

# Recurrence and prognosticators of recurrence in odontogenic keratocyst of the jaws.

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#### **Research Article**

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## Abstract

Introduction: The incidence of recurrence of OKC varied from 2.5%-62%. Studies have linked recurrence to treatment methods and also clinical and pathological features. The aim of this study was to evaluate the 5 year recurrence and the factors associated with recurrence in odontogenic keratocysts of the jaws.

Methods: A retrospective review of records was done from the Institute's Medical Records Directory from 2010-2021. The following data were obtained of the lesion; age at presentation, gender, site, subsite, radiographic presentation (locularity), radiographic borders, presence or absence of satellite cysts, inflammatory infiltrate, and treatment rendered presence or absence of cortical perforation and soft tissue extension and presence or absence of recurrence. Kaplan Meir estimator was used to evaluate recurrence rate and log rank test was used to compare the survival amongst groups. Cox regression analysis was used to evaluate the odds ratio to find out the possible factors influencing risk of recurrence. A p value of <0.05 was considered statistically significant at 95% confidence interval.

Results: In our study cohort 44.44% had recurrence. Multilocular lesions, lesions with scalloped borders, presence of soft tissue extension and cortical perforation, presence of satellite cysts and inflammatory infiltrate and enucleation with peripheral ostectomy were significantly associated with recurrence. However; soft tissue extension, cortical perforation, enucleation with peripheral ostectomy and marsupialization followed by enucleation+ peripheral ostectomy were independent risk factors.

Conclusion: There is still debate on the best treatment modality for the management of OKCs. More studies are required to quantify the results.

#### Introduction

Background: Odontogenic keratocyst (OKC) is re classified as a cyst of developmental origin according to the updated 2017 WHO classification of Head and Neck Tumors.<sup>1</sup> Initially in 1950s all cysts which showed keratin formation were termed as keratocyst.<sup>2</sup> In the 1992 classification the term odontogenic keratocyst wasa used.<sup>2</sup> Shear coined the term keratocystoma on the basis of aggressive nature of the cyst.<sup>3</sup> Based on the works of Reichart and Philipsen, WHO classified it as a benign neoplasm and called it as keratocystic odontogenic tumor.<sup>4,5</sup> However in 2017 the consensus panel lacked strong evidence to classify OKC as a neoplasm.<sup>1</sup>

The incidence of recurrence of OKC varied from 2.5%-62% with great variation in reporting, treatment and follow up.<sup>1,6,7</sup> In 1976 Brannon proposed three mechanisms for OKC recurrence; incomplete removal of the lining, growth of new cysts from daughter cysts or rests left behind after surgery and development of new OKC in adjacent area.<sup>8</sup> The features that were considered to predict recurrence were higher level of cell proliferative activity in the epithelium, budding in the basal layer of the epithelium, parakeratinization of the surface layer, supraepithelial split of the epithelial lining, subepithelial split of the epithelial lining and presence of remnants/cell rests as well as daughter cysts.<sup>1</sup> Although these reasons have been cited

there still remains debate on the exact cause for recurrence. Studies have linked recurrence to treatment methods and also clinical and pathological features (larger size, daughter cysts, cortical perforation, and association with dentition).<sup>9-13</sup> The treatment modalities available include; enucleation (with primary closure, pack open, chemical fixation or cryosurgery), marsupialization (only or followed by enucleation) and resection.<sup>14,15</sup>

Rationale: The aim of this retrospective study was to evaluate the 5 year recurrence and the factors associated with recurrence in odontogenic keratocysts of the jaws.

## Methods

Study Design and setting: A retrospective review of records was done from the Institute's Medical Records Directory from 2010-2021. Ethical clearance was obtained from the ethical committee of the Institute. The following study was conducted in accordance with STROBE guidelines.<sup>16</sup>

Participants: Records were reviewed from January 2010-Decmeber 2021 from the Medical Records Directory. Biopsy proven patients of odontogenic keratocyst were taken into consideration. Patients with adequate preoperative data including imaging, morphological analysis and solitary lesions in the jaws were considered. Inadequate data, multiple jaw lesions, inability to review pathological reports, or archive them were the exclusion criteria. We collected 5 year (60 months) follow up data from the archives. Recurrence free survival was defined as the time frame from the final diagnosis with histological report till the occurrence of relapse or last visit to the department. Patients with less than 5year follow up or who could not contacted for further review and recurrences after 5 years were excluded.

Evaluation and Outcome: From the medical records the following data were obtained of the lesion; age at presentation, gender, site, subsite, radiographic presentation (locularity), radiographic borders, presence or absence of satellite cysts, inflammatory infiltrate, and treatment rendered, presence or absence of cortical perforation and soft tissue extension and presence or absence of recurrence.

