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ORIGINAL ARTICLE

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

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Abstract This retrospective study aimed at evaluating the recurrence rates of keratocystic odontogenic tumors (KCOTs) that were enucleated with and without the application of Carnoy's solution (CS). The study included 36 KCOTs treated between 1996 and 2006. Recurrence rates were investigated in correlation with the respective treatment method applied. Additionally, any damage to the inferior alveolar nerve associated with treatment was analyzed. Treatments consisted of enucleation with (38.9%) or without (61.1%) the application of CS. Median follow-up was 4.5 years. Single enucleation showed a recurrence rate of 50%, but the additional application of CS reduced the recurrence rate to 14.3%. No detrimental effects of CS on the mandibular nerve were detected. Enucleation plus the application of CS reduced the recurrence rate of KCOTs compared with simple enucleation. The application of CS did not cause any damage to the mandibular nerve.

Keywords KCOT · Carnoy's solution · Enucleation · Keratocyst · Mandibular nerve

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Introduction

In the WHO classification of head and neck tumors of 2005, the former odontogenic keratocyst (first described by Philipsen in 1956) was reclassified and renamed keratocystic odontogenic tumor (KCOT). Thus, this tumor was classified not as a cyst but as a benign neoplasm of odontogenic origin [1, 2]. KCOT is defined as a benign, uni- or multicystic, intraosseous tumor arising from the dental lamina or its remnants [1–3]. This tumor may appear as a single lesion or as multiple neoplasms, which are often part of the nevoid basal cell carcinoma syndrome (NBCCS) [1]. The NBCCS, also known as the Gorlin syndrome, is a genetic disorder inherited in an autosomal dominant manner. This syndrome is characterized by keratotic pits on palms and soles, a calcified falx cerebri, rib malformations, and an extraordinary predisposition to basal cell carcinomas and KCOTs [4]. The gene for Gorlin syndrome has been mapped to chromosome 9q22.3–q31 [5–7] and

has been identified as PTCH, the human homolog of the Drosophila "patched" gene PTC that functions as a tumor suppressor [8]. An allelic loss of 9q22 at two or more loci [4, 9] leads to the inactivation of this tumor suppressor gene and to the promotion of tumor growth, which is not only detectable in NBCCS but also in sporadic KCOTs [5, 6, 10–12].

KCOTs often occur in the mandibular ramus and angle region but rarely in other mandibular regions or the maxilla [2, 13]. This tumor has a well-known propensity to recur and the recurrence rate largely depends on the treatment modality [14, 15]. As is known from multiple studies, simple enucleation shows high recurrence rates (Table 1). KCOT resembles ameloblastoma in imaging, and, apart from histology, no reliable criteria exist for pretherapeutic differentiation [15]. In consideration of the far more aggressive treatment modalities of ameloblastomas, some authors have raised the question whether KCOTs should also be simply resected. However, resections have proven minimal recurrence rates but significant morbidity rates. For benign lesions, less aggressive treatment strategies should be preferable. To reduce recurrence rates, the application of modified Carnoy's solution (CS) has been proposed as adjunct treatment to enucleation—an intervention that might present the best compromise. Modified CS was originally developed from Carnoy's fixative in pathology and acts as a cauterizing agent that denaturates proteins, nucleic acids, and almost all other organic molecules. CS penetrates moderately into the tissue, resulting in rapid local fixation and hemostatic action [16].

In the treatment of bony defects, CS aims at eliminating epithelial residues from cyst walls that may have been left after enucleation and thus serve as a possible cause of recurrence [3]. Other centers achieve the same goal by milling out the cavity after enucleation with the visual aid of a microscope [17, 18].

The present study aimed at evaluating the effectiveness of CS as adjunct therapy to enucleation in the treatment of KCOTs in a 10-year retrospective survey. Furthermore, suspected impairment of the alveolar nerve by CS was also assessed.

Materials and methods

In this retrospective study, 34 patients with 36 histologically proven KCOTs were included. The tumors were primarily treated between January 1996 and July 2006. Clinical and radiographic features were reviewed and follow-up data were obtained during tumor recall. KCOT size at first presentation was recorded retrospectively by two-dimensional measurements by panoramic X-rays (lengths and height). Patients with nevoid basal cell carcinoma syndrome were excluded.

