

Refined Topical 5-Fluorouracil Technique for the Targeted Treatment of Odontogenic Keratocysts



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Purpose: An innovation in the treatment of odontogenic keratocysts (OKCs) is the adjunctive application of 5-fluorouracil (5-FU). Although the original approach remains effective, it may often be a challenge for the patient to return postoperatively and/or tolerate non-resorbable packing removal. The purpose of the present study is to determine whether our refined approach, where we directly apply 5-FU-coated absorbable gelatin sponge to the surgical cavity, would be an effective treatment for OKCs with similar efficacy as with our original approach.

Materials and Methods: A retrospective case series studying the treatment efficacy of our refined topical 5-FU approach on OKCs was reviewed. The study population was composed of all patients presenting for evaluation and management of OKCs with our refined technique between September 1, 2017 and July 1, 2022 at Stony Brook University Hospital. The primary outcomes included 1) time to OKC recurrence, and 2) incidence of trigeminal nerve injury following OKC treatment with the refined topical 5% 5-FU technique. Other study variables included age, gender, tumor location, and tumor size. Data analyses included descriptive statistics reported as median [interquartile range], and Kaplan–Meier survival analysis for time to OKC recurrence.

Results: Thirteen patients with 15 OKCs were reviewed (6 women and 7 men). There were no OKC recurrences with a median follow-up time of 28.5 (24) months. Normal bony healing was observed in all cases and there were no adverse local or systemic events, no alterations in sinus function, and no incidences of infraorbital or inferior alveolar nerve paresthesia.

Conclusions: Our case series demonstrates that this refinement further increases technical ease, decreases operating time, and precludes the need for packing removal, with similar efficacy as the original approach.

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Odontogenic keratocysts (OKCs), previously known as keratocystic odontogenic tumors, are benign lesions occurring in the maxilla or mandible with the potential for morbidity. Treatment options for the OKC

may include simple enucleation, marsupialization, curettage, peripheral ostectomy, adjunctive topical application (Carnoy's solution, modified Carnoy's solution, and liquid nitrogen), removal of overlying

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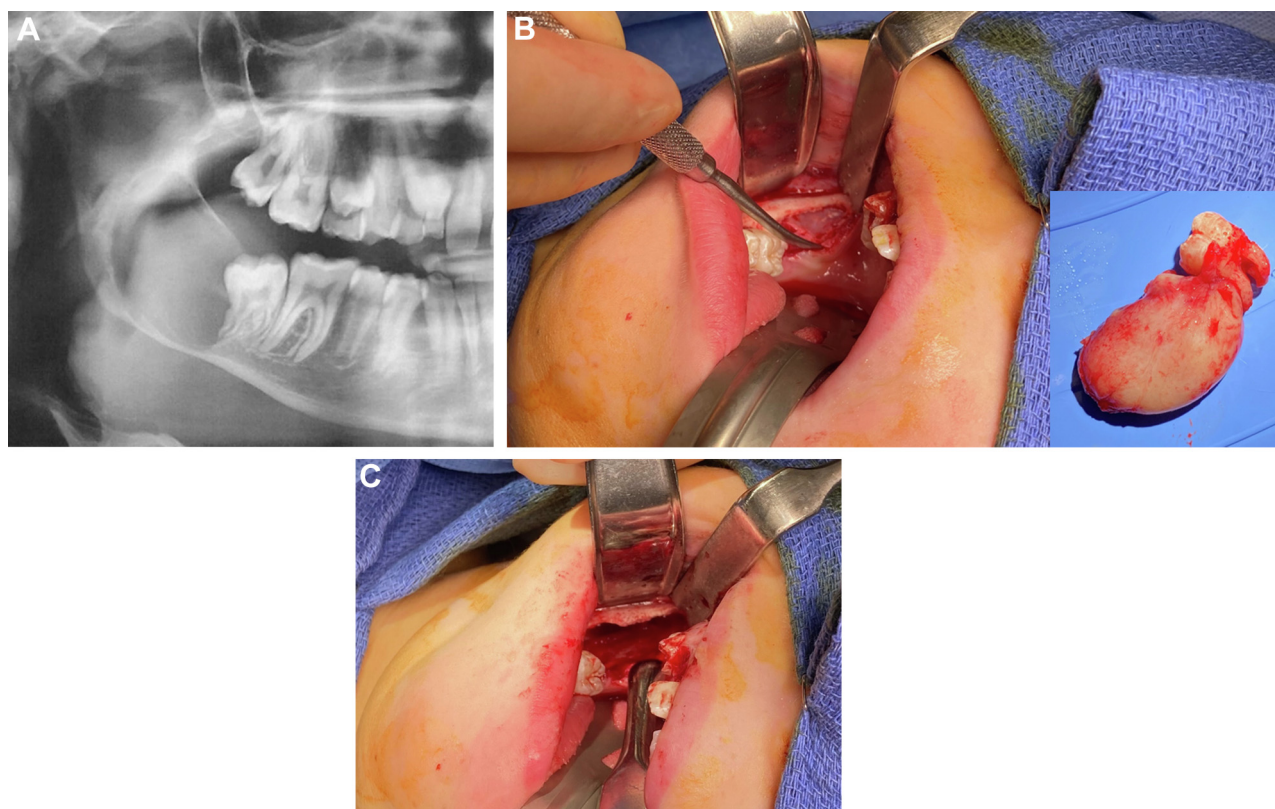


