chloroform) or liquid nitrogen or 5-FU.

In unresponsive cases (when size of lesion does not regress after 6 months of decompression) of multilocular OKCs with resorption of inferior and or posterior mandibular borders; these signs should be considered as indicators of aggressiveness. Thus, such lesions should be treated by radical resection with excision of affected/involved overlying attached mucosa.

For all cases of recurrent OKCs (primary or secondary recurrence) we recommend aggressive treatment; due to the likely contamination of the surrounding environment (bone and mucosa/soft tissue) with offshoots from the cyst lining or epithelial islands and microcysts. Thus, such lesions should be resected with or without continuity defect. In addition, dissection of supra periosteal area of overlying attached mucosa or adjacent soft tissue are highly recommended [13, 54, 63–65].

The management of teeth related with / associated with OKC has received some appreciable attention in literature. Interventions offered ranged from extraction, to endodontic treatment and no treatment at all. Findings from these interventions suggest no statistically significant association between recurrence rate and treatment method applied to related teeth ($p = 0.579$) [58]. Others imply that preservation of teeth involved in the lesion appears to increase the risk of recurrence [66, 67]

Discussion

The propensity of OKC to recur is a major reason for every surgeon's concern, with a view to delivering the most appropriate treatment and achieving a long-term successful outcome. This review and meta-analysis is meant to illuminate the pathway to successful management of OKC with zero or near zero recurrence rate. The parameters employed (locularity, size, presence of cortical perforations, lesion type (primary or secondary), radiological features, and presence of NBCCS) in this proposed evaluation process leading to recommended treatment options are derived from routine clinical examination and investigations done on every patient. Our protocol therefore requires no additional investigations.

Arriving at the correct diagnosis of OKC is critical to the successful management of patients with this controversial lesion. The importance of differentiating OKC from other odontogenic cysts and ameloblastoma, as well as circumventing the challenge of distortion to its lining by inflammation is critical [68]. Perhaps of great importance is the need to understand that the prognosis of unicystic ameloblastoma depends a great deal on the direction of its wall's proliferation. Possible variants are proliferation into the cyst cavity, into the wall of the lining or towards the surrounding tissue with the latter two definitely having the greatest potential to recur. Unfortunately, this vital piece of information with implications for definitive treatment plan and prevention of recurrence is obtained only post operatively.

While the need to consider each case on its own merit and individual surgeons' preference are paramount, we present a decision tree or protocol, to aid the decision-making process that will lead to a treatment plan yielding the least chance of recurrence in the management of OKC.

The radiological size of an average lesion could be set at 3cm widest dimension. We considered this optimum for averagely sized OKCs just as it has been previously reported by other studies [69].

We have prescribed a variety of surgical treatment options in the management of varying sizes, and types of OKC. Lesions greater than 3cm in size radiologically, and recurrent or secondary should receive the most aggressive approach. The locularity remains another major determinant of the preferred line of treatment. Multilocularity increases the index of suspicion for recurrence and therefore informs a more aggressive approach. Furthermore, precautions against recurrence include ensuring free surgical margins through frozen section; peripheral ostectomy, selective treatment of bony cavity (Carnoy's solution (with or without chloroform), or liquid nitrogen or 5-FU) and excision of overlying mucosa in the presence of cortical perforation.

This principle was advocated by Al-Moraissi et al [9] and Stoelinga [70] based on outcomes of their large systematic review and meta-analysis and the consistent association of microcysts and epithelial islands with overlying attached mucosa respectively.

The use of the topical 5% antimetabolite drug, 5-FU has been shown to be effective adjunct post enucleation and peripheral ostectomy without local and systemic complications. Rationale for 5-FU therapy is SMO inhibition and antagonism of SHH transcription factors which is associated with cystic proliferation [26]. While evidence in support of this adjunctive treatment is weak, it may well be an alternative to the less effective modified Carnoy's solution in the nearest future.

Based on the published literature on recurrence of OKCs, we propose post-operative follow up for up to twenty-five years in cases with high potential for recurrence and not less than five years in cases with lower propensity for recurrence [55, 56]. In our opinion, the safest blanket prescription will be a tradition of twenty-five year follow up.

Our proposed treatment protocol is based on systematic reviews, however decision regarding individual patient management presenting with OKC must be personalized to reflect patient factors such as compliance or otherwise with long term follow-up.

This study is limited by potential case selection bias as cases of OKC with follow-up period lesser than 5 years were considered. This was necessary as extensive literature search revealed most cases to have less than 5 years follow-up. In order to minimize such bias in future treatment analysis studies, we strongly recommend that authors endeavor to present cases with at least 5years follow-up period. Alternatively, a prospective multi-center study is desirable.

