The Keratocystic Odontogenic Tumor

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KEYWORDS
• Keratocystic odontogenic tumor • Odontogenic keratocyst • Enucleation • Radiolucency

KEY POINTS
• In 2005, the World Health Organization renamed the lesion previously known as an odontogenic keratocyst as the keratocystic odontogenic tumor.
• The clinical features associated with the keratocystic odontogenic tumor show it to be a unilocular or multilocular radiolucency, occurring most frequently in the posterior mandible.
• These tumors are normally diagnosed histologically from a sample of the lining.
• With simple enucleation, it seems that the recurrence rate may be from 25% to 60%.

In 2005, the World Health Organization renamed the lesion previously known as an odontogenic keratocyst as the keratocystic odontogenic tumor (KOT or KCOT).1,2 The term odontogenic keratocyst was first used by Philipson in 19563 and its clinical and histologic features were confirmed by Browne in 1970 and 1971.4,5 At that time, it was believed to be a benign, but potentially aggressive and recurrent, odontogenic cyst, and probably represented the lesion previously termed a primordial cyst.6 Although most of these cysts were lined by parakeratinized epithelium, a few were orthokeratinized. Over the years, it has generally been agreed that the orthokeratinized versions have a lower incidence of recurrence than the parakeratinized version. As initially described, it was believed that the primitive nature of the epithelium may have a premalignant potential,7 but this is now believed not to be true, and the incidence of malignant transformation is probably extremely low.8 if it exists at all.

However, since its designation, some have believed that although it was designated as an odontogenic cyst, the lesion behaved more like a tumor.9–11 The reasons for this belief include its clinical behavior, with a high recurrence rate after simple enucleation, the histologic appearance, and, more recently, the presence of tumor markers within the cyst. These markers consist of specifically proliferating cell nuclear antigen (PCNA), Ki67, BCE 2 sequence of the enzyme dihydrolipoyl acetyltransferase, matrix metalloproteinase (MMP) 2 and 9, and p53.12–14 This combination of features led to the 2005 reclassification of this lesion, although a PubMed search of articles published since 2005 found that the lesion is still mostly referred to as an odontogenic keratocyst.15 Even the term KCOT refers only to the parakeratinized version of the odontogenic keratocyst, and this leaves the orthokeratinized version of the cyst without a new designation. Until further reclassification, these orthokeratinized cysts are grouped with other benign odontogenic cysts.

CAUSE

It is generally believed that these lesions originate from remnants of the dental lamina in the same way as the primordial cyst.6 However, a tooth is generally not missing and, therefore, they are believed to originate from additional remnants of the lamina not involved in tooth formation. Alternatively, in some cases they may arise from the oral mucosa, particularly in the retromolar region, because daughter cysts are found between the oral mucosa and the cyst in the retromolar
Therefore, there may be 2 possible sites of origin of this lesion (Fig. 1).

CLINICAL FEATURES

The clinical features associated with the KCOT show it to be a unilocular or multilocular radiolucency, occurring most frequently in the posterior mandible (the same site as the primordial cyst). It may or may not be associated with a missing tooth (usually not) (Fig. 2). Expansion of the buccal and lingual plates occurs late with this lesion (in contrast to the ameloblastoma), because it primarily tends to invade the marrow. However, it does cause some expansion of the lingual plate and can cause lingual plate perforation (Fig. 3). Inferior alveolar nerve involvement occurs late. Clinically, the lesion has a high recurrence potential if purely enucleated. Reports in the literature vary, but can show a recurrence rate of from 25% to 60% after local enucleation.17–21 The reasons for this recurrence rate are believed to be 3-fold:

- They have a thin lining, which is friable, and portions are easily left behind.
- Daughter cysts occur beyond the visible margin of the lesion.
- Some of these lesions may originate from the oral mucosa and daughter cysts are seen between the oral mucosa and the cyst itself. Unless these lesions are removed, recurrence is likely (Fig. 4).

