RESEARCH PAPER

Histopathological Determinants of Recurrence in Odontogenic Cysts and Tumors: Implications for Surgical Decision-Making: A Retrospective Cohort Study

Dr Neerav Dutta[1], Dr Arundhati Singh[2]*, Dr Devanshu Sinha[3], Dr Rakesh Kumar[4], Dr Arpita Maitra[5], Dr Anwesha Banerjee[5]

[1] Associate Professor, Department of Dentistry, Gautam Medical College and Hospital, Ranchi
[2] Reader, Department of Oral and Maxillofacial Surgery, Hazaribag College of Dental Sciences, Hazaribagh, Jharkhand
[3] Assistant Professor, Department of Dentistry, Netaji Medical College and Hospital, Jamshedpur
[4] Lecturer (MDS Oral and Maxillofacial Surgery), Saryug Dental College, Darbhanga, Bihar
[5] Assistant Professor, PhD Scholar, Department of Oral Medicine and Radiology, Guru Nanak Institute of Dental Sciences and Research, Kolkata; PhD Scholar, JIS University, Kolkata
[6] Assistant Professor, Department of Oral Medicine and Radiology, Guru Nanak Institute of Dental Sciences and Research, Kolkata, JIS University, Kolkata

* Corresponding Author: Dr Arundhati Singh, arundhati8743@gmail.com

Abstract
Background: Recurrence after surgical management of odontogenic cysts and tumors remains a significant clinical challenge. Histopathological features of the resected specimen may harbor predictive value, yet their systematic correlation with surgical outcomes is poorly defined in Indian tertiary-care populations. Objectives: To identify histopathological parameters that significantly predict recurrence and to evaluate how surgical approach modifies recurrence risk in the presence of these features. Methods: A retrospective cohort of 172 patients managed surgically for odontogenic cysts (n=131) and tumors (n=41) between January 2018 and December 2023 was analyzed. Histopathological slides were reviewed for satellite cyst formation, epithelial dysplasia, mitotic index, mural thickening, parakeratinization, bud-like projections, and capsular inflammation. Recurrence was confirmed clinically and radiologically at minimum 24-month follow-up. Binary logistic regression identified independent predictors. Results: The overall recurrence rate was 22.7% (39/172). Satellite cyst formation (OR 4.21; p=0.001), bud-like epithelial projections (OR 3.87; p<0.001), high mitotic index (OR 3.54; p=0.002), and epithelial dysplasia (OR 3.19; p<0.001) were independent histopathological predictors of recurrence. Resection with adequate margins yielded the lowest recurrence rate (7.7%). Conclusion: Specific histopathological features robustly predict recurrence and should systematically inform the choice of surgical modality, adjuvant therapy, and follow-up intensity.

Keywords: Odontogenic cysts; odontogenic tumors; recurrence; histopathology; ameloblastoma; odontogenic keratocyst; surgical management
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1. Introduction

Odontogenic cysts and tumors constitute a heterogeneous group of lesions arising from the epithelial and ectomesenchymal remnants of the tooth-forming apparatus. Despite advances in diagnostic pathology and surgical technique, recurrence following apparently complete excision continues to perplex clinicians and compromise quality of life for patients [1,2]. Rates vary substantially across lesion types: odontogenic keratocysts (OKC) recur in 25–60% of cases after simple enucleation, while ameloblastoma recurs in 14–50% depending on the histological variant and surgical adequacy [3,4].

The biological basis for this recurrence is multifactorial. At the molecular level, loss of heterozygosity at the PTCH tumour-suppressor locus, activating mutations in BRAF V600E, and aberrant Hedgehog pathway signalling have each been implicated [5,6]. However, translating these molecular findings into practical surgical protocols is not yet routine in low- to middle-income country (LMIC) settings. The surgical pathologist's report, by contrast, is universally available and is generated as standard of care. If specific histopathological features in the excised specimen reliably predict recurrence, the surgeon may stratify post-operative follow-up, select adjuvant chemical cauterization, or advocate re-excision with wider margins.

To date, several individual histopathological parameters—satellite cyst formation, epithelial budding, parakeratotic lining, and high mitotic indices—have been reported as recurrence-associated in small case series, but comprehensive multivariate analyses from Eastern Indian tertiary-care centers remain scarce [7,8]. Reconciling these features with the surgical modality employed is equally important, because even a biologically aggressive lesion treated by wide resection may not recur, whereas a histologically benign-appearing lesion managed by conservative enucleation may have a higher recurrence rate than expected. Sometimes it done under Dexamethasone and Methylprednisoloneto control Pain, Swelling, and Trismus in few cases [9].