In addition, the fact that over the years' different methods have been employed for the treatment of odontogenic keratocyst in an attempt to reduce its recurrence rate is also a potential constraint for a study like this. Management of OKCs have emerged from simple cystic enucleation, curettage, peripheral ostectomy, en-bloc resection to in most recent times use of chemotherapeutic agents like vismodegid

which is a molecularly targeted SHH pathway inhibitor. This drug is proposed as an alternative to surgical treatment and has been reported to significantly reduce the size of OKC in syndromic patients [72].

Conclusion

While this algorithm would be applicable to the management of all OKCs, jaw cysts associated with NBCC is an exception basically because of the multiple nature of these cysts including the presence of other associated pathologic conditions.

Owing to the limited strength of the evidence provided by available literature and consequently our review, we propose (and hope to embark upon) a prospective multicenter study on the treatment of OKCs; as a sure way of clarifying with a high level of evidence, the current confusion concerning the treatment of OKCs.

Declarations

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References

1. Speight P, Devilliers P, Li TJ, Odell EW, Wright JM. Odontogenic keratocyst. In: El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ, eds. WHO classification of head and Neck tumours, 4th ed. Lyon: IARC, 2017:235-6.

2. Nayak MT, Singh A, Singhvi A, Sharma R. Odontogenic keratocyst: What is in the name? J. Nat. Sci. Biol. Med. 2013;4:282–5. https://doi.org/10.4103/0976-9668.116968

3. Stoelinga PJ, Bronkhorst FB. The incidence, multiple presentation and recurrence of aggressive cysts of the jaws. J. Craniomaxillofac Surg.1988;16:184–95. https://doi: 10.1016/s1010-5182(88)80044-1

4. Rogerson KC. Gorlin's syndrome: an update on diagnosis and management. Oral Maxillofac Clin North Am. 1991;3:155.

5. Williams TP. Surgical treatment of odontogenic keratocysts. Oral Maxillofac Clin North Am. 1991;3:137.

6. Ghali GE, Connor MS. Surgical management of the odontogenic keratocyst. Oral Maxillofac. Surg. Clin. 2003;15:383–92. https://doi:10.1016/S1042-3699(03)00042-6.

7. Kolokythas A, Fernandes RP, Pazoki A, Ord RA. Odontogenic keratocyst: to decompress or not to decompress? A comparative study of decompression and enucleation versus resection/peripheral ostectomy. J. Oral Maxillofac. Surg. 2007:65;640–4. https://doi.org/10.1016/j.joms.2006.06.284

8. Kinard BE, Chuang SK, August M, Dodson TB. For treatment of odontogenic keratocysts, is enucleation, when compared to decompression, a less complex management protocol? J. Oral Maxillofac. Surg. 2015;73:641–8. https://doi.org/10.1016/j.joms.2014.11.001

9. Al-Moraissi EA, Dahan AA, Alwadeai MS, Oginni FO, Al-Jamali JM, Alkhutari AS, et al. What surgical treatment has the lowest recurrence rate following the management of keratocystic odontogenic tumor?: A large systematic review and meta-analysis. J. Craniomaxillofac. Surg. 2017;45:131–44. https://doi.org/10.1016/j.jcms.2016.10.013

10. Al-Moraissi EA, Pogrel MA, Ellis E. Enucleation with or without adjuvant therapy versus marsupialization with or without secondary enucleation in the treatment of keratocystic odontogenic tumors: A systematic review and meta-analysis. J. Craniomaxillofac. Surg. 2016;44:1395–403. https://doi.org/10.1016/j.jcms.2016.05.020

11. Al-Moraissi EA, Pogrel MA, Ellis E. Does the Excision of Overlying Oral Mucosa Reduce the Recurrence Rate in the Treatment of the Keratocystic Odontogenic Tumor? A Systematic Review and Meta-Analysis. J. Oral Maxillofac. Surg. 2016;74:1974–82. https://doi.org/10.1016/j.joms.2016.03.043

12. Gosau M, Draenert F, M€uller S, et al: Two modifications in the treatment of keratocystic odontogenic tumors (KCOT) and the use of Carnoy's solution (CS)—A retrospective study lasting between 2 and 10 years. Clin Oral Investig 2010;14:27-34.

13. Pitak-Arnnop P, Chaine A, Oprean N, Dhanuthai K, Bertrand JC, Bertolus C, 2010. Management of odontogenic keratocysts of the jaws: a ten-year experience with 120 consecutive lesions. J. Craniomaxillofac. Surg. 2010;38:358–64. https://doi.org/10.1016/j.jcms.2009.10.006

14. Schmidt B, Pogrel M: The use of enucleation and liquid nitrogen cryotherapy in the management of odontogenic keratocysts. J Oral Maxillofac Surg 2001; 59:720-25.