Data analysis: The statistical analysis was performed using IBM SPSS software, version 21.0 (IBM, Armonk, NY, USA). Kaplan Meir estimator was used to evaluate recurrence rate and log rank test was used to compare the survival amongst groups. Cox regression analysis (univariate and multivariate) was used to evaluate the odds ratio to find out the possible factors influencing risk of recurrence. A p value of <0.05 was considered statistically significant at 95% confidence interval.

#### Results

Based on our selection criteria a total of 180 patient records were accessed for final analysis. The mean age of presentation was 31.82±0.27 years. The median age of presentation was 31 years (25-38). The Male: Female ratio in our study was 1:0.56. In our study cohort a total of 80 patients (44.44%) had recurrence and 100 (55.56%) patients did not experience any recurrence at 5 year follow up.

The most common site of involvement was posterior mandible followed by posterior maxilla, anterior mandible and anterior maxilla. Multilocularity was present in a total of 57.2% of patients. Most of the lesions had well defined borders with scalloped margin being present in 38.9% of patients. Cortical perforation was present in 52.2% of patients and soft tissue extension was present in 48.3% of patients. On histological analysis satellite cysts were present in a total of 53 patients and inflammatory infiltrate was present in 55% of patients. [Table 1] Three treatment procedures were principally carried out in our patients; I(enucleation with peripheral ostectomy), II(marsupialization followed by enucleation and peripheral ostectomy) and resection. Enucleation after marsupialization was done 6 months-15 months following the primary procedure. During this follow up period after marsupialization regular lodoform dressing was done. In none of the maxillary lesions resection was done. Most of the posterior lesions had sinus involvement and marsupialization followed by enucleation was done.

The overall 5 year recurrence free survival (RFS) in our cohort was 53.8%. A number of factors were evaluated which might affect recurrence [Figure 1-10]. Multilocular lesions had a 5 year recurrence free survival of 42.7% compared to 69.2% of unilocular lesions. Lesions with scalloped margin had a 5 year recurrence free survival of 43.6% compared to 60.4% of lesions with well defined borders. Soft tissue extension was associated with RFS of 40.3% compared to 66.7% RFS of lesions without soft tissue extension. Cortical perforation was associated with RFS of 41.8% and presence of inflammatory infiltrate had RFS of 45.6%. Lesions treated with resection had a RFS of 71% compared to 41% RFS of lesions treated in a staged manner. Presence of satellite cysts had a RFS of 41.3% [Table 1].

On univariate analysis radiographic presentation, lesion border, soft tissue extension, cortical perforation, treatment, satellite cysts and inflammatory infiltrate were significantly associated with recurrence. Site of lesions was not significantly associated with recurrence. Recurrence was present in 56.3% of patients with multilocular lesions compared with 28.6% of patients with unilocular lesions (p < 0.001). With regards to lesions margins; recurrence was present in 55.7% of patients with scalloped margin compared to 37.3% of patients with well defined margins (p 0.016). Presence of soft tissue extension was associated with 58.6% recurrence compared to 31.2% of patients with soft tissue extension (p < 0.001). Presence of cortical perforation was associated with 57.4% recurrence compared to 30.2% recurrence in patients without cortical perforation (p < 0.001). Presence of satellite cysts was significantly associated with recurrence (p 0.015). Enucleation with peripheral ostectomy was significantly associated with recurrence (p 0.007) [Table 2].

On multivariate analysis soft tissue extension, cortical perforation and treatment was found as independent risk factors for recurrence. The OR (odds ratio) of having recurrence in the presence of soft tissue extension was 4.875 compared to its absence (p 0.014). Cortical perforation was an independent risk factor for recurrence with OR 5.206 compared to its absence (p 0.013). Both enucleation with peripheral ostectomy and marsupialization followed by enucleation with peripheral ostectomy were independent risk factors for recurrence (p <0.001 and p 0.001 respectively) [Table 3].

## Discussion

Multilocular lesions, scalloped margins on radiograph, soft tissue extension, cortical perforation, presence of inflammatory infiltrate, presence of satellite cysts and enucleation were significantly associated with recurrence. However; presences of soft tissue extension, cortical perforation, enucleation alone or after marsupialization were independent risk factors for recurrence.