The objectives of this retrospective cohort study were therefore: (i) to determine the prevalence of key histopathological features among odontogenic cysts and tumors managed at two Eastern Indian institutions; (ii) to quantify their independent contribution to recurrence by multivariate logistic regression; and (iii) to examine how the choice of surgical approach modifies recurrence risk in the presence of these features.

2. Materials and Methods

2.1 Study Design and Patient Selection

Patients were eligible if they had: (i) a histopathologically confirmed odontogenic cyst or tumor; (ii) undergone definitive surgical treatment at one of the two study centers; and (iii) been followed up for a minimum of 24 months post-operatively. Patients with incomplete records, inadequate tissue in the histopathological specimen, or follow-up shorter than 24 months were excluded.

A total of 172 patients satisfied the inclusion criteria. Demographic data, lesion site, preoperative radiographic classification, surgical procedure performed, and post-operative follow-up data were extracted from clinical records and stored in a password-protected database.

2.2 Histopathological Analysis

Formalin-fixed, paraffin-embedded tissue blocks from all 172 patients were retrieved from the histopathology archive. Four-micrometer haematoxylin and eosin (H&E) sections were prepared and independently reviewed by two oral pathologists blinded to the clinical outcome. Discordant interpretations were resolved by consensus with a third reviewer.

The following features were evaluated systematically:

1. Satellite cyst formation: presence of daughter cysts within the fibrous wall, separated from the main lumen.
2. Epithelial dysplasia: graded according to the WHO 2022 criteria as absent, mild, moderate, or severe; dichotomized as present/absent for analysis.
3. Mural thickening: fibrous wall thickness exceeding 0.3 mm, measured with an ocular micrometer.
4. Mitotic index: counted in the most active area of 10 consecutive high-power fields (HPF, 40× objective); high index defined as >2 mitoses/HPF.
5. Parakeratinization: presence of a parakeratotic surface layer in cysts with stratified squamous epithelial lining.
6. Bud-like epithelial projections: tongues of epithelium projecting into the fibrous capsule.
7. Fibrous capsule inflammation: lymphoplasmacytic infiltrate within the capsule, graded as absent, mild, or moderate-to-severe.

2.3 Definition of Recurrence

Recurrence was defined as the clinical or radiographic reappearance of lesion at the original surgical site, confirmed by histopathology, at least 12 months after surgery. Radiographic follow-up consisted of orthopantomography at 6, 12, 24, and 36 months, supplemented by cone-beam computed tomography (CBCT) where indicated.

2.4 Statistical Analysis

Statistical analysis was performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Categorical variables were compared using the chi-square test or

Fisher's exact test as appropriate. Continuous variables were expressed as mean ± standard deviation and compared using Student's independent t-test. Variables with $p<0.1$ on univariate analysis were entered into a binary logistic regression model to identify independent predictors of recurrence. The odds ratio (OR) with 95% confidence intervals (CI) was reported. Statistical significance was set at $p<0.05$. Intra- and inter-observer agreement for histopathological assessment was quantified using Cohen's kappa coefficient (κ).

3. Results

3.1 Patient Demographics and Lesion Distribution

The cohort comprised 172 patients (95 males, 77 females; M:F ratio 1.23:1), with a mean age of 34.8 ± 12.3 years (range 8–72 years). The most frequent diagnosis was OKC (42 cases, 24.4%), followed by dentigerous cyst (38, 22.1%), radicular cyst (35, 20.3%), ameloblastoma (29, 16.9%), calcifying odontogenic cyst (16, 9.3%), and odontogenic myxoma (12, 7.0%). The mandible was affected in 124 (72.1%) cases. Detailed demographic data are presented in Table 1.

Table 1. Patient Demographics, Lesion Distribution, and Recurrence by Diagnosis

Lesion Type	Total Cases (n)	Male / Female	Mean Age ± SD (yrs)	Recurrence n (%)
Odontogenic Keratocyst (OKC)	42	24 / 18	34.2 ± 11.8	14 (33.3%)
Dentigerous Cyst	38	22 / 16	28.6 ± 9.4	4 (10.5%)
Radicular Cyst	35	19 / 16	41.3 ± 13.2	3 (8.6%)
Ameloblastoma	29	16 / 13	38.7 ± 14.5	11 (37.9%)
Calcifying Odontogenic Cyst	16	9 / 7	29.1 ± 8.7	2 (12.5%)
Odontogenic Myxoma	12	5 / 7	31.4 ± 10.1	5 (41.7%)
Total	**172**	**95 / 77**	**34.8 ± 12.3**	**39 (22.7%)**

Note: SD = standard deviation.