15. Blanas N, Freund B, Schwartz M, et al: Systematic review of the treatment and prognosis of the odontogenic keratocyst. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000; 90:553-58.

16. Ribeiro Junior O, Borba A, Alves C, et al: Keratocystic odontogenic tumors and Carnoy's solution: Results and complications assessment. Oral Dis 2012;18:548-57. 2012

17. Dashow J, McHugh J, Braun T, et al: Significantly decreased recurrence rates in keratocystic odontogenic tumor with simple enucleation and curettage using Carnoy's versus modified Carnoy's solution. J Oral Maxillofac Surg 2015; 73:2132-35
18. Frerich B, Cornelius C,Weitholter H: Critical time of exposure of the rabbit inferior alveolar nerve to Carnoy's solution. J Oral Maxillofac Surg 1994; 52:599-606.
19. Beach D, Somer R: Novel approach to Gorlin syndrome: A patient treated with oral capecitabine. J Clin Oncol 2011; 29:e397-401.
20. Ren C, Amm H, DeVilliers P, et al: Targeting the sonic hedgehog pathway in keratocystic odontogenic tumor. J Biol Chem 2012; 287: 27117-125
21. Rui Z, Li-Ying P, Jia-Fei Q, et al: Smoothened gene alterations in keratocystic odontogenic tumors. Head Face Med 2014;10:1-7.
22. Zhang L, Sun Z, Zhao Y, et al: Inhibition of SHH signaling pathway: Molecular treatment strategy of odontogenic keratocyst. Med Hypotheses 2006;67:1242-44.
23. Booms P, Harth M, Sader R, et al: Vismodegib hedgehog-signaling inhibition and treatment of basal cell carcinomas as well as keratocystic odontogenic tumors in Gorlin syndrome. Ann Maxillofac Surg. 2015; 5:14
24. Wang Q, Huang S, Yang L, et al: Down-regulation of sonic hedgehog signaling pathway activity is involved in 5- fluorouracil induced apoptosis and motility inhibition in Hep3B cells. Acta Biochim Biophys Sin 2008; 40:819-29.
25. Gross K, Kircik L, Kricorian G: 5% 5-Fluorouracil cream for the treatment of small superficial basal cell carcinoma: Efficacy, tolerability, cosmetic outcome, and patient satisfaction. Dermatol Surg 2007; 33:433-40.
26. Ledderhof NJ, Caminiti MF, Bradley G, Lam DK: Topical 5-Fluorouracil is a Novel Targeted Therapy for the Keratocystic Odontogenic Tumor. J Oral Maxillofac Surg 2017,75:514-524.
27. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2006;6, e1000097. https://doi.org/10.1371/journal.pmed.1000097
28. Hahn H, Wicking C, Zaphiropoulos PG, Gailani MR, Shanley S, Chidambaram A, et al. Mutations of the human homolog of Drosophila patched in the nevoid basal cell carcinoma syndrome. Cell 1996;85:841–51. https://doi: 10.1016/s0092-8674(00)81268-4
29. Johnson RL, Rothman AL, Xie J, Goodrich LV, Bare JW, Bonifas JM, et al. Human homolog of patched, a candidate gene for the basal cell nevus syndrome. Science 1996;272:1668–71. https://doi: 10.1126/science.272.5268.1668.
30. Lench NJ, Telford EA, High AS, Markham AF, Wicking C, Wainwright BJ. Characterisation of human patched germ line mutations in naevoid basal cell carcinoma syndrome. Hum. Genet. 1997;100:497–

502 https://doi: 10.1007/s004390050541

31. Barreto DC, Gomez RS, Bale AE, Boson WL, De Marco L. PTCH gene mutations in odontogenic keratocysts. J. Dent. Res. 2000;79:1418–22. https://doi: 10.1177/00220345000790061101

32. Agaram NP, Collins BM, Barnes L, Lomago D, Aldeeb D, Swalsky P, et al. Molecular analysis to demonstrate that odontogenic keratocysts are neoplastic. Arch. Pathol. Lab. Med. 2004;128:313–17.

