5-Fluorouracil Is Associated With a Decreased Recurrence Risk in Odontogenic Keratocyst Management: A Retrospective Cohort Study

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Purpose: The antimetabolite drug, 5-fluorouracil (5-FU), has been suggested as an adjunctive treatment to reduce the recurrence rates of odontogenic keratocysts (OKCs). We report on the use of 5-FU in the management of patients with OKCs as a postenucleation intracavity topical dressing.

Methods: For this retrospective cohort study, we collected all data of sequentially treated cases presenting to the University of Toronto's hospital clinics for the management of biopsy-proven OKCs. Chart reviews were conducted to identify all patients treated with 5-FU cream, and compare them to patients treated with modified Carnoy's solution (MCS). In the treatment group, all patients were treated in an identical manner with enucleation and peripheral ostectomy followed by the application of 5% 5-FU cream for 24 hours. Preoperative and postoperative radiographs were collected to determine the time to recurrence of the disease, and the techniques were compared via a multivariate Cox regression analysis.

Results: Seventy patients were found to be eligible for inclusion in this study. Of these, 34 patients were treated with 5% topical 5-FU, and 36 patients were managed with MCS. The median follow-up time in the 5-FU group was 22 months (interquartile range, 36), compared with 27 months (interquartile range, 37) for the MCS group ($P = .40$). No recurrences were identified in the 5-FU group, compared with 9 recurrences (25%) in patients treated with MCS. 5-FU was shown to be significantly negatively associated with time to disease resolution ($P < .01$).

Conclusions: Results from this study suggest that when used topically, 5-FU effectively lowers the recurrence rates of OKCs. Further large scale, case-controlled studies are being investigated at our center and are warranted to make definitive conclusions regarding the effectiveness of this novel technique when compared with conventional therapies.

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Odontogenic keratocysts (OKCs) are developmental cysts believed to arise from remnants of the dental lamina or the basal cell layer of the oral mucosal epithelium.[1] They are distinguished from other odontogenic cysts because of their high recurrence rates after simple enucleation (25 to 60%), histologic and molecular characteristics, and aggressive clinical behavior in some cases.[2,3] There is controversy over the classification of OKC as a cyst or a benign odontogenic neoplasm.[4,5] The most recent World Health

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Organization classification of head and neck tumors considers OKC as an odontogenic developmental cyst rather than a neoplasm.[4]

The uncertainty over the biological nature of OKCs is reflected in the variation of treatment approaches. OKCs may be managed surgically by enucleation or decompression, although these treatment modalities are associated with high recurrence rates when used alone.[6] Thus, other techniques, such as cryotherapy, chemical cautery, and peripheral ostectomy, are often used in conjunction to reduce risk of recurrence.[3,7,8] However, these techniques pose inherent challenges: cryotherapy predisposes mandibles to fracturing,[9] and chloroform, a key ingredient in Carnoy's solution, is now rarely used because of its carcinogenicity. Modified Carnoy's solution (MCS) without chloroform is often used in place of original Carnoy's solution, although it is less effective.[10] Bone resection is associated with minimal recurrence,[6] but it is a highly invasive treatment and is thus generally reserved for multiple recurrent cases,[11] malignant change, or involvement of the pterygoid muscle.[12] These challenges, combined with a lack of consistency among institutions and surgeons, call for a more effective surgical treatment modality associated with low postoperative morbidity and recurrence.

5-Fluorouracil (5-FU) is an antimetabolite of the pyrimidine synthesis pathway that has been effective and well tolerated in treating superficial basal cell carcinomas (BCCs) as a topical ointment.[13] The cytotoxic effect of 5-FU is initiated by thymidine phosphorylase (TP)-mediated conversion of 5-FU into fluorodeoxyuridine.[14] Thymidine kinase then converts fluorodeoxyuridine into fluorodeoxyuridine monophosphate, the active metabolite of 5-FU responsible for competitively inhibiting thymidylate synthetase (TS).[14] Inhibition of TS deprives actively proliferating cells of thymidine, thereby inducing lethal DNA damage[14] (Fig 1).