FIGURE 1. Refined topical 5-fluorouracil technique for treatment of odontogenic keratocysts. A, Panorex of biopsy-confirmed odontogenic keratocyst in right posterior mandibular body and ramus; B, Enucleation and C, Peripheral osteotomy performed in the usual fashion; (**Fig 1 continued on next page.**)

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mucosa, or resection, alone or in combination.¹⁻⁵ Enucleation alone results in unacceptably high recurrence rates.³ The adjunctive application of Carnoy's or modified Carnoy's solution decreases the recurrence rate after enucleation but may be associated with an increased rate of peripheral nerve injury.⁶ An innovation in the treatment of OKCs is the adjunctive application of the antimetabolite drug, 5-fluorouracil (5-FU).⁷ Topical application of 5-FU, after enucleation and peripheral osteotomy, effectively treats OKCs and is more advantageous because of its ready availability, technical ease, shorter operating time, similar efficacy, and decreased morbidity compared with modified Carnoy's.⁷

The original approach required 5-FU to be coated onto one-fourth-inch ribbon gauze and packed into the residual bony cavity following enucleation and peripheral osteotomy, in a manner that required retrieval of the non-resorbable gauze packing at 24 hours postoperatively.⁷ Although this remains an effective approach, it may often be a challenge for the patient

to return 24 hours postoperatively and/or tolerate packing removal. In addition, there are often OKC lesions that may be too small or impractical to adequately place or secure the ribbon gauze. An absorbable gelatin sponge can similarly obliterate the cystic cavity to provide hemostasis and improve 5-FU contact on residual cavity walls but it can also be more readily placed in cystic cavities of any size and does not need to be removed. Here we describe our refinements to this original approach where we apply 5-FU directly to the bony cavity with a cotton swab following enucleation and peripheral osteotomy, and then substitute the original ribbon gauze for an absorbable gelatin sponge. The purpose of the present study is to determine whether this refined approach would be an effective treatment for OKCs with similar efficacy as with our original approach. The specific aims of the study were as follows: 1) measure time to OKC recurrence, and 2) the incidence of trigeminal nerve injury following OKC treatment with our refined approach.