33. Cohen Jr MM. Nevoid basal cell carcinoma syndrome: molecular biology and new hypotheses. Int. J. Oral Maxillofac. Surg. 1999;28:216–23. https://doi.org/10.1016/S0901-5027(99)80142-8

34. Lench NJ, High AS, Markham AF, Hume WJ, Robinson PA. Investigation of chromosome 9q22. 3-q31 DNA marker loss in odontogenic keratocysts. Eur. J. Cancer. B. Oral Oncol. 1996;32:202–6. https://doi: 10.1016/0964-1955(95)00053-4

35. Levanat S, Pavelić B, Crnić I, Orešković S, Manojlović S. Involvement of PTCH gene in various noninflammatory cysts. J. Mol. Med. 2000;78:140–6. https://doi.org/10.1007/s001090000090

36. Pavelić B, Levanat S, Crnić I, Kobler P, Anić I, Manojlović S, et al. PTCH gene altered in dentigerous cysts. J. Oral Pathol. Med. 2001; 30: 569–76. https://doi: 10.1034/j.1600-0714.2001.300911.x

37. Li TJ, 2011. The odontogenic keratocyst: a cyst, or a cystic neoplasm? J. Dent. Res. 90, 133–42. https:// doi: 10.1177/0022034510379016

38. Qu J, Yu F, Hong Y, Guo Y, Sun L, Li X, et al. Underestimated PTCH1 mutation rate in sporadic keratocystic odontogenic tumors. Oral Oncol. 2015;51:40–5. https://doi: 10.1016/j.oraloncology.2014.09.016

39. Pogrel MA, Jordan RCK. Marsupialization as a definitive treatment for the odontogenic keratocyst. J. Oral Maxillofac. Surg. 2004;62:651–5. https://doi.org/10.1016/j.joms.2003.08.029

40. Wushou A, Zhao YJ, Shao ZM. Marsupialization is the optimal treatment approach for keratocystic odontogenic tumour. J. Craniomaxillofac. Surg. 2014;42:1540-1544. https://doi.org/10.1016/j.jcms.2014.04.027

41. Shear M, Speight PM. Cysts of the oral and maxillofacial regions.4th ed. Oxford: Blackwell Munksgaard; 2007.

42. Scholl RJ, Kellett HM, Neumann DP, Lurie AG. Cysts and cystic lesions of the mandible: clinical and radiologic-histopathologic review. Radiogr. Rev. Publ. Radiol. Soc. N. Am. Inc. 1999;19:1107–24. https://doi.org/10.1148/radiographics.19.5.g99se021107

43. Dunfee BL, Sakai O, Pistey R, Gohel A. Radiologic and pathologic characteristics of benign and malignant lesions of the mandible. Radiogr. Rev. Publ. Radiol. Soc. N. Am. Inc .2006;26:1751–68.

https://doi.org/10.1148/rg.266055189

44. Nazir, H., Latoo, S., 2015. Cystic Fliud–Pathway to Enlighten the Early Diagnosis of Keratocystic Odontogenic Tumor. Sch. J. App. Med. Sci. 2015; 3:2466-9

45. Patidar M, Shetty P, Patidar N, Mittal S, Singh H, Chethna. Biochemical and Cytological Comparison of Keratocystic Odontogenic Tumours to Nonkeratinising Odontogenic Cysts Fluid. J. Clin Diagn Res. 2015; 9: ZC34–ZC38. https://doi.org/10.7860/JCDR/2015/12501.6195

46. Prakash R, Shyamala K, Girish HC, Murgod S, Singh S, Rani PSV. Comparison of components of odontogenic cyst fluids: A review. J. Med. Radiol. Pathol. Surg. 2016;2:15–7. https://doi.org/10.15713/ins.jmrps.51

47. Pindborg JJ, Hansen J. Studies on odontogenic cyst epithelium 2: clinical and roentgenologic aspects of odontogenic keratocysts. Acta Pathol. Microbiol. Scand. 1963;58:283–94. https://doi.org/10.1111/j.1699-0463.1963.tb01572.x

48. Minami M, Kaneda T, Ozawa K, Yamamoto H, Itai Y, Ozawa M, et al. Cystic lesions of the maxillomandibular region: MR imaging distinction of odontogenic keratocysts and ameloblastomas from other cysts. AJR Am. J. Roentgenol. 1996;166:943–9. https://doi.org/10.2214/ajr.166.4.8610578

49. van Rensburg LJ, Paquette M, Morkel JA, Nortjé CJ. Correlative MRI and CT imaging of the odontogenic keratocyst: a review of twenty-one cases. Oral Maxillofac. Surg. Clin. N. Am. 2003;15:363–82. https://doi.org/10.1016/S1042-3699(03)00037-2

50. Asaumi J, Yanagi Y, Konouchi H, Hisatomi M, Matsuzaki H, Shigehara H, et al. Assessment of MRI and dynamic contrast-enhanced MRI in the differential diagnosis of adenomatoid odontogenic tumor. Eur. J. Radiol. 2004;51:252–6. https://doi.org/10.1016/j.ejrad.2003.09.009