Limitations:

- 1. Strict guidelines were not followed for treatment. Many times the treatment was decided based on patient's expectations which might influence survival. Since it was a retrospective study based on medical records this factor could not be changed.
- 2. No additional chemical fixation was carried out after enucleation. This might affect recurrence.
- 3. Adequate data was not available on the nature of basal epithelium of the lining which was taken into consideration in some studies.
- 4. We only considered 5 year recurrence rates. Long term follow ups are needed to actually quantify the results.
- 5. Our study only evaluated results of non syndromic OKCs. The recurrence of OKC in syndromic cases was too few to be evaluated at our centre.
- 6. Due to very few multiple lesions and inadequate data on follow up these lesions were not taken into consideration. Recurrence of multiple lesions and solitary lesions might be different.

Interpretation:

Two recent studies focused on the recurrence and prognosticators of recurrence in OKC. The study by França et al. had a total of 18 (45%) recurrent cases over 5 year follow up and the study by Fidele et al. had a recurrence rate of 15.09% over 2-12 years follow up. Presence of satellite cysts, inflammatory infiltrate and previous decompression or marsupialization was significantly associated with recurrence in the study by França et al. In the study by Fidele et al. preservation of the involved teeth, multilocular lesions and presence of daughter cysts were independent factors for recurrence. Although size >4cm was significantly associated with recurrence it was not an independent risk factor. Similar findings were also found in the study by França et al. with regards to lesion size. Enucleation alone had the highest recurrence rate followed by marsupialization-enucleation and resection. Nineteen of their patients had involved teeth with cortical perforation and recurrence was 100% in these cases. Most of the recurrences occurred in first 5 years with decreasing incidence on subsequent years and the difference was statistically significant.<sup>17,18</sup>

A 2019 study by Kinard et al.<sup>19</sup> had an overall 19% recurrence with a median follow up of 8 months. In their study maxillary lesions had more recurrence compared to mandible and multilocular lesions were significantly associated with recurrence. On multivariate analysis enucleation alone followed by enucleation with peripheral ostectomy had more recurrences compared to decompression followed by

residual cystectomy . OKCs might present as both unilocular and multilocular lesions with unilocular being the predominant.<sup>19</sup> In our study a total of 100 patients had unilocular lesions and 80 had multilocular lesions. Recurrence was more in multilocular lesions however; radiographic presentation was not an independent risk factor.

In OKC satellite cysts takes three different forms; rounded keratin-filled cyst lined by flattened or cuboidal cells which can attain a very big size, squamoid structures with central degeneration occupied by epithelial debris and small irregular shaped cysts with lining indistinguishable from that of the main cyst. Postulation favors basal cell layer budding might be involved in formation of satellite cysts. However; evidence is more in support of satellite cysts being developed from cell rests of Serres. <sup>20</sup> Presence of satellite cysts significantly influenced recurrence in the study by França et al. In the study of Fidele et al both in univariate and multivariate analysis daughter cysts were significantly associated with recurrence. In our study presence of daughter cysts although being significantly associated was not an independent risk factor for recurrence. Presence of inflammatory infiltrate has been shown to be associated with recurrence. Inflammation increases the epithelial thickness and signals the proliferation of epithelial lining cells.

Marsupialization followed by a delayed enucleation has been shown to reduce the recurrence as the residual defect reduces in size. The postulation is that the epithelial cyst lining will undergo metaplasia to become undistinguished from the oral mucosa. The idea behind this treatment is that remnants of the epithelial cyst lining might impact recurrence left over during enucleation.<sup>21,22</sup> A 2019 meta analysis<sup>23</sup> evaluated the effects of enucleation alone versus marsupialization followed by enucleation in the management of OKCs. Marsupialization followed by enucleation reduced recurrence compared to enucleation alone with an odds ratio of 0.57. However; there was no strong evidence to support the statement and concluded on further studies to evaluate the evidence. Marsupialization and delayed enucleation reduced recurrence in 52% of OKCs compared to enucleation alone (OR 0.39, p 0.10). With peripheral ostectomy the recurrence rate was reduced in 26% (OR 0.67, p 0.65). Overall staged procedure reduced the recurrence rate in 34% over enucleation (OR 0.57, p 0.17). A 2017 meta analysis of 6427 cases evaluated the recurrence probability in keratocystic odontogenic tumor.<sup>24</sup> Overall the recurrence was 21.1%; 15.3% in maxilla, 21.5% in mandible, unilocular 14.7%, multilocular 24.4%, marsupialization/decompression 28.7%, decompression + enucleation ± additional therapy 18.6%, enucleation/curettage 22.5%, enucleation + peripheral ostectomy 18.6%, enucleation + Carnoy's solution 5.3%, enucleation + cryotherapy 20.9%, marginal/segmental resection, 2.2%. The recurrence was not statistically significantly affected by lesion location (maxilla vs. mandible, risk ratio [RR] 0.92, P = 0.32) or patient's sex (male vs. female, RR 0.94, P = 0.44), but by locularity (unilocular vs. multilocular, RR 0.67, P = 0.007). Recurrence risk for surgical managements: marsupialization vs. enucleation (RR 1.65, P = 0.0006), marsupialization vs. resection (RR 3.17, P = 0.009), enucleation alone vs. enucleation + peripheral ostectomy (RR 1.66, P = 0.05), enucleation alone vs. enucleation + Carnoy's solution (RR 1.94, P = 0.03), enucleation alone vs. enucleation + cryotherapy (RR 0.88, P = 0.56). Another meta analysis showed an overall recurrence rate of 19% with conservative treatment.<sup>25</sup> Decompression and

