

Exploring the Potential of 5-Fluorouracil in the Management of Odontogenic Keratocyst: A Prospective Study

Dr. Saikrishna Degala¹ and Dr. Soundarya Shaw^{2*}

¹Professor & Head, Department of Oral and Maxillofacial Surgery, JSS Dental College and Hospital, JSS Academy of Higher Education & Research, Mysuru – 570015, Karnataka, India

²Postgraduate Student, Department of Oral and Maxillofacial Surgery, JSS Dental College and Hospital, JSS Academy of Higher Education & Research, Mysuru – 570015, Karnataka, India

*Corresponding Author: Dr. Soundarya Shaw | E-mail: shawsoundarya@gmail.com

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ABSTRACT

Background: Odontogenic keratocyst (OKC) is a developmental odontogenic cyst characterised by aggressive behaviour and high recurrence, driven by Sonic Hedgehog (SHH) pathway dysregulation. Topical 5-Fluorouracil (5-FU), a pyrimidine antimetabolite, offers a biologically selective pharmacological adjunct to surgical enucleation.

Aim: To prospectively evaluate topical 5-FU as an adjunct to enucleation and peripheral ostectomy in OKC management, assessing recurrence, bone formation (CBCT-derived Hounsfield Units), paresthesia, and pain.

Materials and Methods: A prospective single-arm study in Mysuru (May 2024–November 2025). Ten histopathologically confirmed OKC patients received enucleation, peripheral ostectomy, and 5% topical 5-FU via ribbon gauze packed for 24 hours followed by primary closure. Outcomes were assessed at day 1, day 7, 6 months, and 12 months.

Results: Equal gender distribution (5M:5F); mean age 38.30 ± 11.12 years; parakeratinized variant in 70%; posterior mandible most affected (70%). Zero recurrence at 6 and 12 months (100% recurrence-free). VAS pain scores reduced significantly over time ($p < 0.0001$). Post-operative paresthesia in 2 patients (20%), fully resolved by 12 months. Bone formation increased significantly between 6 and 12 months ($p < 0.05$) in all patients. Two pathological fractures (20%) attributed to pre-existing cortical thinning, not to 5-FU.

Conclusion: Topical 5-FU is a safe and biologically rational adjunct in OKC management, demonstrating zero recurrence at one year, preserved neurovascular integrity, and confirmed osteogenesis. Larger randomised trials are warranted.

Keywords: *Odontogenic keratocyst; 5-Fluorouracil; Enucleation; Peripheral ostectomy; Bone healing; Hounsfield units; Recurrence; Sonic Hedgehog pathway*

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1. INTRODUCTION

Odontogenic keratocyst (OKC) is a developmental odontogenic cyst arising from remnants of the dental lamina, formally named by Philipsen in 1956.¹ Despite its benign classification, OKC exhibits aggressive growth, tracks along the medullary cavity without proportionate cortical expansion, and carries recurrence rates of 13–60%.² Satellite cysts and epithelial remnants within the fibrous capsule resist complete surgical clearance and are the primary drivers of recurrence.^{3,4}

At the molecular level, PTCH1 mutations disrupt the Sonic Hedgehog (SHH) signalling pathway, resulting in constitutive SMO and GLI1 activation and unchecked

epithelial proliferation.⁵ Elevated Ki-67, PCNA, and Bcl-2 expression suppresses apoptosis, explaining why even minimal residual epithelium may regenerate the lesion. Surgical adjuncts such as Carnoy's solution and cryotherapy reduce recurrence but carry risks of inferior alveolar nerve injury and bone devitalisation respectively.^{6,7}

5-Fluorouracil (5-FU), a pyrimidine antimetabolite that inhibits thymidylate synthase and disrupts DNA synthesis in proliferating cells, offers pharmacological selectivity toward residual OKC epithelium while sparing osteogenic and stromal cells. Applied topically as a 5% cream, systemic absorption is approximately 10% and is rapidly

*Author for Correspondence: shawsoundarya@gmail.com

catabolised hepatically, limiting systemic toxicity. This prospective study evaluates topical 5-FU across four clinically meaningful parameters: recurrence, quantitative bone formation, neurosensory function, and postoperative pain.