51. Probst FA, Probst M, Pautke C, Kaltsi E, Otto S, Schiel S, et al. Magnetic resonance imaging: a useful tool to distinguish between keratocystic odontogenic tumours and odontogenic cysts. Br. J. Oral Maxillofac. Surg. 2015;53:217–22. https://doi.org/10.1016/j.bjoms.2014.10.014

52. Aronovich S, Kim RY. The sensitivity and specificity of frozen-section histopathology in the management of benign oral and maxillofacial lesions. J. Oral Maxillofac. Surg. 2014;72:914–9. https://doi.org/10.1016/j.joms.2013.10.022

53. Eida S, Hotokezaka Y, Katayama I, Ichikawa Y, Tashiro S, Sumi, T, et al. Apparent diffusion coefficient-based differentiation of cystic lesions of the mandible. Oral Radiol. 2012;28:109–14. https://doi.org/10.1007/s11282-012-0095-z

54. Guthrie D, Peacock ZS, Sadow P, Dodson TB, August M. Preoperative incisional and intraoperative frozen section biopsy techniques have comparable accuracy in the diagnosis of benign intraosseous

jaw pathology. J. Oral Maxillofac. Surg. 2012; 70: 2566–72. https://doi.org/10.1016/j.joms.2011.11.023

55. Gadbail AR, Chaudhary M, Patil S, Gawande M. Actual Proliferating Index and p53 protein expression as prognostic marker in odontogenic cysts. Oral Dis. 2009;15:490-8. https://doi.org/10.1111/j.1601-0825.2009.01590.x
56. Selvi F, Tekkesin MS, Cakarer S, Isler SC, Keskin C. Keratocystic odontogenic tumors: predictive factors of recurrence by Ki-67 and AgNOR labelling. Int J Med Sci. 2012;9(4):262-8. doi: 10.7150/ijms.4243
57. Vered M, Shohat I, Buchner A, Dayan D. Myofibroblasts in the stroma of odontogenic cysts and tumors can contribute to variations in the biologic behavior of lesions. Oral Oncol. 2005;4;41:1028–33. https://doi.org/10.1016/j.oraloncology.2005.06.011
58. Karaca Ç, Dere KA, Er N, Aktaş A, Tosun E, Köseoğlu OT, et al. Recurrence rate of odontogenic keratocyst treated by enucleation and peripheral ostectomy: Retrospective case series with up to 12 years of follow-up. Med Oral Patol Oral Cir Bucal. 2018;23:443-8. http://dx.doi.org/doi:10.4317/medoral.22366
59. Stoelinga PJ. Long-term follow-up on keratocysts treated according to a defined protocol. Int. J. Oral Maxillofac. Surg. 2001;30:14–25. https://doi.org/10.1054/ijom.2000.0027
60. Stoelinga PJ, Bronkhors FB. The incidence, multiple presentation and recurrence of aggressive cysts of the jaws. J. CranioMaxillofac. Surg. 1988;16:184–95. https://doi.org/10.1016/s1010-5182(88)80044-1
61. Rodu B Tate AL, Martinez MG. The implications of inflammation in odontogenic keratocysts. J. Oral Pathol. Med. 1987;16:518–21. https://doi.org/10.1111/j.1600-0714.1987.tb00684.x
62. August M, Faquin WC, Troulis M, Kaban LB. Differentiation of odontogenic keratocysts from nonkeratinizing cysts by use of fine-needle aspiration biopsy and cytokeratin-10 staining. J. Oral Maxillofac. Surg. 2000;58:935–40. https://doi.org/10.1053/joms.2000.8731
63. Pogrel MA. The keratocystic odontogenic tumor. Oral Maxillofac. Surg. Clin. 2013;25:21–30. https://doi.org/10.1016/j.coms.2012.11.003
64. Sumi M, Ichikawa Y, Katayama I, Tashiro S, Nakamura T. Diffusion-weighted MR imaging of ameloblastomas and keratocystic odontogenic tumors: differentiation by apparent diffusion coefficients of cystic lesions. AJNR Am. J. Neuroradiol. 2008;29: 1897–1901. https://doi.org/10.3174/ajnr.A1266
65. Chapelle KA., Stoelinga PJ, de Wilde PC., Brouns JJ, Voorsmit RA. Rational approach to diagnosis and treatment of ameloblastomas and odontogenic keratocysts. Br. J. Oral Maxillofac. Surg. 2004;42:381–90. https://doi.org/10.1016/j.bjoms.2004.04.005

66. Fidele NB, Yueyu Z, Zhao Y, Tianfu W, Liu J, Sun Y, Liu B. Recurrence of odontogenic keratocysts and possible prognostic factors: Review of 455 patients. Med Oral Patol Oral Cir Bucal. 2019 Jul 1;24 (4):e483-90.

