

# A review on the most important management of keratocystic odontogenic tumor

## Přehled nejdůležitějších metod léčby keratocystického odontogenního tumoru

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### Summary

**Background:** Keratocystic odontogenic tumor (KCOT) is a recurrent benign tumor with a keratinized epithelial shape. The treatment methods in KCOT are still debated. The aim of all treatment methods is to eradicate the cyst and to reduce recurrence and surgical complications. This review article was conducted to assess the findings of studies on the diagnosis, management and recurrence of KCOT. **Methods:** Information were gathered by searching keywords such as management, treatment, pharmacology, surgery and keratocystic odontogenic tumor in international databases such as Web of Science, PubMed and Scopus. The search period was between 2010–2020. **Results:** Techniques used for the treatment include decompression, marsupialization, enucleation with or without adjunct, Caldwell-Luc surgery and resection. Of the 40 studies, recurrence was observed in 13 studies and the recurrence ranged from 0 to 48% in different treatment methods. **Conclusion:** Due to the high recurrence of this disease, it is suggested that long term follow-up be considered after treatment to reduce recurrence. Decision on the treatment should be made considering age, tumor size, and the site of involvement in order to reduce the economic and psychological burden of the disease.

### Key words

management – treatment – pharmacology – surgery – keratocystic odontogenic tumor

### Souhrn

**Východiska:** Keratocystický odontogenní tumor (keratocystic odontogenic tumor – KCOT) je rekurentní benigní tumor tvaru keratinizovaného epitelu. Způsob léčby je stále předmětem diskusí. Cílem všech léčebných metod je eradikace cysty a omezení rekurence a pooperačních komplikací. Tento přehledový článek byl vytvořen s cílem zhodnotit závěry studií zaměřených na diagnostiku, léčbu a rekurenci KCOT. **Metody:** Informace byly shromažďovány po zadání slov management, léčba, farmakologie, operace a keratocystický odontogenní tumor do mezinárodních databází Web of Science, PubMed a Scopus. Sledování dat probíhalo v období let 2010–2020. **Výsledky:** Mezi techniky používané při léčbě patří dekomprese, marsupializace, enukleace s následnou operací čelistní dutiny ze zevního přístupu dle Caldwell-Luca nebo bez ní a resekcce. Ze 40 studií byla rekurence pozorována v 13 studiích a u různých léčebných metod se pohybovala v rozmezí 0–48 %. **Závěr:** V důsledku vysoké rekurence onemocnění se po léčbě doporučuje dlouhodobé sledování. Rozhodnutí o způsobu léčby by mělo zohledňovat věk pacienta, velikost nádoru a místo výskytu, aby se co nejvíce snížila ekonomická a psychická zátěž tímto onemocněním.

### Klíčová slova

management – léčba – farmakologie – operace – keratocystický odontogenní tumor

The authors declare they have no potential conflicts of interest concerning drugs, products, or services used in the study.

Autoři deklarují, že v souvislosti s předmětem studie nemají žádné komerční zájmy.

The Editorial Board declares that the manuscript met the ICMJE recommendation for biomedical papers.

Redakční rada potvrzuje, že rukopis práce splnil ICMJE kritéria pro publikace zasílané do biomedicínských časopisů.



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Submitted/Obdrženo: 15. 4. 2021

Accepted/Přijato: 15. 7. 2021

doi: 10.48095/ccko202210

**Introduction**

Philipsen first coined the term odontogenic keratocyst (OKC) in 1956. [1]. The World Health Organization used the term keratocystic odontogenic tumor (KCOT) for a benign but aggressive tumor of odontogenic origin in 2005. Histologically, KOT is characterized by a thin parakeratinized stratified epithelium [1]. KCOT is a benign neoplasm with a keratinized epithelial outline with a high recurrence rate [2]. KOT is a relatively common developmental odontogenic cyst and represents approximately 10–14% of all jaw cysts [3]. The reason for the high recurrence rate in KCOT is due to its neoplastic characteristics including high proliferation rate, angiogenesis, presence of daughter cysts and epithelial islands [4,5]. Incomplete resection of epithelial structure of KCOT due to the fragility of the tumor tissue is another reason for recurrence [4,6]. In radiographic imaging, KCOT is seen as a unilocular or multilocular well-circumscribed radiolucent lesion with scalloped and corticated margins. Involvement of affected tooth is reported in 25–40% of cases [7,8]. In case of suspicious lesions in mandible or maxilla, CT scan, radionuclide imaging or MRI are used as conjunctive diagnostic methods. CT scan is a better method in identifying bone resorption, osteoporosis,

periosteal swelling, destruction and calcification [9].