The pathogenesis of OKCs is believed to be similar to that of BCCs, as suggested by the high frequency of these lesions in a background of loss of function mutations in PTCH1, such as in patients with Gorlin syndrome.[15-17] On the basis of the similarities in the molecular pathogenesis of BCCs and OKCs, we expect that OKCs will respond favorably to topical 5-FU with respect to recurrence. Our group has previously reported that a 24-hour application of topical 5-FU after enucleation and peripheral ostectomy of OKCs was well tolerated by patients.[18] Furthermore, it has been reported in this study that 5-FU targets thymidine kinase and TP in OKC lining and may be a targeted therapeutic intervention in the management of these recurrent cysts. 5-FU also was suggested to effectively minimize postoperative inferior alveolar nerve paresthesia compared with treatment using

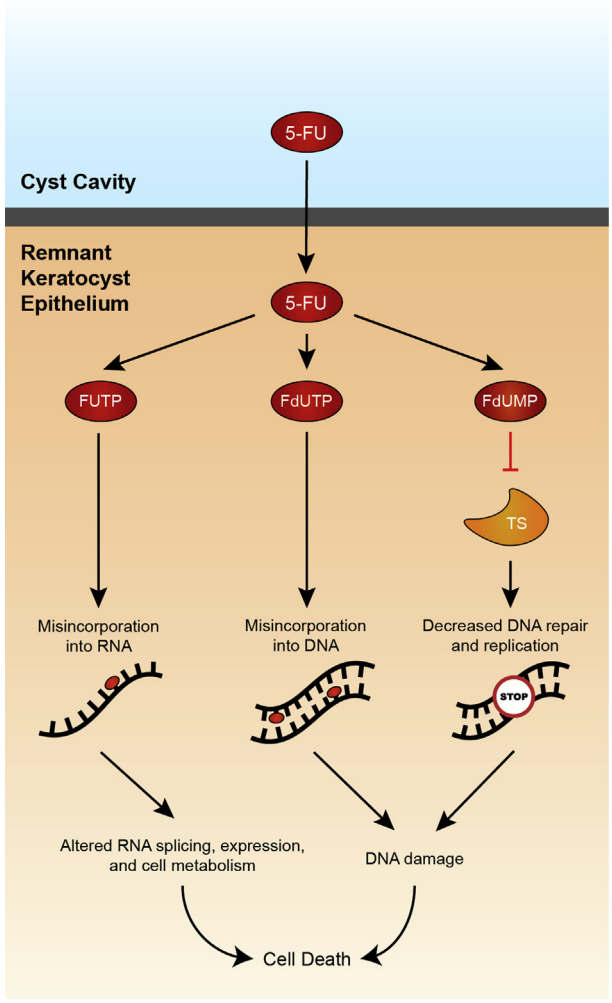

FIGURE 1. Schematic of 5FU metabolism, dihydropyrimidine dehydrogenase, thymidine phosphorylase (TP), and thymidylate synthetase (TS). FdUMP, fluorodeoxyuridine monophosphate; 5-FU, 5-fluorouracil; FdUTP, fluorodeoxyuridine triphosphate.

Caminiti et al. 5-Fluorouracil in Odontogenic Keratocyst Management. J Oral Maxillofac Surg 2020.

MCS.[18] Inflamed OKCs are associated with low TS and high TP levels,[18] 2 features of effective 5-FU response,[19,20] and thus may benefit more from treatment with 5-FU than noninflamed OKCs.

Given the uncertainty regarding the efficacy of topical 5-FU as a means of reducing recurrence rates in OKCs, the purpose of this study was to assess whether topical 5-FU could improve patient outcome in the treatment of OKCs. We hypothesized that OKCs treated with 5-FU as an adjunctive therapy to enucleation and peripheral ostectomy is associated with decreased rates of recurrence compared with MCS-treated lesions. The specific aims of the study were to *1)* show the efficacy of 5-FU in managing OKCs, *2)* compare rates of recurrence of OKCs treated with 5-FU with those treated with MCS, and *3)* compare rates of trigeminal nerve injury between the 2 groups.