67. Cunha JF, Gomes CC, de Mesquita RA, Andrade Goulart EM, de Castro WH, Gomez RS. Clinicopathologic features associated with recurrence of the odontogenic keratocyst: a cohort retrospective analysis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016 Jun;121(6):629-35. doi: 10.1016/j.oooo.2016.01.015. Epub 2016 Jan 29. PMID: 27050804.

68. Ali M, Baughman RA. Maxillary odontogenic keratocyst: a common and serious clinical misdiagnosis. J. Am. Dent. Assoc. 2003;134:877–83. https://doi.org/10.14219/jada.archive.2003.0286

69. Berge TI, Helland SB, Saelen A, Oren M, Johannessen AC, Skartveit L, et al. Pattern of recurrence of nonsyndromic keratocystic odontogenic tumors. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;122:10-6. https://doi.org/10.1016/j.oooo.2016.01.004

70. Stoelinga PJ. The treatment of odontogenic keratocysts by excision of the overlying, attached mucosa, enucleation, and treatment of the bony defect with Carnoy solution. J. Oral Maxillofac. Surg. 2005;63:1662–6. https://doi.org/10.1016/j.joms.2005.08.007

71. Pogrel MA. The keratocystic odontogenic tumour (KCOT)—an odyssey. Int J Oral Maxillofac Surg. 2015;44:1565–8. https://doi.org/10.1016/j.ijom.2015.03.008

72. Ally MS, Tang JY, Joseph T, Thompson B, Lindgren J, Raphael MA, et al. The use of vismodegib to shrink keratocystic odontogenic tumors in patients with basal cell nevus syndrome. JAMA Dermatol. 2014;150(5):542 doi:10.1001/jamadermatol.2013.7444