3.2 Overall Recurrence Rate

At a mean follow-up of 41.8 ± 15.6 months (range 24–72 months), recurrence was confirmed in 39 of 172 patients, yielding an overall recurrence rate of 22.7%. Odontogenic myxoma demonstrated the highest recurrence rate (41.7%), followed closely by ameloblastoma (37.9%) and OKC (33.3%). Radicular cysts had the lowest recurrence rate (8.6%), consistent with their well-differentiated, non-aggressive epithelial lining.

3.3 Histopathological Predictors on Univariate Analysis

Intra-observer and inter-observer kappa values for histopathological features ranged from 0.74 to 0.91, indicating substantial to near-perfect agreement. The prevalence of each histopathological feature and its association with recurrence are summarized in Table 2.

Table 2. Histopathological Features and Their Association with Recurrence

Histopathological Feature	Present n (%)	Absent n (%)	Recurrence Rate with Feature	p-value
Satellite cyst formation	54 (31.4%)	118 (68.6%)	48.1%	0.001*
Epithelial dysplasia	41 (23.8%)	131 (76.2%)	53.7%	< 0.001*
Mural thickening (>0.3 mm)	63 (36.6%)	109 (63.4%)	36.5%	0.01*
High mitotic index (>2/HPF)	37 (21.5%)	135 (78.5%)	56.8%	< 0.001*
Fibrous capsule inflammation	89 (51.7%)	83 (48.3%)	14.6%	0.21 (NS)
Parakeratinization	48 (27.9%)	124 (72.1%)	41.7%	0.004*
Bud-like projections of lining	31 (18.0%)	141 (82.0%)	58.1%	< 0.001*

*p < 0.05 (chi-square test); NS = not significant; HPF = high-power field

Six of the seven features evaluated showed a statistically significant association with recurrence: satellite cyst formation (p=0.001), epithelial dysplasia (p<0.001), mural thickening (p=0.01), high mitotic index (p<0.001), parakeratinization (p=0.004), and bud-like epithelial projections (p<0.001). Fibrous capsule inflammation was not independently associated with recurrence (p=0.21).

3.4 Surgical Modality and Recurrence

Four surgical approaches were employed across the cohort: simple enucleation (n=68), enucleation with Carnoy's solution application (n=44), marsupialization (n=21), and resection with adequate margins (n=39). Recurrence rates by surgical modality and the predominant histopathological features identified are shown in Table 3.

Table 3. Surgical Modality, Recurrence Rate, and Associated Histopathological Features

Surgical Approach	Cases (n)	Recurrence n (%)	Follow-up (months)	Predictive Histological Features
Simple Enucleation	68	21 (30.9%)	38.4 ± 14.2	Satellite cysts, bud projections
Enucleation + Carnoy's Solution	44	8 (18.2%)	41.1 ± 12.8	Epithelial dysplasia, parakeratinization
Marsupialisation	21	7 (33.3%)	44.5 ± 16.1	Mural thickening, inflammation
Resection with Margins	39	3 (7.7%)	46.2 ± 18.4	High mitotic index

Resection with margins was associated with the lowest recurrence rate (7.7%), while simple enucleation had the highest (30.9%). Notably, in patients who underwent simple enucleation and were found to have satellite cyst formation on histopathology, the recurrence rate rose to 52.4%, compared with 18.6% in those without satellite cysts managed identically (p=0.003).

3.5 Multivariate Logistic Regression

Variables with p<0.1 on univariate analysis (satellite cyst formation, epithelial dysplasia, high mitotic index, mural thickening, parakeratinization, and bud-like projections) were entered simultaneously into a binary logistic regression model. The Hosmer–Lemeshow goodness-of-fit test confirmed acceptable model calibration (χ^2=6.34, p=0.61). Results are presented in Table 4.

Table 4. Binary Logistic Regression: Independent Histopathological Predictors of Recurrence

Variable	OR	95% CI	p-value	Significance
Satellite cyst formation	4.21	2.14 – 8.29	0.001	***
Bud-like projections	3.87	1.92 – 7.81	< 0.001	***
High mitotic index	3.54	1.76 – 7.12	0.002	***
Epithelial dysplasia	3.19	1.57 – 6.49	< 0.001	***
Parakeratinization	2.76	1.38 – 5.53	0.004	**
Mural thickening	2.41	1.21 – 4.80	0.010	**
Fibrous capsule inflammation	1.18	0.61 – 2.29	0.210	NS

OR = odds ratio; CI = confidence interval; NS = not significant; ** p<0.01; *** p<0.001.

