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REVIEW ARTICLE

Clinical, diagnostic and therapeutic features of keratocystic odontogenic tumors: a review

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Summary

Keratocystic odontogenic tumors (KCOTs) are benign but locally aggressive lesions of the gnathic skeleton with high propensity to recur following surgical treatment. High proliferative activity of KCOTs epithelial cells is considered as one of the factors contributing to their aggressive clinical behavior. Aggressive growth within the jaws, tendency to invade surrounding anatomical structures and occasional malignant alteration are the features that distinguish KCOTs from other types of odontogenic tumors. Due to their unique clinical and biological features, KCOTs still present an important problem in oral and maxillofacial surgery. This is especially true when a choice of the most appropriate treatment modality should be made. Establishing balance between effective reduction of recurrence risk and selection of a less aggressive surgical procedure is an issue that should be carefully considered for each individual patient.

Key words: clinical features, diagnosis, odontogenic tumors, surgery

Introduction

Keratocystic odontogenic tumors are benign but locally aggressive lesions of the gnathic skeleton with high propensity to recur following surgical treatment. Aggressive growth within the jaws, tendency to invade surrounding anatomical structures and occasional malignant alteration are the features that distinguish KCOTs from other types of odontogenic tumors. Further more, KCOTs are among the most prominent features of nevoid basal cell carcinoma (NBCC) syndrome (Gorlin-Goltz syndrome), a hereditary condition characterized by a wide range of developmental abnormalities and a predisposition to different types of neoplasms [1], clearly indicating strong involvement of genetic factors in their development. Besides this, uncertain etiology and pathogenesis were subjects of extensive research but numerous important issues regarding their etiopathogenesis are still unresolved.

These kind of lesions were first described by Philipsen in 1956 as odontogenic keratocysts (OKCs). Regarding their specific histopathological features (such as keratinization of the epithelium) and clinical behavior, he distinguished them from cholesteatomas occurring in cranial areas. Traditionally, these lesions, under the term of OKCs, were considered to be developmental jaw cysts [2], but due to their unique clinical and molecular features, they were recently reclassified as keratocystic odontogenic tumors (KCOTs). They are defined as benign, odontogenic, uni- or multicystic tumors, having a potential for aggressive and infiltrative growth [3]. Still, despite this new classification (Table 1), the tumorous nature of these lesions remains a subject of debate among investigators.

Etiology and pathogenesis

It is widely accepted that KCOTs originate from the odontogenic epithelium. Remnants of dental lamina and proliferations of basal cell layer of oral epithelium are considered as possible sources of epithelial

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Table 1. Waldron and Mustoe's classification of odontogenic carcinoma

Type 1-PIOC arising from odontogenic cyst
Type 2A-Malignant ameloblastoma
Type 2B-Ameloblastic carcinoma
Type 3-PIOC arising *de novo*
a) Keratinizing type
b) Nonkeratinizing type
Type 4-Intraosseous mucoepidermoid carcinoma

PIOC: primary intraosseous odontogenic carcinoma

cells which, under certain circumstances, proliferate to form a KCOT [4]. The etiology of KCOTs is strongly related to genetic factors, in particular to mutation of the tumor-suppressor PTCH gene. It was demonstrated that mutations of PTCH gene are important not only for the development of KCOT in NBCC syndrome patients, but for the sporadic cases as well [5,6]. Besides PTCH, several other gene alterations including H-ras oncogene activation were detected in these lesions [7].

The high proliferative activity of KCOTs epithelial cells is considered as one of the factors contributing to their aggressive clinical behavior. Using Ki-67 immunolabeling several authors demonstrated high rate of cell proliferation, in particular in the suprabasal epithelial layer of KCOTs [8,9]. Besides from Ki-67, this part of tumorous epithelium also shows high expression of AgNOR (Argyrophilic Nucleolar Organizer Region) and p53 [10]. Also, it was shown that inhibitors of apoptosis, including bcl-2 and survivin are expressed in the epithelial layer of these lesions [11,12], further supporting the opinion on their tumorous nature [13].

Finally, the etiology of some other types of odontogenic cystic lesions of the jaws, like radicular cysts, is closely related to inflammatory stimuli, including production of inflammatory cytokines, such as TNF-alpha and presence of inflammatory cells within the cystic wall [14]. In contrast, KCOTs show lower concentrations of pro-inflammatory cytokines in cystic fluid [15], which suggests that these types of reaction are not crucial for the development of KCOT.