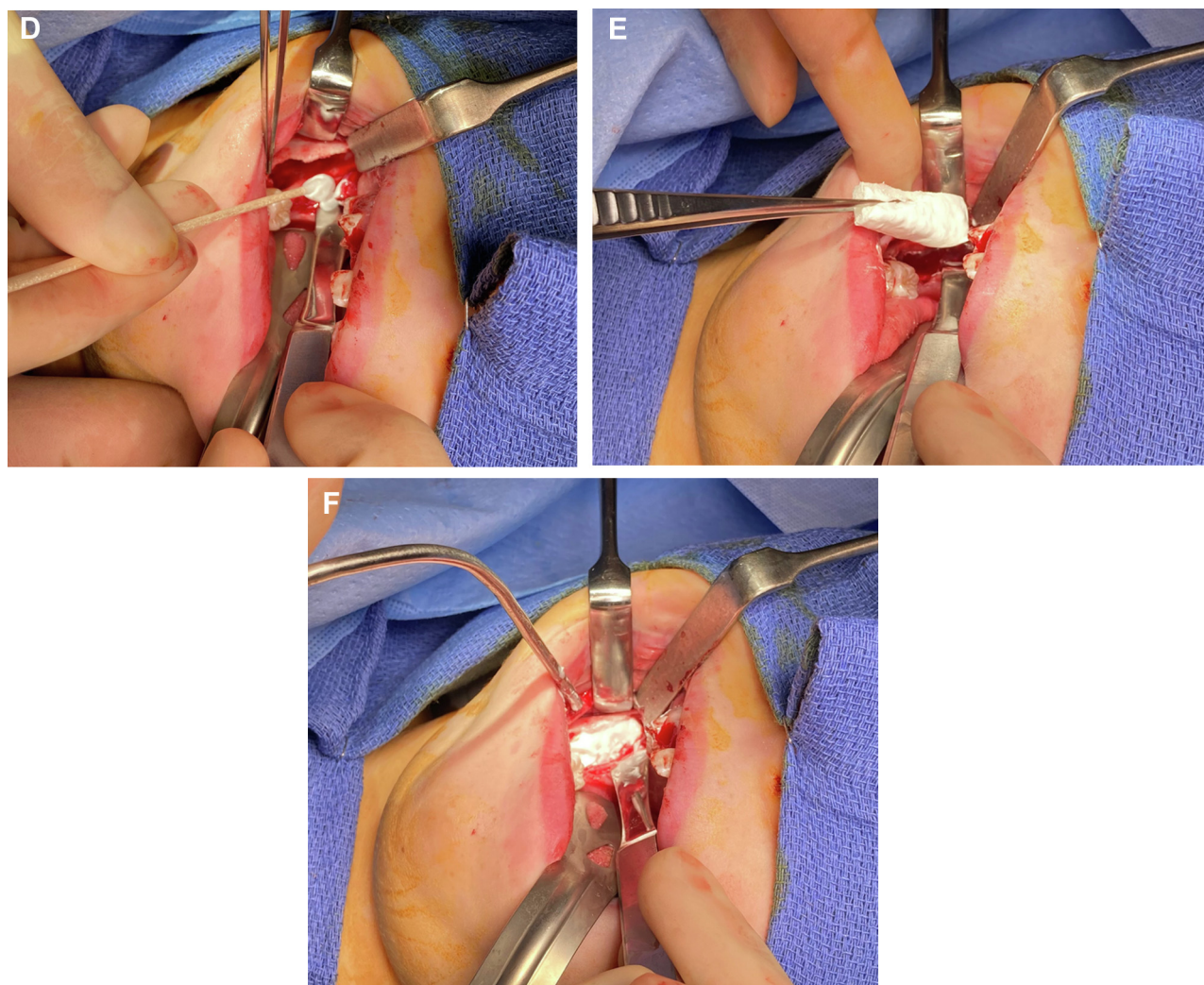


FIGURE 1 (cont'd). D, Topical 5% 5-fluorouracil (Efudex) was applied to all exposed cavity walls; and finally E, Absorbable gelatin sponge (Gelfoam) coated generously with 5% 5-FU was placed into the surgical wound to F, obliterate the entire surgical cavity.