KCOTs were treated with enucleation. According to Voorsmit [16], modified CS (absolute alcohol 6 cc, glacial acetic acid 1 cc, chloroform 3 cc, and ferric chloride 0.1 gm/ml) was applied as adjunct treatment for 3 min prior to surgical enucleation. After enucleation, the cavity was thoroughly rinsed with saline solution (NaCl 0.9%). The decision to additionally apply CS depended on the surgeon and not on the size or location of the KCOT.

The length of the follow-up was calculated from the time point of the first treatment to the last follow-up, up to December 2007. Recurrence was defined as the reappearance of a histopathologically proven KCOT at the same site at least 6 months after treatment. Because of the different observation intervals, recurrence rates were additionally shown in survival curves (Kaplan–Meier) (Fig. 1).

Impairment of mandibular nerve function was assessed by sharp and blunt discrimination in a standardized manner, i.e. lower lip and chin were touched at three different standardized points with both the sharp and the blunt side of a dental probe. Sensitivity was always tested in comparison to the unaffected side while the patient's eyes were covered. The results were classified as follows: anesthesia (no sensitivity, lack of ability to distinguish sharp and blunt), hypesthesia (impaired ability to distinguish sharp and blunt), and normal sensitivity. Sensitivity was tested before and after treatment as well as at every recall.

Prime software version 4.0 was used for statistical analysis. We used Fisher's exact test to analyze the significance of the differences in recurrence rates between the groups and considered a p value<0.05 as significant. SPSS software version 16.0 was used for statistical analysis. Survival curve analysis was used to evaluate the significance of the differences in recurrence rates between the groups.

Results

The study population comprised 21 men (61.8%) and 13 women (38.2%). Age at time of diagnosis ranged from 6 to 74 years (mean 40.9 years, median 37.0 years).

At the first treatment, the 34 patients showed 36 lesions: two were located in the maxilla (5.6%) and 34 in the mandible (94.4%). The mandibular angle represented the most frequently involved region (40.7%), followed by the mandibular ramus (27.1%), the molar and premolar region (22.0%), and the anterior mandible (6.8%).

Each of the 36 lesions was treated with enucleation; 14 were additionally treated with CS (38.9%), whereas 22 were excised without the application of CS (61.1%).

Table 1 Review of the literature on epidemiology and correlation of treatment and the recurrence rate of KCOT with emphasis on Carnoy's solution

Source	Patients	Av. age	M:F	Mandible[%]	Maxilla [%]	Treatment	Recurrence rate [%]
Zachariades et al. [30]	16	n.g.	4.3:1	62.5	37.5	Enucleation (14)	29
						Marsupialization (2)	0
Forssell et al. [31]	75	33	n.g.	85.3	14.6	Enucleation (one piece) (28)	18
						Enucleation (several pieces) (41)	56
						Marsupialization (5)	60
Brondum and Jensen [32]	44	45	1:1	82	18	Enucleation and ostectomy (32)	25
						Marsupialization followed by enucleation (12)	0
Eufinger & Machtens [33]	49	20–40	1.9:1	79	21	Marsupialization (3)	100
						Enucleation (78)	39
						One piece (23)	13
						Curetage (31)	29
						Cystectomy (11)	27
						Carnoy (5)	20
Dammer et al. [34]	38	37	3:1	61.9	38.1	Enucleation (32)	4.6
						Enucleation and Carnoy (2)	50
						Resection (4)	0
Chow [35]	70	32.8	1.86:1	68.5	27.1	Enucleation (68)	8.8
						Enucleation and Carnoy (23) and ostectomy	4.3
						Resection (1)	0
Bataineh et al. [36]	31	n.g.	n.g.	100	0	Resection (31)	0
Blanas et al. [14] (review article)						Curretage (26)	19.2
						Enucleation (387)	28.7
						Enucleation and Carnoy`s solution (60)	2
						Enucleation and ostectomy (6)	16.7
						Enucleation and cryotherapy (16)	31.3
						Marsupialization (45)	24.4
						Resection (38)	0
Schmidt [37]	26	n.g.	n.g.	88.5	11.5	Enucleation and liquid nitrogen	11.5
Stoelinga [38]	80	n.g.	1:1.05	82.9	17.1	Enucleation (33)	18.2
						Enucleation and excision of overlying mucosa and Carnoy (38)	7.9
						Enucleation and excision of overlying mucosa (6)	0
						Enucleation and Carnoy (5)	0
Zhao et al. [13]	255	31.2	1.93:1	66.9	33.1	Enucleation (163)	17.8
						Enucleation and Carnoy (43)	6.7
						Marsupialization followed by enucleation (11)	0
						Resection (76)	0
Nakamura et al. [39]	24	n.g.	1.4:1	92.8	7.2	Marsupialization (5)	0
						Marsupialization followed by enucleation and curetage (25)	26.1
						Enucleation (15)	20
Pogrel and Jordan [40]	10	11–64	1.5:1	80	20	Marsupialization	0
Morgan et al. [19]	40	n.g.	n.g.	n.g.	n.g.	Enucleation (11)	54.5
						Enucleation and Carnoy (2)	50