Patients and Methods

STUDY DESIGN

To address the research purpose, the investigators designed and implemented a retrospective cohort study. The study population consisted of patients with a biopsy-proven diagnosis of OKC, treated at the University of Toronto's outpatient clinic and Mount Sinai Hospital (Toronto, Ontario, Canada) between January 2009 and December 2019. Ethics approval was obtained by the Mount Sinai Hospital (protocol no. 15-0011-E) and the University of Toronto (protocol no. 31638) Research Ethics Boards.

ELIGIBILITY CRITERIA

Inclusion criteria for patients in the study were nonsyndromic patients with *1)* biopsy-proven OKC, evaluated by the University of Toronto or the Mount Sinai Hospital (Toronto, Canada) Oral Pathology Biopsy Service, *2)* complete history and clinical examination before definitive surgical intervention, and *3)* completed surgical intervention for OKC. Patients were excluded if they *1)* were followed for less than 6 months after surgery, *2)* had incomplete data, *3)* had a medical condition that may alter their trigeminal sensory perception, and *4)* had a diagnosis of Gorlin-Goltz syndrome.

DATA COLLECTION METHODS

Patient records were located via a retrograde search of operating room and clinic case lists from 2006 to 2018 by Attending Oral and Maxillofacial Surgical staff. All provincial and hospital codes associated with "cyst" were examined. Key words to identify and locate charts included cyst, enucleation, 5-Fluorouracil, OKC, KOT, Keratocyst, Keratocystic Odontogenic Tumor, and Odontogenic Keratocyst. Operative notes, pathology reports, and associated clinical records were reviewed to collect relevant data for each patient.

STUDY VARIABLES

The predictor variable for this study is the supplemental method used to treat the OKC after enucleation and peripheral ostectomy (ie, 5-FU vs MCS), as described subsequently. The primary outcome variable for this study was the time to recurrence (or the time to last follow-up, if no recurrences were recorded). The secondary outcome variable was the presence of permanent postoperative nerve paresthesia.

Other variables collected for this study were age, gender, location (maxilla vs mandible and anterior vs posterior), whether the cyst was uniloculated or multiloculated, and whether there was an associated tooth (and if it was extracted as part of the enucleation).

INTERVENTION

After enucleation and peripheral ostectomy of the OKC lesion, a sterile radiopaque quarter-inch ribbon gauze was coated with 5% 5-FU cream (Efudex; Valeant Inc, Laval, Quebec, Canada) and packed into the surgical wound. The wound was then closed in the usual manner, leaving a small distal end (approximately 1 cm) of gauze exposed to allow for gauze removal at 24 hours postoperatively (Fig 2). Patients were then seen on postoperative day 1 for removal of the 5-FU packing and thorough irrigation of the wound with normal saline. Orthopantomograms (OPGs) were obtained preoperatively, within 24 hours postoperatively showing the application of the packing, and at 6-month intervals postoperatively. In cases deemed challenging to assess for recurrence with an OPG (eg maxillary lesions), a computed tomography scan was performed at 12 to 18 months.

CONTROL

Patients in the control group were all treated with MCS.[10] After enucleation and peripheral ostectomy of the cyst, MCS-soaked gauze was applied to all

FIGURE 2. Examples of the (*A*) topical 5-fluorouracil cream and (*B*) radiomarked iodoform gauze used in our protocol.

Caminiti et al. 5-Fluorouracil in Odontogenic Keratocyst Management. J Oral Maxillofac Surg 2020.

surfaces of the cyst for 3 minutes, with Vaseline-soaked gauze used to protect the surrounding soft tissues. The cyst cavities were irrigated with normal saline before closure. OPGs were obtained at 6-month intervals postoperatively to assess for recurrence, and computed tomography scans were performed at 12 to 18 months for all maxillary lesions.

OUTCOMES

The primary outcome of this study was the time to cyst recurrence, which was evaluated through radiographic and clinical examinations. All 3-dimensional scans were read by either a board-certified radiologist or oral radiologist, otherwise OPGs were reviewed by the treating surgeon. Data were collected for each patient until the time of their last follow-up, or until first detection of a recurrence. The secondary outcome for this study was the presence of permanent postoperative nerve paresthesia, as identified by history and clinical examination.