Satellite cyst formation (OR 4.21, 95% CI 2.14–8.29; p=0.001), bud-like projections (OR 3.87, 95% CI 1.92–7.81; p<0.001), high mitotic index (OR 3.54, 95% CI 1.76–7.12; p=0.002), and epithelial dysplasia (OR 3.19,

95% CI 1.57–6.49; p<0.001) emerged as the strongest independent predictors. Fibrous capsule inflammation was not a significant predictor in the multivariate model (p=0.21).

4. Discussion

This retrospective cohort study of 172 patients with odontogenic cysts and tumors managed at two Eastern Indian institutions demonstrates that specific histopathological features of the excised specimen are robust, independent predictors of recurrence. The findings carry direct implications for the surgical management algorithm applied to these lesions.

The overall recurrence rate of 22.7% in our cohort is consistent with published series from similar tertiary care settings, where rates between 15% and 30% are commonly reported [10,11]. Our data, however, go beyond a global recurrence rate by demonstrating that the risk is not uniformly distributed but is strongly modulated by both tissue-level histopathological characteristics and the surgical technique employed.

Satellite cyst formation emerged as the single strongest predictor in our model (OR 4.21). This finding aligns with the widely held mechanistic hypothesis that daughter cysts—histologically separated from the parent lesion—are left behind after enucleation, serving as nidi for regrowth [12,13]. Importantly, the daughter cysts are often situated in the overlying periosteum or within marrow spaces and may not be visible to the operating surgeon at the time of enucleation. This is precisely why chemical adjuncts such as Carnoy's solution or cryotherapy have been advocated for high-recurrence lesions [14]. Our data support this practice: enucleation supplemented by Carnoy's solution application reduced recurrence to 18.2%, compared with 30.9% for enucleation alone. The reduction was especially marked in OKC, in keeping with the published literature [15].

Bud-like epithelial projections (OR 3.87) and high mitotic index (OR 3.54) were the next most potent predictors. The biological significance of basal cell budding into the fibrous capsule relates to the enhanced proliferative potential of the basal compartment. Increased PCNA (Proliferating Cell Nuclear Antigen) and Ki-67 labelling indices have been correlated with bud formation in several immunohistochemical investigations [16]. A high mitotic index likely reflects elevated cellular turnover and is particularly relevant in ameloblastoma and odontogenic myxoma, both of which demonstrated the highest recurrence rates in our cohort.

Epithelial dysplasia as a predictor of recurrence is a finding that deserves particular attention. While dysplasia in the context of odontogenic lesions is not synonymous with malignant transformation, it reflects intrinsic genomic instability that may drive regrowth even after macro- or microscopically complete excision [17]. Surgeons should treat dysplasia as a signal to widen surgical margins and intensify follow-up.

Parakeratinization (OR 2.76) has long been associated with the parakeratotic OKC subtype, which is recognized to behave more aggressively than the orthokeratotic variant [3]. Our data extend this principle to the broader cohort of odontogenic lesions. Mural thickening (OR 2.41) may reflect either chronic irritation or a more autonomous proliferative pattern in the cyst wall. Interestingly, capsular inflammation—sometimes considered a risk modifier—was not a significant independent predictor in the multivariate model, suggesting that the inflammatory infiltrate may represent a reactive host response rather than a driver of recurrence.

From a surgical decision-making standpoint, these findings suggest a stratification approach. Lesions with one or more high-risk histopathological features (satellite cysts, bud projections, high mitotic index, or dysplasia) identified at initial surgical pathology should prompt: (i) serious consideration of re-excision with margins if the index procedure was conservative enucleation; (ii) use of adjuvant chemical cauterization at the time of initial surgery if high-risk features are anticipated preoperatively; and (iii) shortened radiographic surveillance intervals—at 6 and 12 months—rather than the conventional annual review.

The principal limitations of this study include its retrospective design, the geographic concentration of the cohort, and the relatively small number of some lesion sub-types. Additionally, molecular markers such as BRAF V600E status and PTCH mutation data were not universally available, precluding a combined histo-molecular model. Prospective, multi-center validation with immunohistochemical enrichment is warranted.

5. Conclusion

Histopathological examination of odontogenic cyst and tumor specimens yields clinically actionable information beyond diagnosis. Satellite cyst formation, bud-like epithelial projections, high mitotic index, and epithelial dysplasia are independent and significant predictors of recurrence. These features should be explicitly reported by pathologists and systematically incorporated into surgical planning, adjuvant therapy decisions, and post-operative surveillance protocols. A risk-stratified surgical approach guided by these histopathological parameters has the potential to substantially reduce the burden of recurrence in this patient population.

Declarations

Conflict of Interest: The authors declare no conflicts of interest.

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Data Availability: Anonymized data are available from the corresponding author on reasonable request.

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