It is believed that keratocysts are originated from dental layer remnants with the following features such as a thin, bandlike lining of stratified squamous epithelium, a corrugated keratinized lining and a spinous cell layer of 8–10 cells in thickness, a thin, inflammation-free connective tissue capsule, and a lumen-containing varying amounts of desquamated keratin. A predominant parakeratin lining predominates in majority (83–97%) of KCOT tumors [10,11].

Various treatment options exist for KCOT ranging from conservative managements, including enucleation (with or without curettage), decompression and marsupialization, to aggressive treatments, including enucleation or cryotherapy with liquid nitrogen, and application of Carnoy’s and jaw resection. No universal approach has yet been proposed for KCOT and the treatment methods in KCOT are still debated. The aim of all treatment methods is to eradicate the cyst and to reduce recurrence and surgical complications [12,13].

KCOT is commonly asymptomatic and is mainly identified in routine radiographic assessments or panoramic radiographic examinations. Early diagnosis and correct treatment of KCOT is of great importance as surgery and treat-

ment of KCOT is complicated and due to its high recurrence rate. Furthermore, there is no comprehensive assessment regarding the superiority of aggressive over conservative management in reducing recurrence. Therefore, this review article was conducted to assess the findings of studies on management and recurrence of KCOT.

**Methods**

This study was conducted as a narrative review. Information was gathered by searching keywords such as management, treatment, pharmacology, surgery and keratocystic odontogenic tumor in international databases such as Web of Science, PubMed and Scopus. The search period was between 2010–2020. As the subject was a narrative review, we studied all types of articles. Then the searched articles were evaluated based on the title, method and results. Finally, the related articles were selected for this review.

**Results**

In the initial search, 1,500 articles were found. After deleting the duplicate, unrelated or incomplete information, and studies performed *in vitro* as well as studies without full text, 40 studies were eventually classified as the main study (Tab. 1).

**Tab. 1. Main information extracted from the studies articles.**

Author’s name	No. of patients	Location	Treatment	Recurrence	Follow-up	Conclusion
Agrawal et al 2014 [37]	1	mandible	enucleation of the cyst, peripheral osteotomy and use of Carnoy’s solution	–	–	Conservative management using bismuth iodoform paraffin paste can be used in cystic lesions, benign lesions, etc.; don’t use in case of malignancies.
Borgonovo et al 2011 [38]	3	left ramus region and mandible	marsupialization; after a mean period of 10 months, enucleation with peripheral osteotomy	no	5 yrs	The preservation of important anatomical structures involved in the lesion and jaw’s continuity is a main advantage of this technique.
Cassoni et al 2013 [39]	77	maxilla (14 cases) and mandible (63 cases)	enucleation (55 cases) and radical resection (22 cases)	19% in enucleation group and no recurrence in resection group	3–5 yrs	Conservative treatment is associated with high recurrence and resection provides the lowest recurrence rate, but causes most suffering to the patient.

Tab. 1 – continuing. Main information extracted from the studies articles.