Clinical features

It is widely accepted that KCOTs (OKCs) represent about 10% of all jaw cysts [4]. Still, there is some uncertainty regarding such data since different studies estimated KCOTs frequency in different types of samples, including odontogenic cysts, epithelial jaw cysts or all types of cystic lesions of the jaws. Moreover, different diagnostic criteria were used, as some studies included lesions exhibiting orthokeratinization of the epithelial layer in contrast to typical KCOTs with parakeratinized squamous epithelium [16]. Still, nowadays it is accepted that lesions exhibiting orthokeratinization represent a separate entity which should not be considered as KCOTs [17]. The lowest reported frequency was 1.5% (51 out of 3353 jaw cysts) [18], while the highest was 17.4% (64 out of 368 odontogenic cysts) [19]. In an epidemiological study performed in 1978, Rachanis and co-workers calculated the incidence of OKCs to be 4.86 and 3.5 per million, per year, for Caucasian males and females, respectively [20]. Such results suggested that males are affected more often than females, which was confirmed in subsequent studies indicating 1.7:1 ratio [4]. In contrast to sporadic KCOTs, it seems that lesions associated to NBCC syndrome are more common in females (55% of syndromic *vs.* 38% of sporadic lesions were diagnosed in female patients) [21,22].

The majority of KCOT patients (40-60%) are in their 2nd and 3rd decade of life. Still, in several studies bimodal distribution of KCOTs among age groups was observed, with the first peak in 2nd and 3rd decade and a second peak in a group of patients aged 50-65 years [4]. Again, in contrast to sporadic lesions, syndromic KCOTs tend to occur in younger patients [22]. The youngest patient with reported KCOT so far is a 19-month-old girl, in whom, at the moment of diagnosis there was not enough elements to support possibility of NBCC syndrome [23].

Although KCOTs might occur in any part of the upper and lower jaw, 69-83% of all KCOTs are localized in the mandible [24,25]. Furthermore, about one half of all lesions are diagnosed in the area of mandibular angle [26]. Despite the fact that most KCOTs are localized in the mandible, it was shown that a raising number of these lesions involves the upper jaw in patients above the age of 50 [27]. Also, the anatomical distribution of these tumors is different in NBCC syndrome patients. While in the area of mandibular angle the majority of KCOTs represent sporadic cases (60% sporadic vs. 44% of syndromic lesions), in the maxillary tuberosity area there is a prevalence of lesions associated to NBCC syndrome (21% syndromic vs. 11% sporadic lesions) [21,22].

Most KCOTs are asymptomatic until they reach a significant size. If symptoms are present, most of the patients will complain of swelling, pain and discharge of cystic fluid into the mouth. Occasionally, involvement of the inferior alveolar nerve might result in paresthesia of the lower lip. KCOTs tend to grow within the medullary bone while bony expansion becomes clinically evident only when a lesion reaches large size, which is a fact that contributes to late diagnosis [26]. Still, aggressive growth of KCOTs is illustrated by numerous case reports of this lesions with unusual clinical presentation.

Involvement of the maxillary sinus and floor of the orbit might result in proptosis as a first clinical sign indicating tumor presence [28,29]. Also, penetration into the surrounding soft tissues [30], orbit and infratemporal fossa [31,32], and even involvement of the skull base [33] have been reported.

While the vast majority of KCOTs occur within the jawbones, peripheral variants of these lesions, occurring in gingiva, is a well recognized phenomenon. These lesions are termed peripheral odontogenic keratocysts [34,35]. Although it is believed that peripheral keratocysts are less aggressive compared to bony counterparts, recurrent cases are reported in the literature [36], suggesting that these two variants, besides histological, might also share some clinical features. Besides this, several cases of solid keratocystic odontogenic tumors have been reported [37-39]. It is interesting that one of these tumors recurred several times, presenting at the beginning as a cystic and afterwards as a solid lesion [38]. Occurrence of solid KCOTs was regarded as an argument to support their neoplastic nature, similar to solid odontogenic ghost cell tumors and calcifying odontogenic cysts [39].