2. AIMS AND OBJECTIVES

Aim: To evaluate topical 5-Fluorouracil as an adjunct in the management of Odontogenic Keratocyst.

Objectives: (1) Evaluate recurrence at 6 and 12 months; (2) assess bone formation by CBCT-derived Hounsfield Units at 6 and 12 months; (3) evaluate post-operative paresthesia; (4) assess pain pre- and post-operatively using the Visual Analog Scale (VAS).

3. MATERIALS AND METHODS

Study Design & Ethics: Prospective, single-arm study at the Department of Oral and Maxillofacial Surgery, Mysuru, Karnataka (May 2024 – November 2025; 18 months). IEC ethical clearance was obtained and written informed consent secured from all participants.

Sample Size & Selection: Calculated as $N = [(Z\alpha + Z\beta)^2 \times S^2] / d^2$ ($Z\alpha = 1.96$; $Z\beta = 0.84$; $S = 5.6$; $d = 5.0$) yielding $n = 10$. Inclusion: histopathologically confirmed OKC (parakeratinized or orthokeratinized) and written consent. Exclusion: pending histopathological diagnosis, significant comorbidities, previously treated OKC, inability to consent.

Surgical Protocol: Degloving incision and mucoperiosteal flap raised to expose the full lesion. Cyst enucleated; peripheral ostectomy performed with surgical burs; curettage and betadine-saline irrigation completed. Sterile ribbon gauze soaked in 5% topical 5-FU cream packed into the cystic cavity; wound closed leaving ~1 cm gauze externally. Gauze removed at 24 hours; primary closure with Vicryl 3-0. Postoperative antibiotics (Amoxicillin + Clavulanic acid 1.2 g BD, Metronidazole 500 mg TDS) and analgesia (Paracetamol 1 g BD) given for 5 days.

Outcome Assessment: Patients reviewed at day 1, day 7, 6 months, and 12 months. Recurrence: CBCT at 6 and 12 months; suspicious findings confirmed by biopsy. Bone formation: CBCT-derived HU values; paired t-test. Paresthesia: yes/no scale at each visit. Pain: VAS (0–10) at all time points; one-way ANOVA with post-hoc testing.

4. ILLUSTRATIVE CASE REPORTS

Case 1

A patient presented with swelling in the left posterior mandible. After incisional biopsy was done which revealed it to be Odontogenic Keratocyst (parakeratinised). Cyst Enucleation, peripheral ostectomy, and chemical fixation using 5-FU soaked gauze was performed. Healing was uneventful. Patient was regularly followed up. CBCT-derived HU values progressed from 889 HU at 6 months to 1010 HU at 12 months, confirming active bone regeneration.

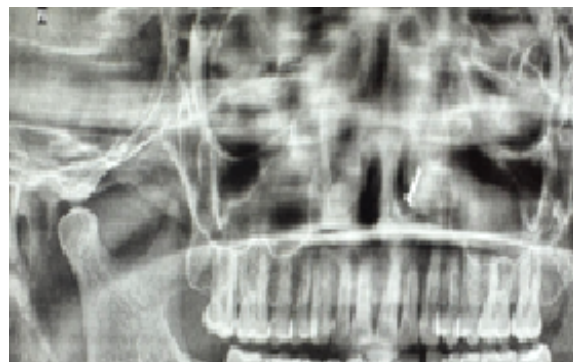


Fig 1: Pre op OPG denoting Radiolucent lesion wrt 36 and 37 region



Fig 2: Pre op intra oral photograph showing vestibular obliteration wrt 36 and 37 region.



Fig 3: Cyst enucleated in toto



Fig 4: Curettage, Peripheral ostectomy and 5 fu soaked ribbon gauze placed.

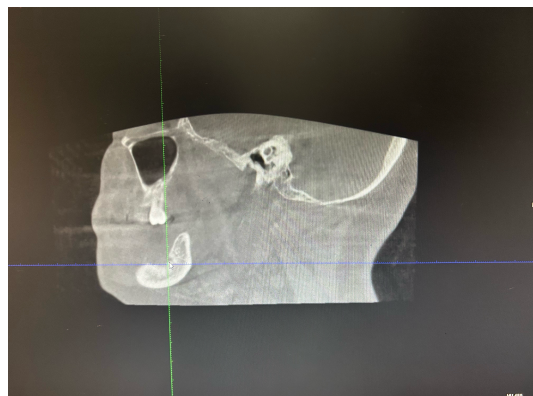


Fig 5: CBCT at 6 months showed 889 HU



Fig 6: CBCT at 12 months showed 1010 HU representing bone formation.