The basal cell nevus syndrome (also called Gorlin syndrome or Gorlin-Goltz syndrome) is a genetic condition with an autosomal-dominant inheritance pattern that includes a triad of KCOTs of the jaws,

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Fig. 1. KCOT with daughter cyst beyond the lining of the cyst and daughter cysts between the cyst and the alveolar mucosa. The area of alveolar mucosa that should be excised with the lesion is indicated. There is also a lingual perforation with associated daughter cysts. (Adapted from Bradley PF, Fisher AD. The cryosurgery of bone, an experimental and clinical assessment. Br J Oral Surg 1975;13:122; with permission.)

Fig. 2. A multilocular, multicystic KCOT of the right mandible not associated with a missing tooth. The complexity of the lesion contributes to difficulty in total removal.

Fig. 3. A coronal cone-beam computed tomography scan showing a multilocular, multicystic KCOT, with lingual perforation and the inferior alveolar nerve embedded in the base of the lesion.
other skeletal abnormalities (often including bifid ribs, abnormalities in the length of the fingers and toes, frontal bossing, and calcification of the falx cerebri), as well as cutaneous manifestations such as basal cell carcinomas, palmar pitting of the hands, and other skin abnormalities.22,23 Renal abnormalities and medulloblastomas in the newborn may also be manifestations of this condition. Whether sporadic or hereditary, most cases are related genetically and show aberrations in the hedgehog signaling pathway. The hedgehog signaling pathway involves a dynamic relationship between a series of tumor suppressor genes and oncogenes.

The basal cell carcinomas in this condition are atypical in that they occur on skin that is not sun-exposed and seem to be relatively benign and are often treated effectively with liquid nitrogen or silver nitrate sticks. Conversely, the KCOTs have often been believed to be particularly aggressive, with a tendency to recur, but in retrospect this may be more a question of the patient’s developing additional lesions rather than recurrences of the previous ones. This condition seems most active up until the time that growth ceases, and patients often form many KCOTs during this period. Usually after growth ceases, the growth of the tumors slows considerably and new tumors develop more rarely. Because these tumors occur during the age of tooth development, it is often preferable to treat them by extensive marsupialization to expose the lining and allow the teeth to erupt, which seems to be successful and does not lead to a higher incidence of recurrence of the lesions. However, when this procedure is not appropriate, they can be managed in the usual way for KCOTs, with aggressive enucleation and curettage or even with peripheral, marginal, or segmental resection for particularly aggressive lesions.

**DIAGNOSIS**

These tumors are normally diagnosed histologically from a sample of the lining. This diagnosis requires a surgical biopsy, and difficulties can arise when the cyst has been previously exposed or inflamed, when the lining tends to become thicker and less obviously parakeratinized. Diagnosis is normally made on permanent paraffin-stained sections, although attempts have been made to diagnose it from frozen section so that definitive treatment can be performed at the same time as the biopsy. However, frozen sections of KCOTs have a high error rate of more than 35%, which may render this technique impractical.21 Attempts have also been made to diagnose KCOTs from examination of a fluid aspirate. If subject to immediate histologic examination, keratin can often be seen under the microscope, and if the fluid is analyzed, the protein content (at <4.0 g/100 mL) is lower than that in serum (7.1 g/100 mL), which is also the protein content of a dentigerous cyst. It is also lower than that of an ameloblastoma, usually around 5.5 g/100 m.24

**TREATMENT**

With simple enucleation, it seems that the recurrence rate may be from 25% to 60%. When treating the lesion as one would an ameloblastoma, including resection with 1-cm margins (this often necessitates a segmental resection), the recurrence rate can be virtually zero. However, this treatment may cause excessive morbidity. Therefore, although both of these techniques may be possible (simple enucleation in a patient with a limited life expectancy or segmental resection for a large lesion that has multiple cortical perforations), most of the search has been for an intermediate technique that gives an acceptable cure rate with an acceptable morbidity. Several of these techniques have been proposed.