STATISTICAL PLAN

Descriptive statistics for the 2 groups were presented as means or proportions when appropriate. Baseline comparisons between the 2 groups were conducted via *t* tests and Fisher's exact tests as appropriate. For the primary outcome, a multivariate Cox regression analysis was conducted to compare the time to recurrence between the 2 groups. Furthermore, the comparison of time to recurrence was presented in an unadjusted manner as a Kalpan-Meier curve. A comparison of permanent postoperative nerve paresthesia was conducted via a multivariate logistic regression. The following potential confounders were controlled in both analyses: location of the cyst (maxilla vs mandible), whether the associated tooth (if present) was extracted, and whether the cyst had a previous history of recurrence.

All evaluations were considered significant at $P < .05$. All statistical tests were conducted via R (version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria).[21]

Results

A total of 70 patients were deemed eligible for inclusion in this study. Of these, 34 patients were treated with 5% topical 5-FU, and 36 patients were managed with MCS. The baseline characteristics of the 2 groups are detailed in Table 1. Of note, the median follow-up time in the 5-FU group was 22 months (interquartile range, 36), compared with 27 months (interquartile range, 37) for the MCS group ($P = .40$).

No recurrences were identified in the 5-FU group, compared with 9 recurrences within the 36 patients treated with MCS (Fig 3). The multivariate Cox proportional hazards model (Table 2), controlling for potential confounders, showed 5-FU to be significantly negatively associated with time to disease resolution ($P < .01$; hazard ratio not estimable as no recurrences were found in the 5-FU group). No other factors in this model were significantly associated with recurrence.

Results of the logistic regression model (Table 3), controlling for potential confounders, showed no

Table 1. DESCRIPTIVE STATISTICS

	Treatment		
	5-FU (n = 34)	MCS (n = 36)	*P* Value*
Age	47 ± 18	38 ± 13	*<.05**
Gender			*<.05**
Male	22	14	
Female	12	22	
Location			*.05*
Maxilla	12	5	
Mandible	22	31	
Locularity			*.61*
Unilocular	24	24	
Multilocular	9	12	
Associated tooth			*.15*
Yes	24	31	
No	10	5	
Impacted tooth			*.57*
Yes	9	7	
No	25	29	
Tooth extracted			*.22*
Yes	18	25	
No	16	11	
History of previous recurrence			*.13*
Yes	9	4	
No	25	32	
Postoperative paresthesias			*.78*
Yes	7	9	
No	27	25	
Follow-up period (mo), mean ± SD	30 ± 24	35 ± 26	*.40*
<12	11	7	
12-23	7	7	
24-35	5	7	
>36	11	15	
Recurrences	0/34	9/36	

Italic values indicate $P < .05$.
Abbreviations: 5-FU, 5-fluorouracil; MCS, modified Carnoy's solution; SD, standard deviation.
* Unpaired *t* test or Fisher's exact test were used as appropriate.

Caminiti et al. 5-Fluorouracil in Odontogenic Keratocyst Management. J Oral Maxillofac Surg 2020.

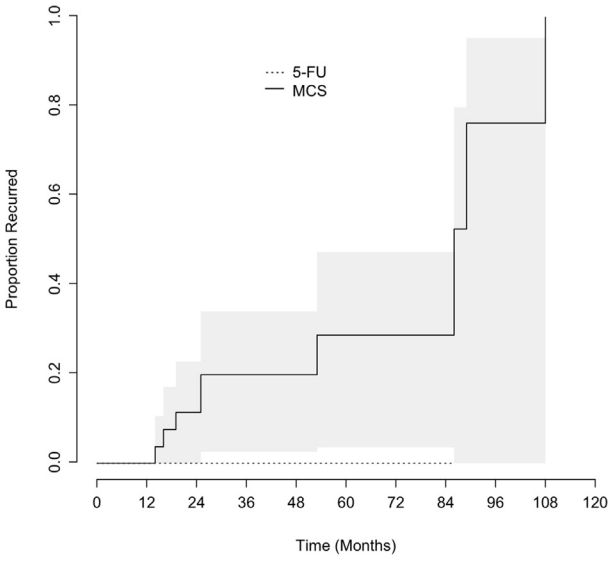

FIGURE 3. Depiction of the Kaplan-Meier curve, comparing time to recurrence between the 5-FU and MCS groups, with 95% Greenwood confidence intervals. 5-FU, 5-fluorouracil; MCS, modified Carnoy's solution.