Author's name	No. of patients	Location	Treatment	Recurrence	Follow-up	Conclusion
Davoodi et al 2013 [40]	1	mandible	full surgical extraction, including the 2 <sup>nd</sup> and 3 <sup>rd</sup> left molars	no	6 mos	A cervical abscess with a traumatic bone cyst was the result of infected KCOT.
Deboni et al 2012 [41]	2	mandible body	marsupialization	no	7 yrs	In young patients, conservative management with a low rate of adverse effects should be considered as treatment choice.
de Molon et al 2015 [42]	1	left side of mandible	marsupialization for lesion decompression and consequent lesion size reduction; enucleation for complete KCOT removal followed by extraction of 3 <sup>rd</sup> mandibular molar	no	5 yrs	This therapy procedure was a safe and effective way to control KCOT, allowing the original lesion to be reduced while anatomical components were preserved.
Ebenezer and Ramalingam 2014 [43]	8	mandible and maxilla	resection (3 cases) and enucleation followed by application of Carnoy's solution (5 cases)	no	–	Treatment modality should be decided on age, extent, aggressiveness and nature of the tumour.
Güler et al 2011 [44]	39	mandible (76.7%) and maxilla (23.3%)	enucleation (18 cases), enucleation with Carnoy's solution (10 cases); marsupialization followed by enucleation with Carnoy's solution (15 cases)	no	40.5 ± 23.0 mos	Enucleation and Carnoy's solution in tiny lesions as well as marsupialization in large lesions were successful therapeutic procedures.
Gao et al 2014 [45]	20	–	decompression with customized thermo-plastic resin stents	no	1–24 mos	Decompression was effective in increasing bone density and reducing odontogenic cystic lesions of the jaw, secondary definitive surgery was necessary for aggressive lesions.
Guimarães et al 2013 [46]	3	left mandibular ramus, right mandibular angle region, right mandibular angle	surgical resection	no	4 yrs 6 mos 9 mos	Understanding both biological and molecular levels could lead to therapy and prognosis guidelines for people with this condition.
Hasheminia et al 2014 [47]	1	mandibular body and maxilla	marsupialization	no	30 mos	Marsupialization with or without adjunctive treatments is a conservative and effective protocol with low morbidity and cost.
Kebede et al 2016 [48]	1	right mandibular angle to left mandibular ramus	total mandibulectomy	no	6 mos	Occurrence of KCOT should be considered at the time of clinical diagnosis, although it is rare.

Tab. 1 – continuing. Main information extracted from the studies articles.

Author's name	No. of patients	Location	Treatment	Recurrence	Follow-up	Conclusion
Kim et al 2017 [49]	1	mandibular left primary molar	marsupialization, decompression after 2 yrs, curettage after 1 yr, decompression repeated after 1 yr	yes (2,3 and 4 yrs after first surgery)	4 yrs	Initial decompression and later peripheral ostectomy can be a good conservative treatment option for young patients.
Koçak-Berberoğlu et al 2012 [50]	4	maxilla (3 cases), maxilla and mandible (1 case)	enucleation	–	–	Lesions in the maxillofacial region could be better shown in the correct dimensions by cone beam computed tomography vs. panoramic radiograph.
Kunihiro et al 2014 [51]	1	maxilla	enucleation, the whole tumor was successfully removed using a bidirectional approach from the fistula and from the antrostomy in the middle meatus	no	6 mos	Collaboration between an oral surgeon and an otorhinolaryngologist could provide a minimally invasive and also radical surgical treatment for certain kinds of tumor in the head and neck region.
Lacarbonara et al 2014 [52]	1	upper left maxillary region	surgical antral cystectomy with the Caldwell-Luc method to remove the lesion and infected sinus mucosa	no	24 mons	To create a proper therapeutic protocol and achieve a favorable prognosis for the management of this patient, interdisciplinary collaboration of different specialities and careful preparation are essential.
Ledderhof et al 2017 [53]	32	mandible (27 cases) and maxilla (5 cases)	topical application of 5% 5-FU (11 cases) or modified Carnoy's solution (21 cases) after enucleation and peripheral ostectomy	no (in 5-FU group), yes (4 recurrences in Carnoy's solution group)	41.3 ± 3.8 mos and 35.0 ± 8.5 mos	Topical 5-FU is a new medication for KOTs that takes a molecularly targeted approach to treatment.
Leung et al 2016 [24]	105	mandible (83 cases) and maxilla (22 cases)	enucleation and application of Carnoy's solution, assessment of surgical morbidities associated with this treatment	11.4%	24–313 mos	Enucleation and application of Carnoy's solution for the treatment of KCOTs leads to relatively low recurrence and surgical morbidity rates.
Liu et al 2012 [54]	1	right mandible	segmental mandibulectomy	yes	14 yrs	When a lesion occurs in the ascending ramus of the mandible, particularly when the cortical bone is perforated, KCOT may reoccur in the surrounding soft tissue.
Zhao et al 2012 [55]	19	mandible (15 cases), maxilla (4 cases)	enucleation (12 cases) or enucleation with Carnoy's solution (7 cases)	yes (15 out of 19 (78.9%) recurred within 6 yrs, while 4 (21.1%) recurred after 6 yrs)	6 yrs	The recurrent KCOTs had a tendency to be more unilocular or multilocular than the primary cases, with a unilocular-to-multilocular ratio of 1.1 : 1.