Case 2

A 34 year male patient came with swelling in his mandibular anterior region. OPG was taken which revealed well defined radiolucency wrt mandibular anterior region (35-45). Incisional biopsy was done which revealed parakeratinised variant of odontogenic keratocyst extending from 35 to 45. Patient underwent cyst Enucleation, peripheral ostectomy, and chemical fixation using 5-FU soaked gauze. Patient was followed up

regularly and presented with pain after 1 month post surgery. Postoperative CBCT at 1 month revealed pathological fracture in the left parasymphysis, attributed to severe cortical thinning from the cystic lesion and managed conservatively by intermaxillary fixation for 3 weeks. Bone formation progressed from 1059 HU (6 months) to 1471 HU (12 months) — the highest in the cohort.

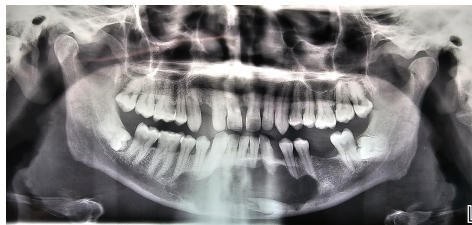


Fig 7: Pre op OPG revealing radiolucency wrt mandibular anterior region.



Fig 8: Pre op intra oral photograph denoting vestibular obliteration wrt mandibular anterior region.

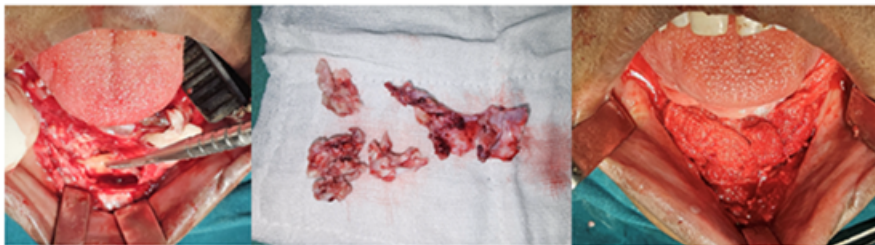


Fig 9: INTRA OP: Cyst exposed, enucleated in piece meal, curettage and peripheral ostectomy done followed with placement of 5 FU soaked ribbon gauze



Fig 10: Primary closure achieved leaving 1 inch of ribbon gauze in the oral cavity for easy retrieval after 24 hours.

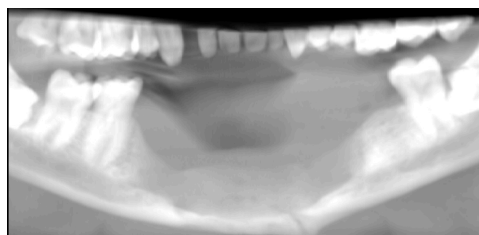


Fig 11: 1 month post operatively, cacti was taken as patient complained of pain and it revealed pathological fracture wrt left parasymphysis region. Eyelet and IMF was done for 3 weeks.

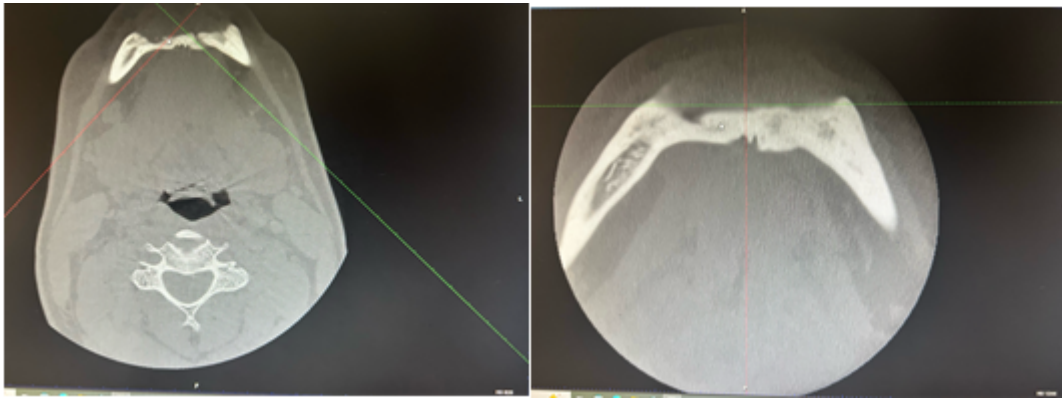


Fig 12: CBCT at 6 months revealed 1059 HU and at 12 months revealed 1471 HU depicting good bone formation.