Caminiti et al. 5-Fluorouracil in Odontogenic Keratocyst Management. J Oral Maxillofac Surg 2020.

significant differences between the effects of 5-FU versus MCS on permanent nerve paresthesia (odds ratio = 0.79; 95% confidence interval, 0.23 to 2.65; $P = .71$).

Discussion

The purpose of this study was to compare the effects of topical 5-FU to the standard approach of using MCS as a supplement to reduce risk of recurrence of OKCs. The results of this study suggest that 5-FU is effective as an adjunctive treatment to significantly reduce the risk of recurrence of OKCs when compared with the conventional approach of using MCS postcurettage. Compared with the recurrence rate of 25% in the MCS group (which is similar to reported recurrence rates in the literature[10]), our 5-FU group yielded no recurrences to date.

Through this study, it was shown that when controlling for potential confounders, 5-FU was significantly associated with a reduction in time to recurrence of OKCs. To control for the variabilities in follow-up times between the 2 groups, a survival analysis was conducted. Of note, no other variables were found to be significantly associated with the outcome of interest. Furthermore, although our initial study showed a significantly reduced proportion of patients with permanent postoperative nerve paresthesia with the use of 5-FU, our study failed to find a significant association.

5-FU is an antimetabolite that targets proliferating cells. The findings in this study support our hypothesis that topical application of 5-FU to the wound cavity immediately after curettage and peripheral ostectomy is effective in eliminating remnants of keratocyst epithelium and satellite cysts, which are thought to be the cause of recurrence. The mode of action of topical 5-FU differs from that of MCS or liquid nitrogen, which causes nonselective tissue necrosis. The pharmacologic effect of 5-FU is affected by 3 enzymes: TS, TP, and dihydropyrimidine dehydrogenase (DPD). Our previous immunohistochemical study suggested that 5-FU may be more effective in preventing recurrence in cases of inflamed OKCs compared with noninflamed OKCs.[18] Greater TP expression in the epithelial lining of inflamed OKCs may promote conversion of 5-FU to active metabolites, including fluorodeoxyuridine monophosphate, and thereby enhance destruction of remaining OKC epithelial lining and microscopic satellite cysts inadvertently left behind after surgical removal. The low TS and high TP expression in inflamed OKCs suggest that procedures such as prior incisional biopsy, marsupialization, and intraoperative enucleation and curettage, which induce inflammation, may increase the efficacy of 5-FU treatment of OKCs. 5-FU itself has been suggested to induce an intense inflammatory reaction when

Table 2. SUMMARY OF THE RESULTS OF THE COX PROPORTIONAL HAZARDS MODEL, EVALUATING THE DIFFERENCES BETWEEN 5-FU VERSUS MCS ON RECURRENCE RATES, WHILE CONTROLLING FOR POTENTIAL CONFOUNDING VARIABLES

Variable	Coefficient	Adjusted Hazard Ratio (95% CI)	*P* Value (Likelihood Ratio Test)
5-FU (vs modified Carnoy's)	Not estimable†	Not estimable†	<.01*
Mandible (vs maxilla)	0.44	1.55 (0.12-19.4)	.73
Associated tooth not extracted	0.54	1.72 (0.19-15.7)	.65
History of recurrence	0.70	2.01 (0.31-13.1)	.48

Abbreviations: 5-FU, 5-fluorouracil; CI, confidence interval; MCS, modified Carnoy's solution.

* Significant at $P < .05$.

† Not estimable as no recurrences occurred in the 5-FU group.

Caminiti et al. 5-Fluorouracil in Odontogenic Keratocyst Management. J Oral Maxillofac Surg 2020.