Table 1 (continued)

Source	Patients	Av. age	M:F	Mandible[%]	Maxilla [%]	Treatment	Recurrence rate [%]
						Peripheral ostectomy (11)	18.2
						Periph ostectomy and Carnoy (13)	0
						en-bloc-resection (3)	0
Chirapthomsakul et al. [26]	51	36.9	1:1.2	68.7	31.3	Marsupialization (13)	16.7
						Enucleation (30)	13.3
						Enucleation and Carnoy (11)	20
						Enucleation and curetage (2)	100
						Marginal resection (1)	0
						Segmental resection (6)	16.7
Maurette et al. [41]	28	40.9	1:1.73	n.g.	n.g.	Marsupialization followed by enucleation and curetage (20)	14.3
						Enucleation and curetage (10)	0
Driemel et al. [15]	86	47	2:1	80.9	19.1	Marsupialization (6)	66.7
						Enucleation (46)	13
						Enucleation and curetage (17)	17.6
						Enucleation and ostectomy (14)	14.3
						Resection (11)	0
Habibi et al. [2]	83	27.1	1.45:1	67.5	32.5	Enucleation (66)	7.6
						Marsupialization (6)	33.3
						Marsupialization followed by enucleation (11)	0
Our Study	34	39.8	1.6:1	88	12	Enucleation (22)	50.0
						Enucleation and Carnoy (14)	16.7

Overall, 33.1% (13 out of 36) lesions recurred. The mean number of months until recurrence was 33.0 (range 7 to 86). Eleven lesions recurred only once during follow-up, two lesions recurred twice. All recurrences were treated with enucleation and CS.

Enucleation without CS showed a recurrence rate of 50.0% (11 out of 22). Twenty-two lesions were distributed in 20 patients (12 men, eight women); patient age at diagnosis was 41.5 years on average (6 to 70 years); follow-up time was 67.4 months (range 12 to 120 months). Two patients presented KCOT in the maxilla and 20 patients in the mandible. The mandibular angle (34.2%) and molar and premolar (28.9%) region represented the most frequent sites (Table 2). The average surface area of the KCOTs measured radiograpically was 13.3 cm².

Enucleation with CS showed a recurrence rate of 14.3% (two out of 14). These 14 lesions were found in 14 patients (nine men, five women); patient age at diagnosis was 40.1 years on average (16 to 74 years); follow-up time was 45.6 months (range 12 to 120 months). Each of the 14 KCOTs was located in the mandible, and the mandibular angle (46.4%) and the ramus (35.8%) represented the most frequent sites. The average surface area of the KCOTs measured radiograpically was 14.8 cm². The average surface area of the KCOTs of patients with recurrences (16.1 cm²) was larger than those without (13.4 cm²) (Fig. 2). The recurrence rate according to survival curve analysis was 14.3% with Carnoy and 50% without.

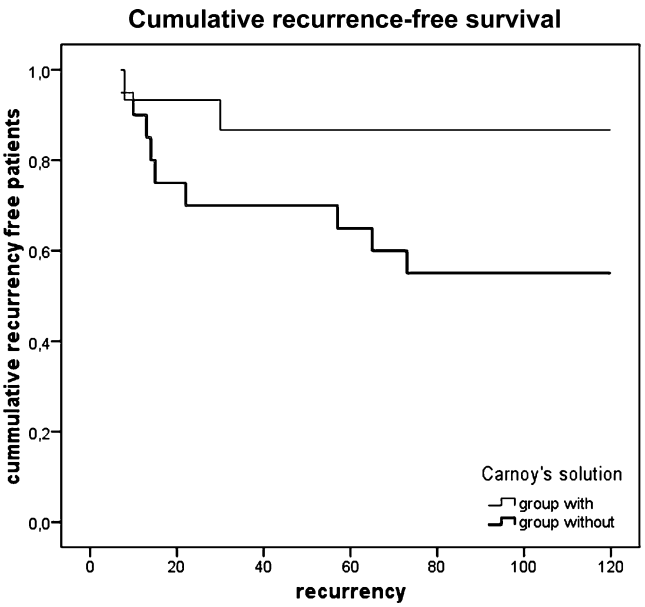

Fig. 1 Kaplan–Meier analysis of KCOT with and without Carnoy's solution shows a significant difference in recurrence rates