5. RESULTS

5.1 Gender Distribution

The study comprised 5 males and 5 females (1:1 ratio) (Table 1).

Table 1: Distribution according to gender

Gender	No. of Subjects	Percentage
Male	5	50%
Female	5	50%

5.2 Age Distribution

Age ranged from 20–60 years; mean 38.30 ± 11.12 years (Table 2; Figure 16). Mean age: males 42.80 ± 10.76 years, females 33.80 ± 11.54 years; difference not statistically significant ($p = 0.238$, Student's t-test) (Table 2).

Table 2: Distribution of subjects according to age

Age Range (years)	No. of Subjects
20–30	3
31–40	2
41–50	2
51–60	3

Table 3: Gender and mean age comparison (Student's t-test, $p = 0.238$, NS)

Gender	N	Mean Age (yrs)	SD
Male	5	42.80	10.76
Female	5	33.80	11.54
Total	10	38.30	11.12

5.3 Histological Variant

Parakeratinized OKC predominated (70%, $n = 7$); orthokeratinized OKC constituted 30% ($n = 3$) (Table 4).

Table 4: Distribution according to OKC variant

Type of OKC	No. of Cases	Percentage
Parakeratinized OKC	7	70%
Orthokeratinized OKC	3	30%

5.4 Location of Lesion

Posterior mandible most common (70%), followed by posterior maxilla (20%) and anterior mandible (10%). No anterior maxillary lesions (Table 5).

Table 5: Distribution according to location of cyst

S.No.	Location	No. of	Percentage
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	of Cyst	Patients	
1	Posterior Mandible	7	70%
2	Posterior Maxilla	2	20%
3	Anterior Mandible	1	10%
4	Anterior Maxilla	0	0%
Total		10	100%

5.5 Teeth and Root Resorption

Teeth were present in relation to the lesion in all 10 patients (Table 6). Root resorption was absent in every case on radiographic examination (Table 6).

Table 6: Distribution according to teeth in region of cyst

Patients with Teeth Present	Patients with Teeth Absent
10	0

Table 7: Root resorption in the region of cyst

Root Resorption Present	Root Resorption Absent
0	10

5.6 Postoperative Complications

Two patients (20%) developed pathological fractures attributable to cortical thinning from the cystic lesion, both managed conservatively. Eight patients (80%) demonstrated uneventful healing. No recurrence was observed at either follow-up (Table 8).

Table 8: Postoperative complications

Postoperative Complication	No. of Cases	Percentage
Pathological Fracture	2	20%
Recurrence	0	0%
Uneventful Healing	8	80%

5.7 Postoperative Pain (VAS)

Pain scores showed a statistically significant progressive reduction from the preoperative period through 12 months (one-way ANOVA, $p < 0.0001$). Significant pairwise differences were observed between preoperative and all

postoperative intervals. No significant difference was found between 6-month and 12-month scores ($p = 0.3446$) or between day 1 and day 7 ($p = 0.5275$), indicating pain stabilisation from 6 months onward (Table 9).

Table 9: Mean VAS pain scores across follow-up intervals

Statistic	Pre-op	Day 1	Day 7	6 Months	12 Months
Mean VAS	4.8	6.7	5.5	1.8	1.5
SD	1.14	1.06	0.97	0.79	0.71
p-value (ANOVA)	< 0.0001	—	—	—	—

5.8 Postoperative Paresthesia

No preoperative paresthesia was recorded. Post-operative paresthesia occurred in 2 patients (20%), attributed to surgical manipulation near the inferior alveolar nerve. Both patients recovered full neurosensory function by 12 months (Table 10).