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Materials and Methods

STUDY DESIGN/SAMPLE

We reviewed a retrospective case series of patients treated with the refined topical 5-FU technique after enucleation and peripheral ostectomy of OKCs. The study population was composed of all patients presenting for evaluation and management of OKCs with our refined technique between September 1, 2017 and July 1, 2022 at Stony Brook University Hospital (Stony Brook, NY, USA).

To be included in the study sample, patients had to have 1) a biopsy-proven OKC, 2) a complete history and clinical examination before definitive surgical intervention, and 3) completed surgical intervention for OKC. Patients were excluded as study subjects if they had 1) a diagnosed psychiatric condition, 2) a prior trigeminal nerve injury or existing paresthesia,

or 3) a diagnosis of orthokeratinizing odontogenic cyst or odontogenic keratocyst of the orthokeratinized variant.

VARIABLES

Primary outcomes included 1) time to OKC recurrence (months) and 2) incidence of trigeminal nerve (infraorbital or inferior alveolar) injury following OKC treatment with the refined topical 5% 5-FU technique. Other study variables included age (years), gender, tumor location (mandible or maxilla), and tumor size (millimeters).

DATA COLLECTION METHODS

Ethics approval was obtained from the Stony Brook University Office of Research Compliance (IRB2021-00384). Patient records were located by a retrograde

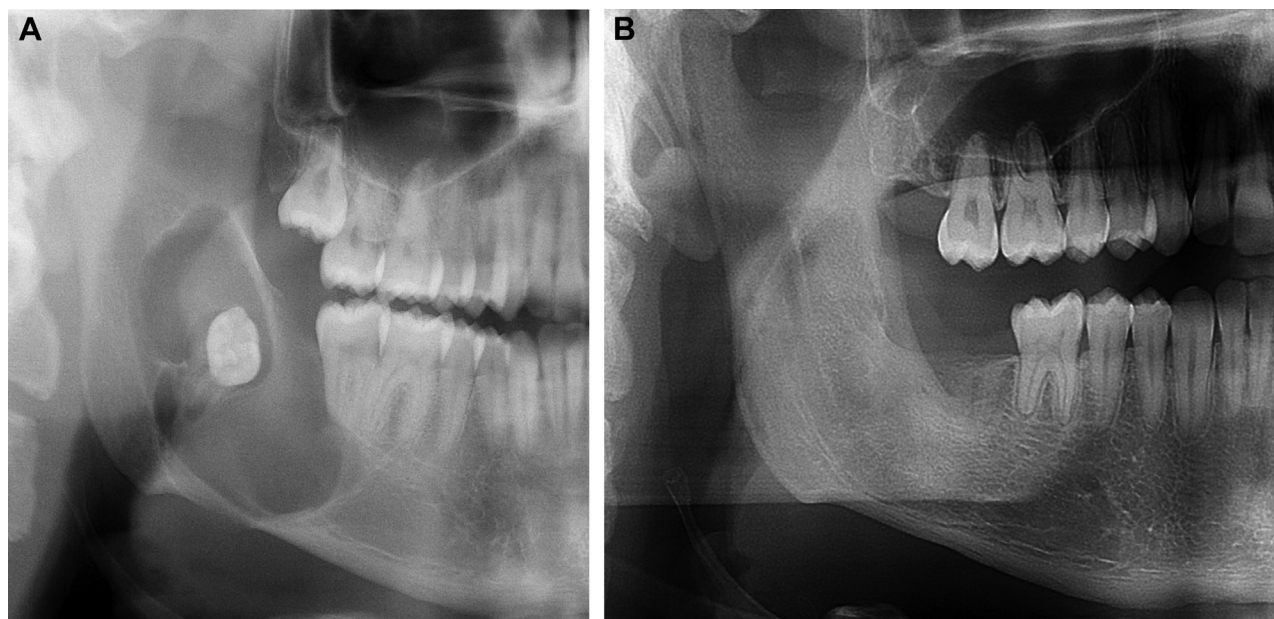


FIGURE 2. Representative example of odontogenic keratocyst treated with refined topical 5-fluorouracil technique. A, Preoperative Panorex radiograph showing a biopsy-confirmed odontogenic keratocyst involving the right mandibular body, and ramus. B, Six-month postoperative Panorex radiograph showing a well-healed, cyst-free right mandible treated with enucleation, peripheral ostectomy, and refined topical 5-fluorouracil technique.