Table 2 Clinical data of the two treatment lines

	Enucleation without CS	Enucleation with CS
Number (patients/lesions)	20/22	14/14
Male/female ratio	1.5:1	1.8:1
Location of KCOT[a]		
Maxilla	2/(5.3)	0
Mandibular ramus	7/(18.4)	10/(35.8)
Mandibular angle	13/(34.2)	13/(46.4)
Molar and premolar region	11/(28.9)	5/(17.9)
Anterior mandible	5/(13.2)	0
Follow-up time (months)	67.4	45.6
Recurrence rate[a]	11/22 (50.0)	2/14 (14.3)
Average time until recurrence (months)	35.6	18.5

[a] absolute numbers, percentage in parantheses)

Based on the operation protocols, the inferior alveolar nerve was visible within the lesion in 11 patients. Two patients already showed preoperative hypesthesia in the lower lip. Newly developed hypesthesia or anesthesia immediately after surgery were detected in six (26.1%) (4=hypesthesia and 2=anesthesia) out of 23 patients. All patients with hypesthesia eventually recovered to normal sensitivity, after 2 years at the latest. The two patients with postoperative anesthesia—one had been treated with CS, the other one had not—experienced permanent anesthesia for 2 years, but the anesthetic area became smaller over time. Of the patients with hypesthesia, one was treated with CS and three were not.

Statistical analysis showed no significant difference with regard to gender, age, and average size and site of KCOT at the first treatment. Only follow-up time differed significantly between the two groups, as the group receiving enucleation plus CS had a shorter follow-up time (Table 3).

Discussion

The mean age of 40.9 years as well as the male preponderance for patients with KCOT is similar to the results of other studies [2, 16, 19–22]. KCOTs frequently present in the mandibular angle and ramus, which confirms the findings of other studies [2, 3, 16, 19, 20, 22, 23].Our study showed an overall recurrence rate of 33.1%. The literature reports of recurrence rates ranging from 2.5% to 62.5% (see Table 1) [2, 24]. For the sole use of simple enucleation, a recurrence rate between 17% and 56% was quoted [14]. With the additional application of CS, a recurrence rate between 1% and 8.7% was reported [14]. We recorded a recurrence rate of 50.0% without CS and 14.3% with CS. Admittedly, the recurrence rate in our patient group may slightly increase within the next few years, because some patients only have had a follow-up period of 1 to 2 years so far (five patients). Usually, recurrences show within the first 5 years; however, recurrences may occur 10 or more years after the first surgical treatment [13, 25].