Tab. 1 – continuing. Main information extracted from the studies articles.

Author's name	No. of patients	Location	Treatment	Recurrence	Follow-up	Conclusion
Morais de Melo et al 2012 [56]	1	mandible	decompression; after 6 mos the lesion cyst was lower than before decompression surgery; enucleation and curettage of the cyst	no	3 years	The success rate of decompression is as high as that of an aggressive treatment.
Motwani et al 2011 [57]	2	maxilla, right mandible	both our cases were treated by enucleation along with extraction of associated teeth	no	1 yr	Considering the high recurrence rate of these lesions, post-operative follow-up of at least 5 years is necessary.
Naruse et al 2017 [58]	63	mandible (44 cases), maxilla (18 cases), mandible and maxilla (1 case)	conservative (37 cases including 29 cases of no treatment and 8 cases of apicoectomy), radical treatment (22 extractions and 6 cases with no contact with the root)	yes (3 tumors)	–	Conservative treatment was the biggest independent risk factor for tumor recurrence.
Nomura et al 2015 [59]	1	maxilla	endoscopic modified medial maxillectomy technique	no	1 year	Endoscopic modified medial maxillectomy is a minimally invasive procedure that allows for a direct field of vision for maxillary KCOT treatment.
Ohki 2012 [60]	1	right maxillary sinus	endoscopic sinus surgery to widen the maxillary ostium and remove a piece of the cystic wall during transnasal marsupialization	no	1 year	Reductive change and minimal surgical invasion, making it advantageous in the case of secondary surgery, for full removal with less problems in the bones and surrounding tissue.
Ribeiro Jr. et al 2012 [61]	22	mandible (16 cases), maxilla (6 cases)	Carnoy's solution combined with peripheral ostectomy	4.5%	mean of 42.9 mos	KOTs can be effectively treated with Carnoy's solution and peripheral ostectomy.
Roopak et al 2013 [62]	3	mandible	decompression and marsupialization to avoid secondary deformity (1 case), enucleation with excision of overlying mucosa and chemical cauterization carried out using Carnoy's solution (1 case), enucleation and peripheral osteotomy (1 case)	no	3 mos, 1 yr 2 yrs	The priority of the treatment method chosen should depend on the morbidity, size of the lesion, recurrence rate and patients' quality of life. Large cysts can be successfully treated with conservative approach.

**Tab. 1 – continuing. Main information extracted from the studies articles.**

Author's name	No. of patients	Location	Treatment	Recurrence	Follow-up	Conclusion
Scartezini et al 2012 [63]	1	left mandibular ramus	surgery involved osteotomy, detachment of cystic lesion and removal of 36 <sup>th</sup> , 37 <sup>th</sup> and 38 <sup>th</sup> teeth	no	12 mos	Accurate radiographic, microscopic and clinical examinations are essential to choose the most effective therapy and definitive diagnosis.
Schussel et al 2012 [64]	25	mandible (20 cases), maxilla (4 cases), mandible and maxilla (1 case)	surgical treatment associated or not with adjuvant therapy, i.e. cryotherapy and Carnoy's solution	48%	mean of 18 mos	Previous diagnosis before enucleation procedure and long-term follow-up for recurrence early detection is important.
Bharani et al 2012 [65]	1	right mandibular posterior region, left hemi-maxilla	a transoral approach, enucleation of mandibular cyst, followed by application of Carnoy's solution; extraction of affected teeth; treatment of maxillary cyst by similar method	no	2 yrs–10 mos	–
Srivatsan et al 2014 [66]	2	mandible	marsupialization by excision of the overlying mucosa and opening of appropriately sized window	no	2 yrs	The marsupialization approach resulted in the complete clearance of the lesion, eliminating the need for further definitive cystectomy treatment
Sivanmalai et al 2012 [67]	1	mandible	enucleation, peripheral osteotomy, followed by single application of Carnoy's solution, including over the inferior alveolar plexus	no	36 mos	Carnoy's solution is a supplementary treatment for keratocystic odontogenic tumors applied to the inferior alveolar vascular–nervous plexus.
Vázquez-Romero et al 2016 [68]	1	maxilla	curettage of the bone tissue to remove the cyst	no	6 mos	–
Warburton et al 2014 [69]	80	mandible and maxilla	12 patients treated by resection and 68 patients managed by enucleation and curettage, enucleation with peripheral osteotomy, or decompression with secondary enucleation	yes	2–168 mos	The involvement of the pterygoid muscles was the most common reason for KCOT excision, but malignant alteration was also a factor.
Zhou et al 2014 [70]	1	maxilla	modified treatment with enucleation, grinding and cryotherapy were effective methods of treatment for KCOT	no	8 mos	A suitable treatment option for giant KCOTs may be modified.