Figures

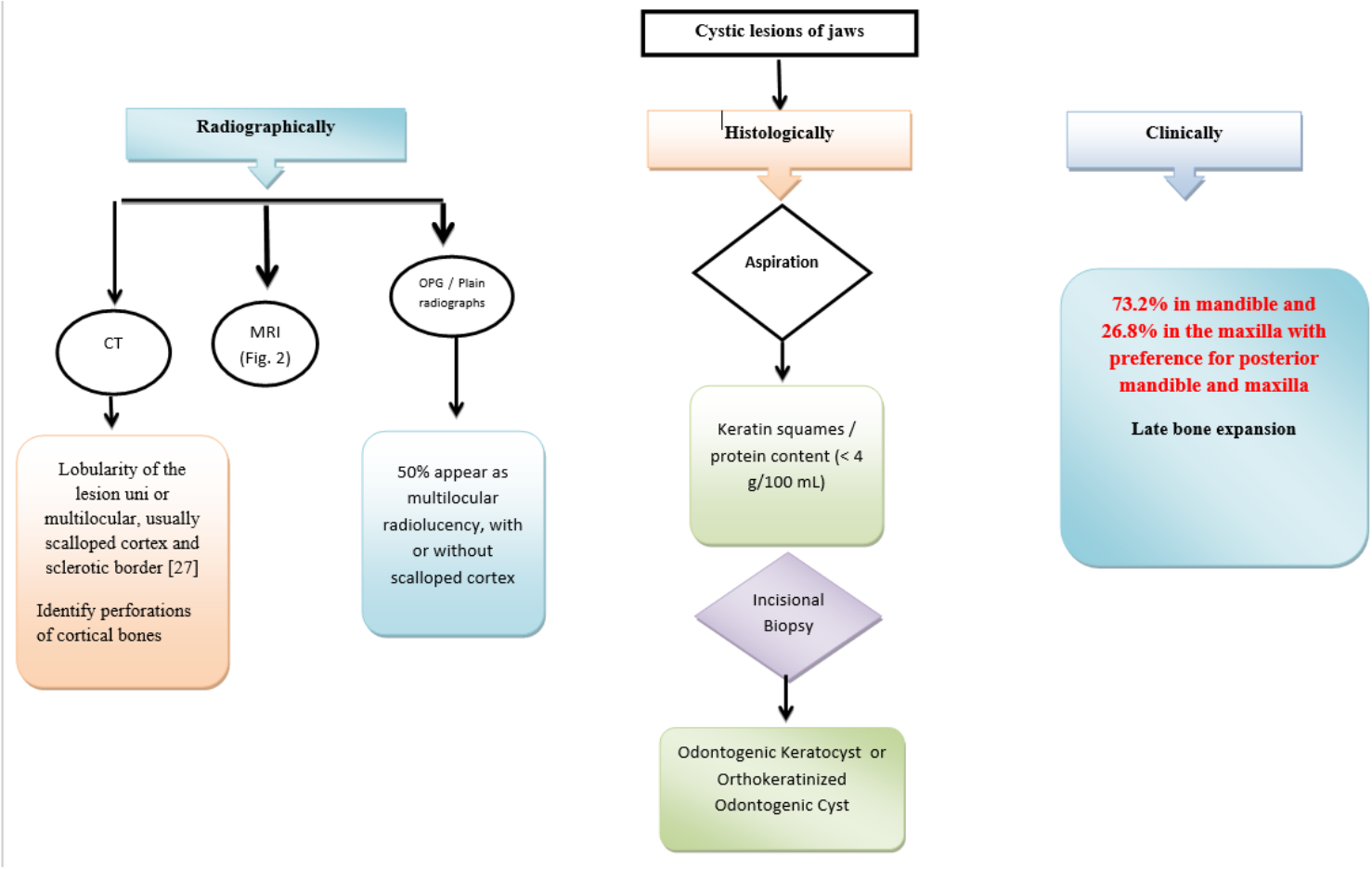

Figure 1

Diagnostic algorithm of odontogenic keratocysts

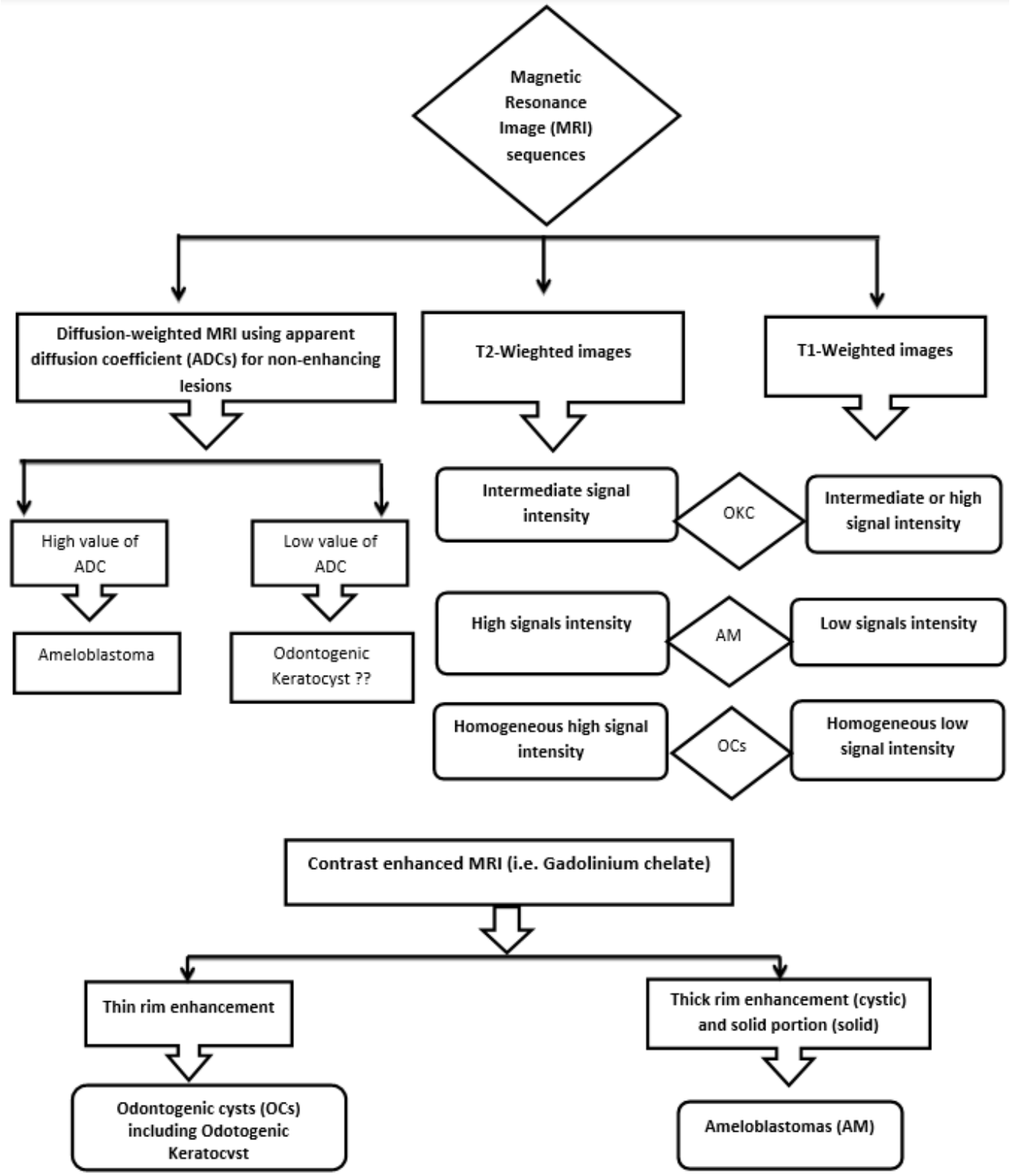

Figure 2