**Marsupialization or Decompression**

It was well known in the preantibiotic era that most dental cysts could be marsupialized and that this cured them. Marsupialization in its purest form consists of opening up the cyst to the oral cavity and suturing the cyst lining to the oral mucosa, creating a permanent opening into the cyst (Fig. 5). The cyst is, therefore, decompressed (most cysts grow by osmosis,25 although the KCOT may also grow by bone resorption from prostaglandin production).26 and decreases in size as new bone is laid down around it. This procedure was originally known as the Partsch I
technique. With the advent of antibiotics, this technique was generally abandoned in favor of more definitive enucleation of dental cysts (the Partsch II technique). However, the technique has been resurrected for the management of the KCOT. It is either used in its classic form of suturing the cyst lining to the oral mucosa (Fig. 5) or it is used more as a decompression technique, in which a smaller opening is made into the cyst, without suturing the lining and by use of a decompression tube of some kind (Fig. 6). It has been noted in several studies that if this technique is used, the cyst decreases considerably in size and in most cases disappears completely radiographically. It has also been noted on biopsy of the lining that as the cyst decreases in size, the lining transforms from the thin parakeratinized lining to a thicker lining more resembling the oral mucosa. It is not known whether this process happens by metaplasia in the KCOT lining or by overgrowth of more normal epithelium. In some techniques, it is recommended that the decompression be used for cure and complete resolution of the lesion (Fig. 7), whereas in others it is used to decompress the lesion and decrease its size, thicken the lining so that it is easier to remove, and when the cyst has decreased in size enough to be away from other structures (the inferior alveolar nerve and adjacent teeth), it can be enucleated. If this decompression technique is used for cure, then there does seem to be a 10% recurrence rate using the most currently available data. If the decompression is used to decrease the size only, followed by more definitive enucleation of a lesion with a thicker lining, the long-term cure rate is undefined but may be higher.

**Enucleation with Peripheral Ostectomy**

If one accepts that the high recurrence rate after simple enucleation is caused by the presence of retained fragments of lining plus daughter cysts that are left behind, then it may be that removal of 1 to 2 mm of bone beyond the visible margin of the lesion is adequate to improve the cure rate. However, it is difficult to estimate how much bone to remove with a drill. This process is made easier by the use of a vital staining technique. Methylene blue or crystal violet (or any other vital stain) can be painted on the bony walls of the enucleated cyst and allowed to penetrate into the bone. The cavity is then washed out and any bone retaining the stain is removed with a drill (see Fig. 8). This process usually removes around 2 mm of bone in the marrow and about 1 mm of cortical bone. Good studies of the success rate of this technique do not exist, but it is believed to improve the cure rate.

**Physicochemical Treatment**

**Chemical treatment with Carnoy solution**

The only chemical agent in use to increase the cure rate of the KCOT is Carnoy solution, and this remains controversial (Fig. 9). Originally used as a histologic fixative, it has been used clinically. Its classic ingredients are as follows:

- Absolute alcohol: 6 mL
- Chloroform: 3 mL
- Ferric chloride: 1 g
- Glacial acetic acid: 1 mL

![Fig. 5. Technique of marsupialization, with suturing of the cyst lining to the alveolar mucosa. (From Pogrel MA. Decompression and marsupialization as a treatment for the odontogenic keratocyst. Oral Maxillofac Surg Clin North Am 2003;15:416; with permission.)](image1)

![Fig. 6. Decompression of a KCOT of the right posterior mandible by means of a drainage tube wired to the first molar. The drainage tube often has to stay in place for 9 months to a year and be irrigated twice a day with normal saline by the patient, so it needs to be secure.](image2)
The most usual technique involves enucleation of the lesion followed by painting the sides of the cavity with Carnoy solution, leaving it in place for 5 minutes, and then washing out the cavity. After washing out, the cavity has brown, denatured bone on its wall. Some practitioners leave this bone in place, whereas others remove it with a drill to get down to normal bone. This technique generally involves a removal of 1 to 2 mm of bone. Carnoy solution is neurotoxic and chemically fixes the inferior alveolar or lingual nerves if it comes in contact with them for up to 2 minutes. The nerve should therefore be protected; bone wax can be used for protection of the inferior alveolar nerve. The other issue with Carnoy solution, as originally formulated, is that it contains chloroform, now classified as a borderline carcinogen by the US Environmental Protection Agency (EPA) and as an outright carcinogen by the California EPA. For this reason, practitioners have used the solution without the chloroform, but cure rates with the modified Carnoy solution are not available. In addition, there is some debate as to whether or not Carnoy solution should be mixed fresh before use. Some investigators state that it should be mixed fresh and used within 2 days, whereas others state that it can be left for several months. When supplied in the United States, the US Food and Drug Administration does approve it for up to 6 months. Results with the use of Carnoy solution show a low recurrence rate, in the order of 2.5%.\(^{16,41–43}\)