**Tab. 1 – continuing. Main information extracted from the studies articles.**

Author's name	No. of patients	Location	Treatment	Recurrence	Follow-up	Conclusion
Yang et al 2011 [71]	181 (220 KCOTs)	mandible (153 cases), maxilla (67 cases)	enucleation or curettage (164 cases), marsupialization or decompression (17 cases), lateral decortication (13 cases)	10.78%	5 yrs	The most common treatment method was enucleation or curettage, followed by marsupialization or decompression and lateral decortication.
Yildirim et al 2010 [72]	3	mandible (2 cases), maxilla (1 case)	conservative treatment (enucleation followed by open packing)	no	2 yrs	This technique could be a possible choice with a view of offering low morbidity rate and low recurrence rate, particularly in young patients.
Jafaripozve et al 2013 [73]	1	right side of the mandible at molar region	surgical treatment by enucleation and curettage 5 years ago, resection	yes	5 yrs	The patient's rate of recurrence and morbidity is reduced when the optimum treatment method is chosen and followed up on on a regular basis throughout his or her life.
Ribeiro-Júnior et al 2017 [74]	40	mandible (27 cases), maxilla (13 cases)	27 lesions treated by enucleation and 13 underwent decompression	15%	12–102 mos	Significant difference for the recurrence of lesions was not shown; this could be due to the effectiveness of the complementary treatments.
Oliveira et al 2017 [75]	1	mandible	decompression technique (during 8 mos), recurrence in mandibular ramus in a follow-up of 1 year and 6 months, enucleation and curettage associated with cryotherapy	no recurrence 3 years later	3 yrs	–

5-FU – 5-fluorouracil, KCOT – keratocystic odontogenic tumor, mo(s) – month(s), yr(s) – year(s)

In these studies, the sample size varied from 1 person to 181 people. The study showed that the site of KCOT was mostly in the mandible. Techniques used for treatment included decompression, marsupialization, enucleation with or without adjunct (Carnoy's solution, 5-fluorouracil (5-FU)), Caldwell-Luc surgery and resection, for example mandibulotomy, antrostomy, endoscopic modified medial maxillectomy (EMMM), etc. Of the 40 studies, recurrence was observed in 13 studies and the recurrence ranged from 0 to 48% in different treatment methods.

## Discussion

The aim of this review article was to assess the effective management methods in KCOT. A total of 40 original articles were

reviewed. Majority of the articles were case reports. The most common affected site was mandible. The sample size varied from one to 181 subjects in different studies. The difference in sample size made the interpretation of the findings difficult.

Review of the studies indicated that the management methods used for KCOT comprised of various surgical approaches, including decompression, marsupialization, enucleation with or without adjunct (Carnoy's solution, 5-FU), Caldwell-Luc surgery and resection, for example mandibulotomy, antrostomy, EMMM, etc.

## Decompression

Decompression is defined as any technique that reduces the pressure inside the cyst. Increased pressure inside the

cyst results in the growth and expansion of the cyst [14]. Decompression is considered as an alternative and a more conservative approach that annihilates the predisposing factors for tumor expansion by continues drainage of the cyst [15].

Decompression minimizes adjacent tissue injury. However the effects of decompression on prevention of recurrence is yet to be discussed [16,17]. The important superiority of marsupialization over decompression is preserving the important anatomical structures including inferior alveolar nerve and preventing following deformities [18].

## Marsupialization

Marsupialization was first described by Partch in 1892 [19]. This approach in-

cludes incision of a part of the body of KCOT tumor and suturing the borders in adjacent mucus. The resultant surgical window opens the cyst in oral cavity. In decompression technique, a drain is placed inside the lesion that connects the cyst to the oral cavity. This will reduce intracystic pressure and causes bone formation [20]. The difference between decompression and marsupialization is in the use of a cylindrical device (drain) for preventing mucosal closure [21]. Based on the findings of the study by Tabrizi et al, the recurrence rate might be lower in decompression compared to marsupialization [22].