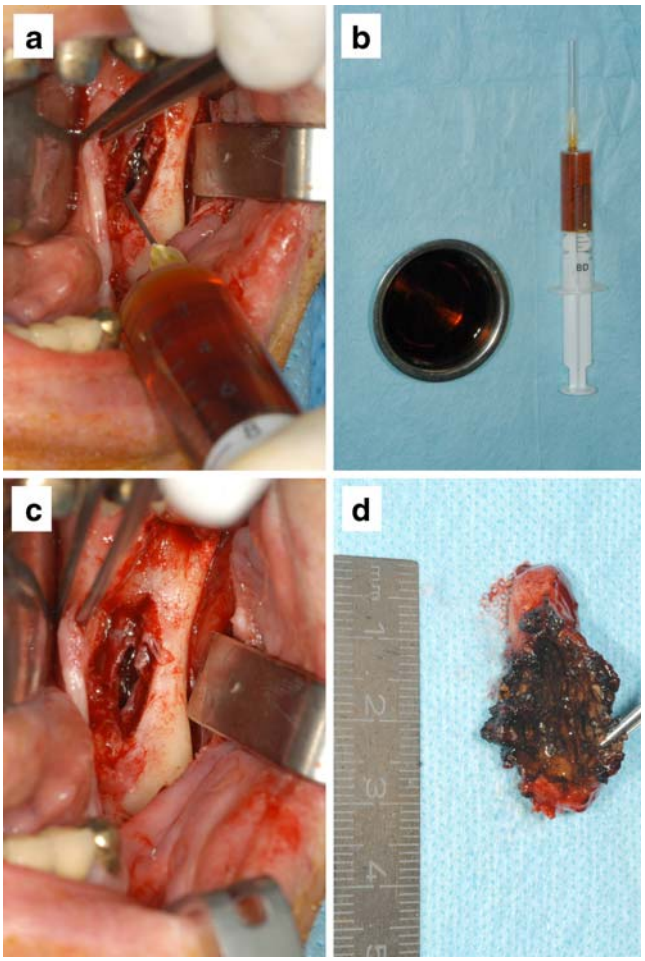

Fig. 2 Treatment of KCOT in combination with Carnoy's solution (intraoperative pictures): **a** opening of the cyst, **b** Carnoy's solution, **c** application of Carnoy's solution, **d** enucleation of the entire KCOT fixated with Carnoy's solution

Table 3 Clinical data of patients with recurrences

Initials	Gender	Age at time of first operation	Location	Surface size (cm²)	Lesions	Status of alveolar nerve postoperative	Carnoy	Time in recall (months)	Time until first recurrence (months)	Second recurrence (months)
BA	F	37	Ramus, angle, molar and premolar region right	26.25	1		No	41	7	
BP	M	66	Ramus, angle, molar and premolar region right	24	1		No	49	42	62
GF	M	24	Ramus, angle, molar region right	17	1		No	64	14	60
GK	M	37	Angle right and maxilla anterior right	8 mand. 7.7 max.	2		No	86	57 (mandible)	
HC	M	12	Angle right	10.5	1		No	31	13	
KJ	M	70	Premolar region right until premolar region left	19.5	1	Anesthesia right	No	120	26	
LJ	M	50	Ramus, angle, molar region left	20.5	1		No	63	57	
RH	M	57	Ramus left	16.5	1		No	120	86	
SK	M	27	Molar region right	18	1		No	37	10	
SM	F	16	Molar region left	7	1		No	93	15	
WB	M	39	Premolar region right until premolar region left	21	1		No	77	65	
FR	F	56	Angle and ramus right	15	1	Hypesthesia right	Yes	20	12	
MM	F	33	Angle right	6	1		Yes	35	29	

In the literature, additional treatments such as curettage or peripheral ostectomy after enucleation did not lower recurrence rates compared to enucleation alone (see Table 1) [14, 19, 26]. No significant demographic or KCOT-related differences exist between the two groups except the length of follow-up, which is shorter in the group treated with enucleation and CS.

In our case series, recurrences more often occurred in larger lesions than in smaller ones. Of course, the two-dimensional measurement of the average surface area is just an indication for the real size of a lesion, which could only be calculated by volume measurement after its examination by means of computed tomography and three-dimensional reconstruction, a procedure that was not done for all patients.

Animal experiments showed that—dependent of the time of application—CS may harm the mandibular nerve if applied directly [27–29]. In our study, postoperative impairment of sensitivity in the mandible was quite rare and no difference existed between the treatment groups. Nevertheless, direct exposure of the mandibular nerve to CS should be limited or the nerve should be protected during its application [3]. Results of animal experiments suggest that an exposure time of more than 3 min should not be exceeded to avoid detrimental effects on nerve function [14, 27, 28]. Furthermore, to avoid long-lasting effects, defects should be rinsed thoroughly with saline solution after CS application [3]. CS may also cause burning of the lips and the mucosa and should therefore only be used with great care.

Similar to our study, Voorsmit [16] reported a decreased recurrence rate after enucleation plus CS (2.5%) compared to simple enucleation (13.5%). Morgan [19] could not find an association between the reduction in the recurrence rate and the use of CS. However, the group treated by enucleation plus CS (two patients) seemed far too small for evaluating the advantages of CS.

In their systematic review in reference to animal experiments [28], Blanas et al. [14] state that applying CS to the tumor cavity for 3 min after enucleation should not harm the inferior alveolar nerve. CS application results in a recurrence rate comparable to that of resection but without unneccessarily aggressive surgery. KCOTs should only be resected in patients with multiple recurrences, in tumors that cannot be managed by other methods, for instance in KCOTs present in the condyle, as well as in tumors with malignant transformation.

Conclusion

The present study demonstrates that enucleation of keratocystic odontogenic tumors (KCOT) in combination with the

application of Carnoy's solution—compared to simple enucleation—significantly reduces the recurrence rate of KCOT. If used properly, the application of CS does not harm the alveolar nerve.

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