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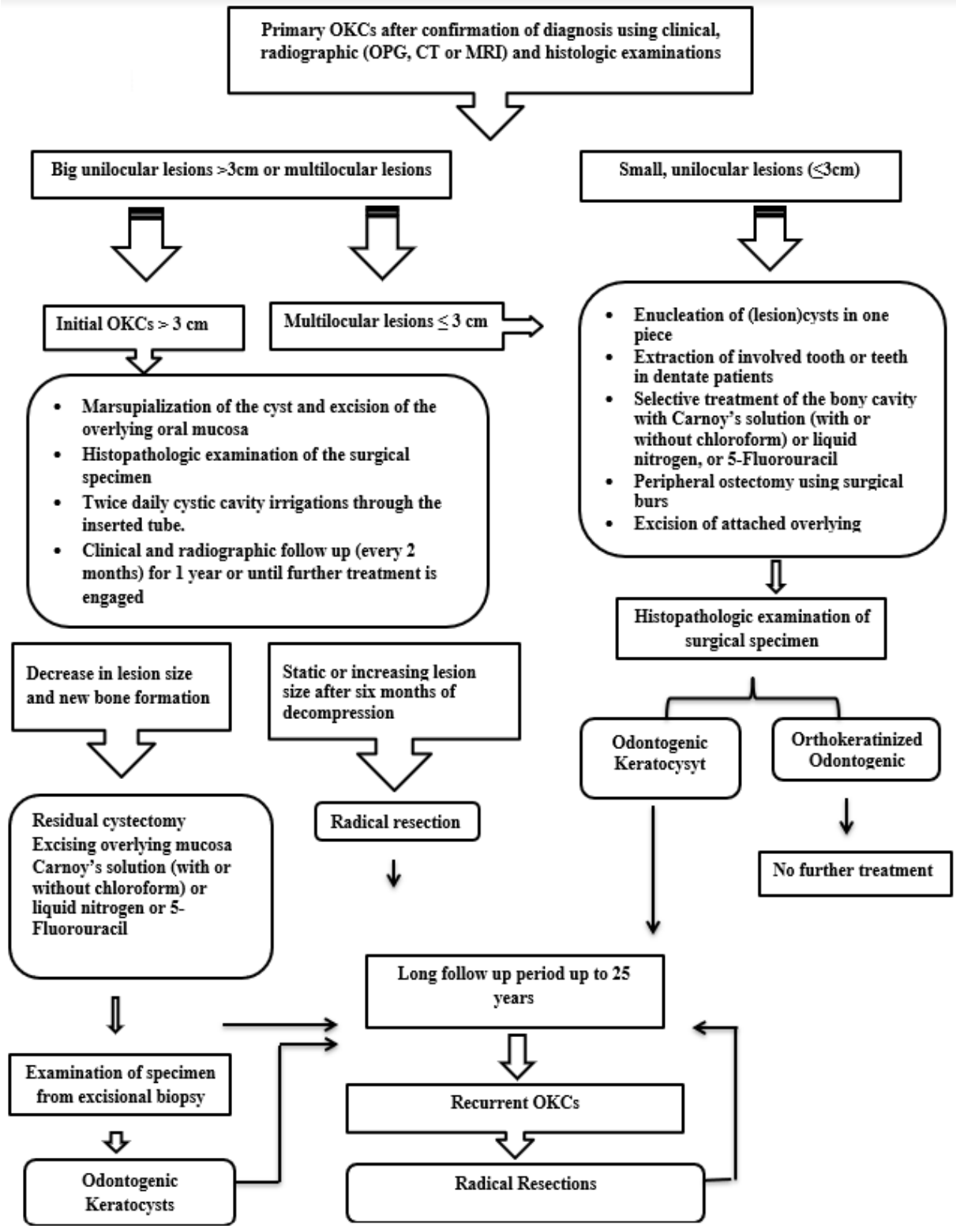

Figure 3

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