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search of operating room case lists and by searching cyst enucleation codes for procedures performed for attending oral and maxillofacial surgeons at Stony Brook University Hospital from 2017 through 2022. Operative notes, pathology reports, and associated clinical records were reviewed.

REFINED TOPICAL 5-FU TECHNIQUE

A clinical case is presented to illustrate the refined topical 5-FU technique. A 13-year-old girl presented with a $5.0 \times 3.8 \times 2.5$ -cm unilocular biopsy-confirmed OKC involving the right posterior mandibular body and ramus (Fig 1A). After enucleation and peripheral ostectomy of the OKC lesion (Figs 1B, C), the surgical cavity was irrigated with copious sterile normal saline, and topical 5% 5-FU (Efudex, Valeant Inc, Laval, QC, Canada) was generously applied to all exposed bony cavity walls (including soft tissue as necessary with bony dehiscences/fenestrations) with a cotton swab (Fig 1D). Finally, absorbable gelatin sponge (Gelfoam®) coated generously with 5% 5-FU was placed into the surgical wound to obliterate the entire surgical cavity (Figs 1E, F). The wound was then closed in the usual manner.

DATA ANALYSES

Descriptive statistics are reported as median [interquartile range]. Kaplan–Meier survival analysis for the time to OKC recurrence.

Results

Thirteen patients with 15 OKCs treated with the refined topical 5-FU technique (Fig 1) were reviewed (6 women and 7 men). The median age at diagnosis was 21 (40) years. Mandibular lesions accounted for 8 of 15 OKCs, with the remaining 7 found in the maxilla. Three of these lesions were recurrent lesions (2 maxilla, 1 mandible). Median OKC measurements were 31.6×37.3 mm [4.0×5.5 mm]. All OKCs were treated by enucleation, peripheral ostectomy, and the refined topical 5-FU technique. There were

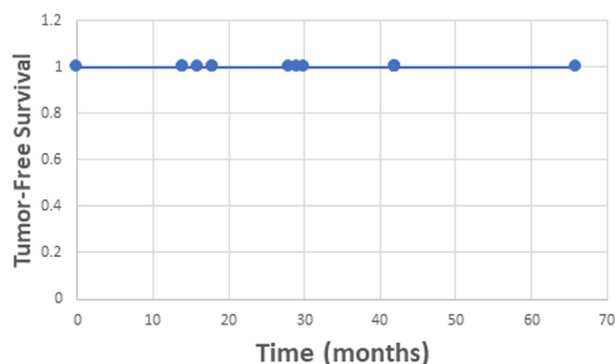


FIGURE 3. Kaplan–Meier survival analysis for patients treated with refined topical 5-fluorouracil technique. The y-axis represents the percentage of patients free of odontogenic keratocysts and x-axis denotes time in months.

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no recurrences with a median follow-up time of 28.5 (24) months. All 5-FU-treated cases exhibited normal bony healing (Fig 2). There were no adverse local or systemic events, no alterations in sinus function, and no incidences of infraorbital or inferior alveolar nerve paresthesia, in response to the refined topical 5-FU technique. A Kaplan–Meier analysis (Fig 3) was performed to illustrate the time to recurrence.