Nevoid basal cell carcinoma syndrome

Nevoid basal cell carcinoma syndrome, also known as Gorlin or Gorlin-Goltz syndrome, is an autosomal dominant inherited condition caused by mutations of PTCH gene, which is mapped to chromosome 9q22.3-q31. Principal clinical features of NBCC syndrome include multiple nevoid basal cell carcinomas and KCOTs, congenital skeletal abnormalities, ectopic calcifications, and plantar or palmar pits [40]. Multiple KCOTs are among the most prominent features of the syndrome, present in 75-90% of the patients [1,41].

It was demonstrated that syndromic KCOTs show pronounced epithelial budding and higher number of satellite microcysts compared to sporadic tumors [21,42]. Also, it seems that syndromic lesions are more common in younger patients, in females and in the posterior maxilla, which is in strong contrast to sporadic KCOTs [21,22,27]. Still, differential diagnosis of these two types of lesions is impossible, both by histological and clinical features. Therefore, NBCS syndrome diagnosis is made upon thorough clinical and radiographic examination and according to established major and minor diagnostic criteria. Major criteria include multiple basal cell carcinomas (or basal cell carcinoma before the age of 20), KCOTs, palmar and/or plantar pits, calcified falx cerebri, bifid or fused ribs, and NBCC syndrome diagnosis in a first-degree relative. Minor criteria include macrocephaly, frontal bossing, hypertelorism, chest abnormalities, syndactyly, cardiac and/or ovarian fibromas and medulloblastomas. The diagnosis is made once 2 major or 1 major and 2 minor criteria are met [1].

Medulloblastomas usually occur during 1st or 2nd year of life, in approximately 1-2% of the patients [43,44]. It seems that prognosis of these tumors is somewhat better compared to isolated cases, regarding the fact that most of medulloblastomas in NBCC syndrome patients are of desmoplastic type, which is associated with improved survival rates [1]. Besides medulloblastomas, most of other NBCC syndrome features are not life-threatening so prognosis for these patient is generally good. Still, repeated operations, both for skin tumors and KCOTs, might result in significant cosmetic and functional problems for the patient.

Recurrences

From the clinical perspective it is certain that frequent recurrences are the most striking feature of these tumors. In various studies, different recurrence rates were reported, ranging from 3% [45] to even 62% [46]. This high diversity in the reported data is related to different surgical procedures used for KCOTs treatment, but also to the duration of follow-up period. In a study from Myoung and co-workers, out of 132 cases treated by enucleation, 77 (58.3%) recurred during the observation period of up to 86 months and in 9 patients (11.7%) multiple recurrences were noted [47]. Well documented cases of late recurrences, occurring even 16-20 years postoperatively [25,48] emphasize the importance of long-term follow-up of these patients, but also rise a question regarding the reasons for this phenomenon.

In the available literature, 3 possible explanations for the high recurrence rates of KCOTs have been discussed. Since KCOT wall might be very thin and fragile the most obvious reason is retention of parts of the cystic wall following enucleation. It was shown that significantly higher recurrence rates were reported for lesions removed in several pieces compared to those enucleated in one part [49]. Also, retention of satellite microcysts and continued proliferation of the basal epithelial layer of the mucosa overlying the lesion are possible reasons for KCOTs recurrence [45]. Still, it is hard to accept that retention of cystic wall might be involved in recurrences occurring many years after the initial surgery.

Finally, the factor that significantly affects the reported recurrence rates is the type of surgical procedure used for removal of KCOTs. In a retrospective analysis of 255 KCOTs, followed from 3 to 29 years, recurrence was noted in 29 out of 163 (17.8%) of KCOTs treated by simple enucleation. In contrast, after enucleation

and application of Carnoy's solution, the recurrence rate dropped to 6.7% (2 out of 29 lesions). Also, in cases treated by marsupialization and subsequent enucleation, as well in cases when resection of the involved jaw was performed, no recurrences were recorded [50].

Malignant transformation

Primary intraosseous odontogenic carcinomas (PIOC) are squamous cell carcinomas arising within the jaws, probably from remnants of odontogenic epithelium. Apart from other classifications, the most widely used is the one from Waldron and Mustoe [51] (Table 1). Although several other types of odontogenic carcinomas were reported, including clear cell odontogenic carcinoma [52], odontogenic ghost cell carcinoma [53] and the malignant variant of calcifying epithelial odontogenic tumor [54], the term PIOC is most commonly used for carcinomas arising *de novo* or from odontogenic cysts.