marsupialization alone had a recurrence rate of 18.5% and 18.2% respectively. Decompression followed by enucleation and marsupialization followed by enucleation had a recurrence rate of 11.9% and 17.8% respectively. Enucleation alone had a recurrence of 20.8%. Decompression followed by enucleation had a recurrence of 15.8% compared to 27.2% with enucleation alone (OR 0.48, p 0.0163). Marsupialization followed by enucleation had fewer recurrence compared to enucleation alone, however; the results were not statistically significant. Comparing marsupialization alone versus enucleation also did not show statistical significant results. Similar insignificant difference was obtained for decompression alone compared to enucleation. However; enucleation was favored compared to either decompression or marsupialization alone in reducing recurrence and marsupialization followed by enucleation was also favored.

## Conclusion

Multilocular lesions, lesions with scalloped borders, presence of soft tissue extension and cortical perforation, presence of satellite cysts and inflammatory infiltrate and enucleation with peripheral ostectomy were significantly associated with recurrence. However; soft tissue extension, cortical perforation, enucleation with peripheral ostectomy and marsupialization followed by enucleation+ peripheral ostectomy were independent risk factors.

## Declarations

Ethical APPROVAL: CPGIDSH/21/0185-A.

**CONSENT FOR PUBLICATION:** Authors give full consent to publish.

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#### Tables

Table1: Log rank test of the predictor variables to recurrence free survival.

	Frequency	Percentage	5 year survival	p value
RECURRENCE FREE SURVIVAL			53.8%	
Predictor variable				
Sex				
Male	115	63.9	55.2%	0.382
Female	65	36.1	51.4%	
Site				
Mandible	135	75	53.0%	0.645
Maxilla	45	25	56.5%	
Sub Site				
Ant. Mandible	27	15	51.7%	0.859
Post. Mandible	108	60	53.2%	
Ant. maxilla	5	2.8	40.0%	
Post. maxilla	40	22.2	58.8%	
Radiographic Presentation				
Unilocular	77	42.7	69.2%	<0.001
Multilocular	103	57.2	42.7%	
Borders				
Well defined	110	61.1	60.4%	0.004
Scalloped	70	38.9	43.6%	
Soft tissue extension				
Absent	93	51.7	66.7%	<0.001
Present	87	48.3	40.3%	
Cortical Perforation				
Absent	86	47.8	67.3%	<0.001
Present	94	52.2	41.8%	
Satellite Cysts				
Absent	127	70.6	58.8%	0.001
Present	53	29.4	41.3%	
Pag	e 10/24			

Treatment				
I (enucleation+ peripheral ostectomy)	70	38.9%	41%	<0.001
II (decompression-enucleation+peripheral ostectomy)	65	36.1%	55.9%	
III (resection)	45	25%	71.0%	
Inflammatory Infiltrate				
Absent	81	45	64.0%	0.004
Present	99	55	45.6%	
Total	180	100		

Table 2: Univariate regression to assess the relationship of predictor variables to recurrence.

Recurrence			Univariate Regression				
Predictor variable	absent	present	Total	OR	95% Lower	95% Upper	p value
Site							
Mandible	74(54.8%)	61(45.2%)	135(100%)	Reference			
Maxilla	26(57.8%)	19(42.2%)	45(100%)	1.753	0.887	0.448	0.729
Sub_Site							
Ant. Mandible	15(55.6%)	12(44.4%)	27(100%)	Reference			
Post. Mandible	59(54.6%)	49(45.4%)	108(100%)	2.425	1.038	0.444	0.931
Ant. maxilla	2(40%)	3(60%)	5(100%)	13.094	1.875	0.268	0.526
Post. maxilla	24(60%)	16(40%)	40(100%)	2.238	0.833	0.310	0.718
Radiographic Pr	esentation						
Unilocular	55 (71.4%)	22 (28.6%)	110 (100%)	Reference			
Multilocular	45 (43.7%)	58 (56.3%)	70 (100%)	3.222	1.717	6.046	<0.001
Borders							
Well defined	69(62.7%)	41(37.3%)	110(100%)	Reference			
Scalloped	31(44.3%)	39(55.7%)	70(100%)	3.896	2.117	1.151	0.016
Soft tissue exter	nsion						
Absent	64(62.1%)	29(31.2%)	93(100%)	Reference			
Present	36(41.4%)	51(58.6%)	87(100%)	5.765	3.126	1.695	<0.001
Bone Perforation	ו						
Absent	60(69.8%)	26(30.2%)	86(100%)	Reference			
Present	40(42.6%)	54(57.4%)	94(100%)	5.766	3.115	1.683	<0.001
Satellite Cysts							
Absent	78(61.4%)	49(38.6%)	127(100%)	Reference			
Present	22(41.5%)	31(58.5%)	53(100%)	4.309	2.243	1.168	0.015
Treatment							
III	32(71.1%)	13(28.9%)	45(100%)	Reference			