#### **Enucleation with and without adjuncts**

Enucleate refers to the removal of a tumor's envelope in its entirety. Curettage is the process of removing growths or other material from the cavity's wall. This technique has been used as a treatment approach for KCOT for many years. Although enucleation or curettage are superior to marsupialization in providing adequate sample for tissue analysis, but the reported recurrence rate (62.5%) is not considered desirable for a treatment approach. Some studies combined enucleation or curettage with adjuvant therapy including chemical solutions (Carnoy's) or cryosurgical agents (liquid nitrogen) for the treatment of KCOT [23,24]. Similarly, a study reported a significant effect for combined enucleation with 5-FU in the treatment of KCOT, with fewer post-operative complications and recurrence compared to modified Carnoy's solution.

#### **Enucleation with Carnoy's solution**

Carnoy's solution was first used for the treatment of cystic lesions and fistulae by Cutler and Zollinger [25]. Later some studies reported the use of Carnoy's solution in the treatment of unicystic ameloblastoma and ossifying fibroma. Actually, of the difficulty of enucleating the friable and thin wall of the KCOT as one piece, and due to the small satellite cysts, consequently, treatment should be targeted to eliminate the possible vital cells left behind in the defect. This

is due to the use of a light, non-penetrating cauterizing agent such as Carnoy's solution (3 mL chloroform, 6 mL pure ethanol, 1 mL glacial acetic acid, and 1 g ferric chloride) [26]. Furthermore, Carnoy's solution might penetrate cancellous spaces and deviate or fix the remaining tumor [27]. Currently the reformulated Carnoy's solution, without chloroform, is being used as exposure to chloroform may result in cancer or affect fertility [28]. Electrocauterization has been used to prevent recurrence in cases where KCOT invades buccal or lingual cortex [29].

Various studies and evaluations have pointed out to the high efficacy of the administration of Carnoy's solution in combination with enucleation. The use of Carnoy's solution during surgical treatment of invasive cystic lesions reduced the recurrence risk from 6–80% to 6.6% [24,30–32]. Furthermore, some studies used Carnoy's solution as an adjuvant therapy after peripheral osteotomy, which reduced recurrence rate [33]. Güler et al also suggested to use this technique in small unilocular lesions [22].

#### **Resection with or without preservation of the continuity of the jaw**

Segmental resection refers to the surgical removal of a segment of the mandible or maxilla without retaining bone continuity, while marginal resection refers to the surgical excision of a lesion intact with a rim of uninvolved bone while keeping bone continuity [24,34].

Resection technique is used in KCOT cases with very large lesions with pterygoid muscles involvement, malignant changes or frequent recurrences. Another indication for resection is perforation of bone cortex and involvement of soft tissue with the probability of vital structure involvement including lateral skull base and orbit [34].

Although some studies reported that the recurrence rate after resection was zero [34,35], but resection is considered as an extreme method as it results in significant complications and requires reconstruction measures for the restoration of functional and aesthetic

purposes. This will add the psychological and economic burden of the disease and may reduce the quality of life in KCOT patients at all age groups, especially in the youth.

KCOT tumors have high recurrence rate [31,36]. The findings of this review indicated that the recurrence ranged from 0 to 48% in different treatment methods. Therefore, it is suggested that long term follow-up should be considered after treatment to reduce recurrence. This review also found that the recurrence rate was higher in conservative treatments compared to aggressive treatments; therefore, it is suggested that the treatment method should be decided carefully. Decision on the treatment should be made considering age, tumor size, and the site of involvement in order to reduce the economic and psychological burden of the disease.

#### **Conclusion**

Current developments in genetic and molecular techniques have increased our knowledge about KCOT and resulted in new treatment choices. Due to the high recurrence of this disease, it is suggested that long term follow-up be considered after treatment to reduce recurrence. Also it is recommended that the treatment method be selected carefully. We suggest that physicians should consider age, tumor size and other factors in choosing the treatment option in order to prevent recurrence. According to the studies reviewed, the use of enucleation and Carnoy's solution for small lesions, marsupialization and decompressing for larger lesions and resection for very large lesions is suggested. As KCOT is more common in the second decade of life, long term follow-up is recommended.

#### **Data availability**

All generated data were used in this study.

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