**Physical treatment with cryotherapy**

Freezing is known to cause cell death. However, to cause cell death (as in frostbite), freezing must be rapid and thawing should be slow, and temperatures less than \(-20^\circ\text{C}\) must be achieved. The only commonly available agent that can achieve this temperature is liquid nitrogen, which boils at \(-196^\circ\text{C}\). Carbon dioxide and nitrous oxide both boil at temperatures high enough (\(-78.5^\circ\text{C}\) and \(-89.7^\circ\text{C}\), respectively) that they cannot maintain \(-20^\circ\text{C}\) consistently, particularly if there is any heat sink effect caused by adjacent blood vessels.\(^{44}\) The technique using liquid nitrogen involves enucleation of the lesion followed by protection of the soft tissues with a combination of wooden tongue blades and dry gauze followed by treatment of the cyst cavity with the liquid nitrogen.

![Fig. 7. (A) A large, multilocular KCOT of the mandible on initial presentation. (B) The same lesion 9 months later after biopsy, to establish the diagnosis, and insertion of 2 drainage tubes (seen on the radiograph) for decompression. The patient irrigated the drains twice daily with normal saline. The drains were removed after 1 year.](image)

![Fig. 8. (A) The cavity remaining after a cyst has been enucleated, and stained with methylene blue. (B) The same cavity after removing the methylene blue with a peripheral ostectomy using a pineapple-type bur.](image)
For a cyst of less than 1.5 cm, the cyst cavity can be filled with a conductive medium such as KY jelly and a liquid nitrogen probe placed within it to freeze the whole mass (Fig. 11). For a larger cavity, the liquid nitrogen must be sprayed into the cavity, and for this, a long (about 20.3 cm [8 inches]) intravenous-type cannula is preferred, because it can be directed into any part of the cavity. The technique involves freezing the cavity walls until a frost forms (Fig. 12). The frost should be maintained for 1 minute with repeated sprays and then allowed to thaw. The thaw should be slow and natural, because this increases cell death by causing osmotic imbalance. Once it is thawed, the freeze is then normally repeated at least 1 more time for completeness in case any areas were missed on the first freeze. Some practitioners prefer to give the area 3 freezes to be certain that no area is missed. Studies have shown that liquid nitrogen penetrates to at least 1.5 mm around the cavity. If the inferior alveolar nerve is involved, the neuron degenerates, but the axon sheath is intact, and nerve regeneration is good, with most patients achieving at least some return of sensation and many patients achieving full return of sensation. If teeth are affected by the cryotherapy, degenerative changes can occur in the pulpal tissues, but they often recover, and pulpal necrosis rarely needs treatment. However, liquid nitrogen cryotherapy for bone does significantly weaken the bone until new osteogenesis occurs. This bone weakness reaches its maximum about 8 weeks after cryotherapy, and mandibular fractures around this time have been reported. For this reason, we now recommend simultaneous cancellous marrow bone grafting for lesions grater than 3 to 4 cm to accelerate osteogenesis and decrease the chance of mandibular fracture. Using this cryotherapy technique seems to be associated with a recurrence rate of around 10%, which is better than with enucleation alone.
Maxillary Tumors

Fortunately, keratocystic odontogenic tumors of the maxilla are unusual compared with those in the mandible (Fig. 13). However, there are potentially more issues and possible complications with maxillary lesions.