Table 10: Postoperative paresthesia

Paresthesia Status	No. of Patients	Percentage
Pre-operative Paresthesia	0	0%
Post-operative Paresthesia	2	20%
No Paresthesia	8	80%
Total	10	100%

5.9 Recurrence

No recurrence was detected at 6 or 12 months in any patient — 100% recurrence-free rate at one year (Table 11).

Table 11: Distribution of patients according to recurrence

Follow-up Period	Recurrence Present	Recurrence Absent	% Recurrence-Free
6 Months	0	10	100%
12 Months	0	10	100%

5.10 Bone Formation (CBCT-derived Hounsfield Units)

A statistically significant increase in HU values was observed between 6 and 12 months in all patients (paired t-test, $p < 0.05$). Negative HU values in patients 2 and 6 at 6 months reflected maxillary sinus proximity; both shifted progressively toward zero by 12 months. No case demonstrated osteonecrosis or delayed healing (Table 12).

Table 12: CBCT-derived Hounsfield Unit values at 6 and 12 months

Patient	Bone Formation at 6 Months	Bone Formation at 12 Months
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No.	6 Months (HU)	12 Months (HU)
1	889	1010
2	-189	-106
3	1059	1471
4	300	673
5	496	906
6	-159	-104
7	820	1244
8	932	1250
9	476	518
10	387	714

6. DISCUSSION

OKC has been a subject of surgical debate since Philipsen's original description in 1956.¹ Recurrence is primarily attributed to daughter cysts and epithelial remnants in the fibrous capsule.^{3,4} PTCH1 mutations disrupt the SHH pathway,⁵ leading to constitutive epithelial proliferation; elevated PCNA, Ki-67, and Bcl-2 suppress apoptosis,⁸ explaining why minimal residual epithelium can regenerate the lesion. This molecular substrate is precisely what 5-FU targets: inhibiting thymidylate synthase during the S-phase of the cell cycle, it induces apoptosis in proliferating epithelial cells while sparing quiescent osteogenic tissue.

Ledderhof et al.⁹ provided early combined evidence favouring 5-FU over Carnoy's solution — zero recurrences and significantly fewer cases of inferior alveolar nerve paresthesia. Subsequent evidence from Lone et al.,¹⁰ Caminiti et al.,¹¹ Mishra et al.,¹² and the meta-analyses of Singh et al.¹³ and Jacobs et al.¹⁴ have consistently corroborated its efficacy and safety.

The present study is consistent with this literature. Parakeratinized OKC constituted 70% of cases, aligning with its recognised higher frequency and proliferative potential.^{3,4} Posterior mandible was most frequently involved (70%).² Critically, zero recurrence was recorded at 6 or 12 months — compared with 17–30% with enucleation alone.¹⁵ VAS pain scores reduced significantly ($p < 0.0001$), stabilising between 6 and 12 months. Postoperative paresthesia in 2 patients (20%) was transient and attributed to surgical manipulation, not to 5-FU.^{6,13}

Bone formation, quantified by CBCT-derived HU values, increased significantly between 6 and 12 months ($p < 0.05$) in all patients, with robust mineralisation approaching cortical bone density in several mandibular cases. Crucially, no osteonecrosis was observed — in marked contrast to the recognised risks of Carnoy's solution and cryotherapy.^{6,7} The two pathological fractures were attributable to pre-existing cortical thinning from the lesion, not to 5-FU. The limitations of this study include a small sample size ($n = 10$), absence of a control arm, and 12-month follow-up. Larger multicentre randomised trials with extended follow-up are needed.

7. CONCLUSION

This prospective study evaluated topical 5-Fluorouracil as an adjunct to enucleation and peripheral ostectomy in 10

OKC patients over 12 months. Zero recurrence was detected at 6 or 12 months (100% recurrence-free). VAS pain scores reduced significantly ($p < 0.0001$). Post-operative paresthesia resolved fully in both affected patients by 12 months. Bone formation increased significantly between 6 and 12 months ($p < 0.05$) with no osteonecrosis. Two pathological fractures were due to cortical thinning, not 5-FU. Topical 5-FU is a safe, biologically rational, and effective adjunct, offering zero recurrence at one year, preserved neurovascular integrity, and confirmed osteogenesis — advantages over conventional adjuncts such as Carnoy's solution and cryotherapy. Larger randomised multicentre trials with extended follow-up are warranted.

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