Several well documented cases of PIOC arising from odontogenic keratocyst (KCOT) were reported in the literature [55-59]. Regarding the recent introduction of the term KCOT instead of odontogenic keratocyst, in a WHO classification of head and neck tumors the new entity was included-primary intraosseous squamous cell carcinoma derived from KCOT [3]. Having in mind the reclassification of these lesions into odontogenic tumors, it is interesting that the results of the recent literature review haven't demonstrated any pronounced tendency of KCOTs to malignant transformation compared to other cystic lesions of the jaws. Out of 134 PIOC cases, 82 of type 1 (ex odontogenic cysts) and 52 of type 3 (PIOC *de novo*) were identified. Regarding type 1, the majority of the cases arose from residual cysts, followed by dentigerous cysts and KCOTs being in the third place [59], suggesting that KCOTs don't show particular tendency for malignant changes.

Radiographic features

KCOTs are typically presented as round or ovoid radiolucencies with smooth or scalloped margins. Therefore, 3 distinct radiographic types are recognized-unilocular, multilocular and multilobular lesions. It has been suggested that multilobular KCOTs with scalloped margins are a result of unequal growth activity in different parts of the tumorous wall [4] but such an opinion requires further scientific support. About one quarter of all lesions exhibit multilocular appearance with bony septa within the lumen. In a series of 135 KCOTs, 25% were of multilocular type [60], all of them located in the mandible (Figure 1). Under such circumstances it is particularly important to establish differential diagnosis of KCOTs and ameloblastomas.

Occasionally, root resorption might be noted. In a sample of 90 OKCs resorption of neighboring teeth was noted in 24% of the cases [60], while in a series of 82 OKCs this was the case in 11% of the lesions [60]. Also, in 25-40% of the cases, an impacted tooth was present within the KCOT lumen (Figure 2), when these lesions should be distinguished from dentigerous cysts [41]. As already mentioned, KCOTs cause minimal expansion of the mandibular body. However, in the region of the mandibular angle and ramus, such an expansion might be considerable, which is a feature with potential diagnostic significance [61,62].

Although radiographic features might be suggestive of KCOT, it was shown that radiographic and histological diagnosis were in agreement in only 25.2% of the cases [47]. However, use of advanced imaging techniques might improve the reliability of KCOTs radiographic diagnosis. It was shown that an increased attenuation area (IAA) might be identified on computer-

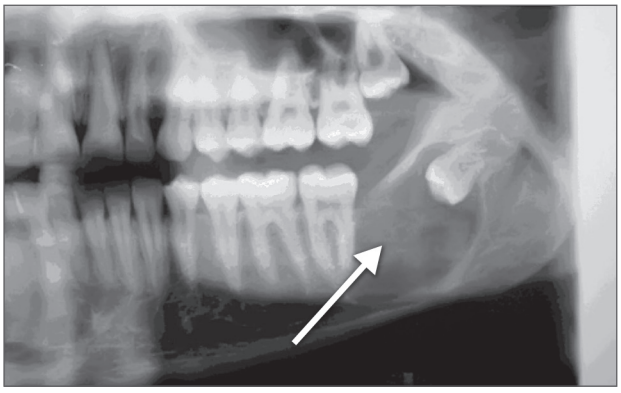

Figure 1. Radiography of KCOT in the mandible (arrow).

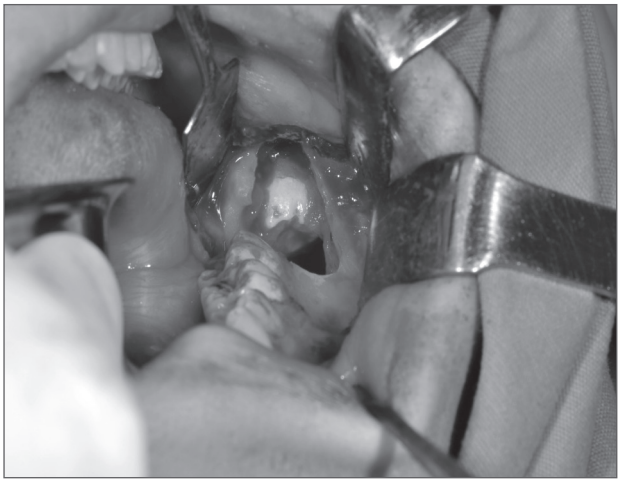

Figure 2. KCOT with tooth in lumen.

ized tomography (CT) scans of KCOTs, indicating presence of keratin within the lumen and possibly serving as an aid in radiographic diagnosis [63]. Also, magnetic resonance images (MRI) might be useful in differentiating KCOTs and ameloblastomas [64]. In a series of 21 lesions, using T2-weighted MRI, a diagnosis of KCOT was established in 85% of the cases [65]. It is of interest that in CT ameloblastomas and KCOTs showed similar density patterns, although KCOTs showed highest heterogeneity of CT values [66].