II	38(58.5%)	27(41.5%)	65(100%)	1.749	0.777	3.938	0.177	
Ι	30(42.9%)	40(57.1%)	70(100%)	3.282	1.475	7.303	0.004	
Inflammatory Infiltrate								
Absent	54(66.7%)	27(33.3%)	81(100%)	Reference				
Present	46(46.5%)	53(53.5%)	99(100%)	4.232	2.304	1.255	0.007	

Table 3: Multivariate regression analysis of predictor variable to recurrence.

Recurrence			Multivariate Regression				
Predictor variable	absent	present	Total	OR	95% Lower	95% Upper	p value
Site							
Mandible	74(54.8%)	61(45.2%)	135(100%)	Reference			
Maxilla	26(57.8%)	19(42.2%)	45(100%)	0.27	0.044	1.678	0.16
Sub Site							
Ant. Mandible	15(55.6%)	12(44.4%)	27(100%)	Reference			
Post. Mandible	59(54.6%)	49(45.4%)	108(100%)	0.793	0.181	3.464	0.757
Ant. maxilla	2(40%)	3(60%)	5(100%)	6.833	0.721	64.795	0.094
Post. maxilla	24(60%)	16(40%)	40(100%)	0.27	0.044	1.678	0.16
Radiographic Pr	resentation						
Unilocular	55 (71.4%)	22 (28.6%)	110 (100%)	Reference			
Multilocular	45 (43.7%)	58 (56.3%)	70 (100%)	2.51	0.814	7.74	0.109
Borders							
Well defined	69(62.7%)	41(37.3%)	110(100%)	Reference			
Scalloped	31(44.3%)	39(55.7%)	70(100%)	0.174	0.03	0.999	0.05
Soft tissue exter	nsion						
Absent	64(62.1%)	29(31.2%)	93(100%)	Reference			
Present	36(41.4%)	51(58.6%)	87(100%)	4.875	1.377	17.256	0.014
Bone Perforation	n						
Absent	60(69.8%)	26(30.2%)	86(100%)	Reference			
Present	40(42.6%)	54(57.4%)	94(100%)	5.206	1.414	19.17	0.013
Satellite Cysts							
Absent	78(61.4%)	49(38.6%)	127(100%)	Reference			
Present	22(41.5%)	31(58.5%)	53(100%)	1.81	0.463	7.072	0.394
Treatment							
111	32(71.1%)	13(28.9%)	45(100%)	Reference			

II	38(58.5%)	27(41.5%)	65(100%)	8.646	2.395	31.216	0.001	
I	30(42.9%)	40(57.1%)	70(100%)	6.299	2.342	16.946	<0.001	
Inflammatory Infiltrate								
Absent	54(66.7%)	27(33.3%)	81(100%)	Reference				
Present	46(46.5%)	53(53.5%)	99(100%)	0.888	0.19	4.158	0.88	

#### Figures



#### Figure 1

Kaplan Meier estimator of sex as a prognosticator of recurrence.





Kaplan Meier estimator of tumor site as a prognosticator of recurrence.





Kaplan Meier estimator of tumor sub-site as a prognosticator of recurrence.





Kaplan Meier estimator of radiographic presentation as a prognosticator of recurrence





Kaplan Meier estimator of radiographic border as a prognosticator of recurrence.





Kaplan Meier estimator of soft tissue extension as a prognosticator of recurrence





Kaplan Meier estimator of bone perforation as a prognosticator of recurrence





Kaplan Meier estimator of satellite cysts as a prognosticator of recurrence





Kaplan Meier estimator of treatment as a prognosticator of recurrence





Kaplan Meier estimator of inflammatory infiltrate as a prognosticator of recurrence