Discussion

We describe a refined technique for the topical application of 5-FU for the treatment of OKCs. This refined technique further increases technical ease, decreases operative time, and precludes the need for packing removal, with similar efficacy as the original approach.⁷

Topical 5-FU is a novel therapy for OKCs and provides a targeted molecular approach to treatment.⁷ 5-FU is a known, well-studied, and readily accessible drug. The advantages of topical 5-FU application for the treatment of OKCs with both the original and refined techniques include decreased postoperative morbidity, lower risk of reoperation, lower cost, and a straightforward technique. Other than precluding the need for packing removal, the use of an absorbable gelatin sponge in the refined technique may provide additional benefits. The absorbable gelatin sponge can readily obliterate and expand to better contour, and adapt to the bony walls of the residual bony cavity to improve 5-FU contact on these recurrence-susceptible surfaces. Since it generally takes 4 to 6 weeks to totally resorb, the absorbable gelatin sponge may also prolong 5-FU contact time on these cavity surfaces, mimicking the 4 to 6 weeks duration of repeated 5-FU topical application recommended for the treatment of actinic keratoses and basal cell carcinomas.

There were no recurrences for all cases, including one patient with over 5 years follow-up, treated with the refined technique. The median follow-up period for patients treated with our refined technique is greater than the mean recurrence time reported in prior studies.^{7,8} Based on our experience and follow-up, thus far, our refined technique has similar efficacy as the original technique with topical 5-FU. In addition, we demonstrate that the refined technique may be effective in the treatment of recurrent OKCs. OKCs in the maxilla recur more frequently than OKCs in the mandible due to the greater degree of marrow spaces and therefore higher degree of difficulty in removing these lesions in their entirety.⁹ The findings from our study suggest that the refined topical 5-FU technique may be ideal for these lesional cavities with greater concern for morbidity and lower success.

Despite substituting the removable ribbon gauze with absorbable gelatin sponge, normal bony healing

occurred in all cases treated with the refined topical 5-FU technique. There were no alterations in sinus or nerve function, and no adverse local or systemic responses to topical application of 5-FU using the refined technique in our study. This is in agreement with the absence of adverse systemic effects in patients treated with the original topical 5-FU approach.⁷ The original approach recommended leaving gauze in the cavity for 24 hours, since there were reported cases of excessive edema when the gauze was left in place beyond 72 hours. Despite the prolonged 5-FU contact time on cavity surfaces with our refined approach, there was no observable increase in edema using the absorbable gelatin sponge compared with the original approach leaving gauze in the cavity for 24 hours. As such, the reported increased edema is more likely secondary to prolonged retention of the gauze itself, rather than prolonged 5-FU contact. The average bony cavity defect treated with the refined topical 5-FU technique in the present study (31.6×37.3 mm) required approximately 1.25 grams of 5% 5-FU cream.¹⁰ Since every 1 gram of 5% 5-FU contains 50 mg of 5-FU, the average residual cavity required approximately 62.5 mg of 5-FU. Only 5.98% of the topical dose of 5-FU has been shown to be absorbed systemically, as such the average systemic absorption of topical 5-FU would be in the range of 3.75 mg which is lower than the LD50 of greater than 500 mg/kg in rats.¹¹ Taken together, our findings suggest it is both safe and effective to retain the absorbable sponge as a topical 5-FU delivery device in the residual cavity.

However, systemic administration of 5-FU may result in adverse responses, particularly in the 3 to 5% of the population with partial dihydropyrimidine dehydrogenase (DPD) enzyme deficiency.^{12,13} Although it is extremely unlikely for anyone, even DPD deficient individuals, to experience systemic toxicities because of the exceedingly low dose in our study, caution should be exercised with any high risk individuals such as individuals who are DPD-deficient or have experienced severe systemic reactions to chemotherapeutics involving 5-FU.

A well-designed, long-term, prospective, randomized, double-blinded, controlled clinical trial would further support the above findings. A prospective study is currently underway at our institution. Consideration of additional targeted medications, such as smoothened or sonic hedgehog inhibitors are also suggested candidates for the targeted topical treatment of OKCs.

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