Diagnosis

Although several clinical and radiographic features might be suggestive of KCOT, diagnosis of this kind of lesions is largely based on histological examination of surgical specimens. Typical features include parakeratinized squamous epithelial layer, usually 6-8 cells in thickness, with palisaded basal layer of cuboidal or columnar cells. Thin fibrous tissue wall is typically devoid of inflammatory cells [41]. However, once the lesion becomes secondarily infected, inflammation of the fibrous wall results in loss of typical histological features of KCOT [67] which might result in misdiagnosis of these lesions.

It was shown that the profile of cytokeratin expression might be useful as a diagnostic marker for this type of tumors. Based on immunocytochemical detection of cytokeratin 10 in specimens obtained by fine needle aspiration biopsy of KCOTs, it was possible to differentiate these tumors from dentigerous and radicular cysts [68]. Also, cytokeratin 17 was detected in 93.3% KCOTs, in contrast to 38% of dentigerous and radicular cysts [69]. However, some other studies failed to identify these cytokeratins within the KCOTs wall [70], indicating that further research is needed before these markers might be used for KCOT diagnosis.

Treatment

Thin and fragile KCOTs wall, multilocularity and high propensity to recur postoperatively are the factors affecting the surgical treatment of these lesions. Still, being benign lesions without significant tendency for malignant transformation, routine use of radical surgery, such as resection of the involved jaw, is questionable, both from medical and ethical point of view. Therefore, it is not surprising that numerous adjunctive techniques were developed for the treatment of KCOTs.

Having in mind the high recurrence rates, it is accepted that the standard procedure of enucleation is not an adequate technique for the treatment of these lesions [71]. In order to improve the results of enucleation, peripheral ostectomy was introduced, aimed at eliminating the remnants of tumorous tissue or satellite microcysts from the periphery of the defect, particularly in multilobular and multilocular cases (Figure 3). Still, the lack of ability to control the amount of the removed bone is considered as a major disadvantage of this procedure [71].

In contrast to enucleation, resection of the affected jaw proved very effective in the prevention of recurrences. Actually, it is the only technique for which case series without recurrences were reported [50,61,72,73]. Still, having in mind the high morbidity associated with this operation and the necessity for additional reconstructive interventions, it was suggested that such a procedure should be reserved only for specific situations-large, recurrent lesions, lesions involving the condylar process, and lesions with malignant transformation or pathological fracture of the jaw [71].

In an attempt to bridge the gap between simple enucleation and radical surgery, different techniques were proposed in order to minimize the risk of KCOTs recurrences (Figure 4). Decompression of the lesion and subsequent enucleation of its remnants is a well known concept, used for other cystic lesions of the jaws as well.

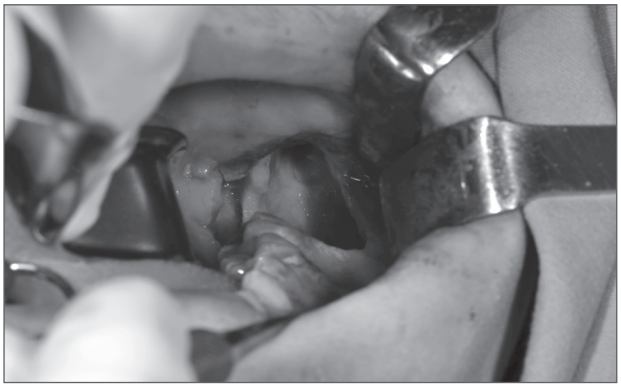

Figure 3. Intra-osseous defect after KCOT enucleation.

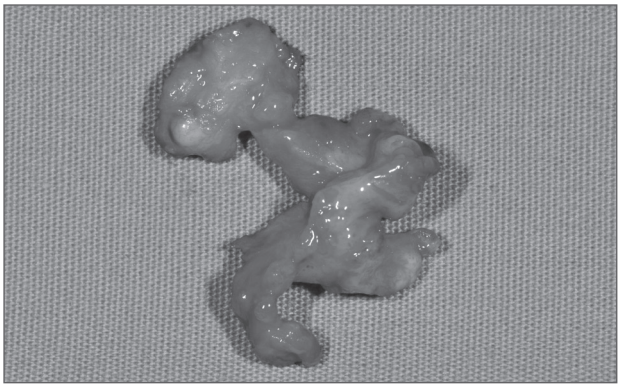

Figure 4. Enucleated KCOT with cyst wall.