- The cortical bone is thinner so perforation can occur sooner.
- The presence of the maxillary sinus and nasal cavity mean that involvement of these areas can occur early.
- Radiographically, it is often difficult to separate the cyst from the maxillary sinus, even with CT scanning.
- Perforation into the pterygopalatine space can occur with lesions posteriorly placed in the maxilla and can make subsequent complete removal very difficult.

For tumors of the anterior maxilla, treatment is essentially the same as for the mandible. As one moves more posteriorly in the maxilla, marsupialization is still a very viable option and the cavities normally shrink quickly. Unerupted teeth that have been displaced by the tumor may also start to erupt. This treatment may be particularly indicated in patients with Gorlin’s syndrome. The cyst is normally decompressed or marsupialized into the buccal sulcus of the oral cavity, but theoretically it can be marsupialized into the maxillary sinus itself or even into the nasal cavity and these approaches have been described.

Lesions of the posterior maxilla, particularly those which are in proximity to the pterygomaxillary space may respond to marsupialization and decompression, but one should have a low threshold for carrying out a partial posterior maxillectomy with immediate reconstruction. An obturator is rarely necessary except for the largest lesions, and although this may mean the loss of teeth and alveolus, it stands the best chance of avoiding spread to the pterygomaxillary space. Carnoy’s solution or liquid nitrogen can be used in smaller cysts which are completely surrounded by bony walls, but if there is any question of continuity with the sinus or nasal cavity, these modalities are best avoided and particularly in lesions which extend up to the orbital floor.

THE AUTHOR’S CURRENT TECHNIQUE

Because none of these techniques seems to be associated with a zero recurrence rate, the author’s current technique is as follows:

1. Obtain a tissue biopsy of the cyst. At the same time, a drainage tube is placed. This tube is normally made from either a piece of intravenous

**Fig. 11.** (A) A smaller lesion treated with liquid nitrogen by the technique of filling the cavity with KY jelly and placing a liquid nitrogen probe in it and freezing the whole cavity. (B) The cryoprobe has been removed, showing the frozen KY jelly and surrounding bony walls of the cyst cavity. These frozen areas are allowed to thaw naturally and slowly and then the freeze is repeated. This technique can be used only for small lesions less than about 1.5 cm.

**Fig. 12.** A larger cavity where the bony walls of the cavity have been frozen by a liquid nitrogen spray. The frost is kept in place for 1 minute and is followed by a slow thawing process. This process can be repeated up to another 2 times.
tubing or a pediatric feeding tube. They are similar to those advocated by Brodnum (Fig. 6).31

2. If the diagnosis comes back as a KCOT, the drainage tube is left in place, the patient irrigates it twice a day with normal saline, and the size of the cyst is monitored radiographically every 3 months. The cysts normally start to regress quickly, and by 9 months to a year, have become smaller (Fig. 7). If the biopsy shows a lesion other than KCOT, it is treated accordingly.

3. When the radiolucency has decreased to about 2 cm or less in diameter and is not in contact with adjacent teeth or the inferior alveolar nerve, it is enucleated and the cavity treated with liquid nitrogen cryotherapy given by means of a cryospray (Figs. 11 and 12). If an adjacent tooth is still involved, it must be removed. At the same time as enucleation of the lesion, the overlying mucosa is excised to eliminate any daughter cysts between the overlying mucosa and the cyst. After cryotherapy, excellent soft tissue closure is required, because otherwise, wound breakdown is possible. A combination of vertical mattress sutures and simple interrupted sutures is preferred.

The author has been using this particular technique for 3.5 years and has treated 25 lesions in this manner. There have been no recurrences, although it is recognized that 3.5 years is an inadequate length of time to monitor these lesions. We recommend follow-up, primarily with panorex-type radiographs, every 6 months for 2 years, every year for 5 years, and every 2 years for 10 years in asymptomatic patients.

REFERENCES

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Fig. 13. Panorex of a KCOT of the left posterior maxilla, displacing the associated third molar. This KCOT needs to be imaged in 3 dimensions by means of a computed tomography scan and is probably treated by attempted decompression with a drainage tube followed by a partial posteroinferior maxillectomy and immediate reconstruction.