It is expected that following decompression, KCOT should gradually decrease in size, allowing easier enucleation without damage of the neighboring anatomical structures e.g. teeth, inferior alveolar nerve, nasal cavity or maxillary sinus. Still, whether such a procedure reduces the risk of recurrences is a doubtful question. In a study from Brondum and Jensen, in a series of 12 KCOTs treated by decompression and subsequent enucleation no recurrences were recorded in contrast to 44 lesions treated by enucleation alone, in which the recurrence rate reached 18% (8 cases) [74]. Also, no recurrences were noted in 11 cases of Zhao and co-workers, applying the same concept of two-stage surgery [50]. Relatively low recurrence rate of 8.7% (2 out of 23 cases) was noted in patients in whom enucleation was performed one year after the initial decompression of the lesion [75]. In contrast, in a comparative study including 23 KCOTs treated by two-stage surgery and 15 KCOTs treated by enucleation in one act, no significant differences in recurrence rates were noted. During the follow-up period of up to 16 years, in the first group 6 out of 23 lesions (26.1%) recurred, while in the second group 3 out of 15 lesions (20%) recurred [76].

In addition, several researchers investigated the results of marsupialization as a definitive treatment for KCOTs. In a series of 10 cases, Pogrel and Jordan demonstrated complete resolution of KCOTs following this kind of treatment, both clinically and radiographically. Microscopic examination of the mucosa in an area of previously marsupialized lesion failed to identify remnants of cystic epithelium and immunohistochemical analysis of bcl-2 expression demonstrated lack of immunostaining for this marker, consistently expressed in the cystic epithelium but not in healthy oral mucosa [77,78]. Although during the follow-up period ranging from 1.8 to 4.8 years no recurrences were noted, in an extended follow-up of 42 patients, 5 recurrences were recorded (12%) [79], resulting in partial retraction of previous publications.

Also, in order to eliminate satellite microcysts and eventual remnants of tumorous tissue after KCOT enucleation, several techniques of chemical or thermal tissue fixation were developed. The most widely used is the application of Carnoy's solution which acts as a fixative and hemostatic agent. In several studies reduction in the number of recurrences was noted in groups of patients treated by enucleation and application of Carnoy's solution compared to enucleation alone. In a study by Voorsmith and co-workers comprising 92 KCOTs, recurrence rates were 2.5 and 13.5%, respectively [45]. Similar results were obtained in a follow-up study of 255 Chinese patients, where recurrence rate dropped from 17.8 to 6.7% when Carnoy's solution was used after the enucleation [50]. Developing this technique, Stoelinga and co-workers proposed a treatment protocol comprising application of Carnoy's solution following enucleation and excision of soft tissues in contact with the lesion. This concept was based on the observation that the highest frequency of epithelial basal cells budding was noted in an area where oral mucosa was attached to cystic lining, and it was believed that such epithelial cells offshoots might constitute a source of KCOTs recurrences. Using this protocol the frequency of recurrences was reduced from 18% for cases treated only by enucleation to 6% for cases treated by enucleation with Carnoy's solution and soft tissues excision [48].

Finally, in a meta-analysis of 578 cases, Blanas and colleagues demonstrated that resection of the involved jaw yielded no recurrences, while among other less aggressive treatment options the lowest frequency of recurrences was noted for enucleation in combination with Carnoy's solution (1.6%). Enucleation alone, as well as marsupialization and enucleation and cryosurgery resulted in 28.7, 24.4 and 31.3% recurrence rates, respectively [80].

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Conclusions

Due to their unique clinical and biological features, KCOTs still represent an important problem in oral and maxillofacial surgery. This is especially true when a choice of the most appropriate treatment modality should be made. Establishing balance between effective reduction of recurrence risk and selection of less aggressive surgical procedure is an issue that should be carefully considered for each individual patient. Still, better understanding of KCOTs pathogenesis might provide clues for new treatment strategies, including the usage of survivin and Sonic hedgehog (Shh) signaling pathways inhibitors.

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