Table 3. SUMMARY OF THE RESULTS OF THE LOGISTIC REGRESSION MODEL, EVALUATING THE DIFFERENCES BETWEEN 5-FU VERSUS MCS ON PERMANENT NERVE PARESTHESIA, WHILE CONTROLLING FOR POTENTIAL CONFOUNDING VARIABLES

Variable	Coefficient	Adjusted Odds Ratio (95% CI)	*P* Value (Likelihood Ratio Test)
5-FU (vs modified Carnoy's)	−0.23	0.79 (0.24-2.65)	.71
Mandible (vs maxilla)	1.05	2.85 (0.55-14.9)	.21
Associated tooth not extracted	−0.042	0.96 (0.22-4.12)	.95
History of recurrence	0.38	1.47(0.31-6.99)	.63

Abbreviations: CI, confidence interval; 5-FU, 5-fluorouracil; MCS, modified Carnoy's solution.

Caminiti et al. 5-Fluorouracil in Odontogenic Keratocyst Management. J Oral Maxillofac Surg 2020.

applied topically to skin within the first 24 hours.[22] On the other hand, increased DPD expression in the lining epithelium of inflamed OKCs may result in decreased efficacy of 5-FU treatment because of breakdown of 5-FU into inactive metabolites. We were not able to compare the efficacy of 5-FU treatment in inflamed and noninflamed OKCs because to date, there has been no recurrence in the 5-FU–treated group.

Other than providing focused antiproliferative therapy for OKC treatment, 5-FU application may be preferable to other adjunctive therapies such as MCS or liquid nitrogen because of its availability and technical ease of use. The 5% 5-FU cream is simply coated onto ¼ inch ribbon gauze and packed into the bone cavity in a manner that allows for easy removal at 24 hours postoperatively. This is in contrast to application of Carnoy's solution, which substantially increases operating time because of precautions required to prevent damage to adjacent tissues. However, our clinical experience indicates that the 5-FU–coated gauze should be carefully applied to contact all surfaces of the wound cavity. Areas that lack exposure to the 5-FU gauze may in theory give rise to recurrence of the OKC. An immediate postoperative OPG is required to confirm placement of the 5-FU gauze into the entire wound cavity (Fig 4).

In our study, there were no significant differences between topical 5-FU and MCS in adverse effects, including permanent nerve paresthesia. 5-FU is not known to be neurotoxic and paresthesia may be attributed to the location and size of the OKC rather than contact with 5-FU. Published reports have indicated that periorbital connective tissues seem to be unaffected by application of topical 5-FU twice daily when used to treat ocular surface squamous neoplasia.[23] No studies to date have shown direct application of topical 5-FU to major blood vessels. A twice weekly application of topical 5% 5-FU for 4 weeks after medial maxillectomy and sphenoethmoidectomy for ethmoidal adenocarcinoma had neither mention of adverse effects on the infraorbital nerve nor the remaining sinus mucosa.[24,25]

In contrast to local application, systemic administration of 5-FU may result in adverse responses including mucositis, granulocytopenia, neuropathy, cardiac toxicities, nausea, vomiting, pallor, hypotension, general malaise, and death.[26,27] An important consideration is that approximately 3 to 5% of the population is partially DPD enzyme deficient. This is most prevalent in African American females with up to 12% of this particular demographic to be DPD deficient. Capecitabine is an orally administered prodrug of 5-FU, which is a widely used chemotherapeutic agent incorporated in the treatment of several malignancies. This systemic administration of 5-FU can cause an intense toxicity, and manifestations reported include prolonged pancytopenia with signs and symptoms of sepsis, gastrointestinal toxicities, diarrhea, nausea, vomiting, and mucositis in DPD-deficient individuals.[27]

The benefit of topical application is the avoidance of any systemic exposure; however, to our knowledge there is 1 reported case of a patient with severe DPD deficiency who had a severe toxic reaction after excessive application for scalp basal cell lesions.[26] We use a protocol of 5-FU application on gauze for 24 hours after enucleation and peripheral ostectomy. The gauze is removed intact and the bone cavity irrigated to terminate the exposure of tissues to 5-FU. In view of the possibility of an idiosyncratic reaction or sensitivity because of enzyme deficiency, adherence to the 24-hour period of application and close monitoring of the patient are required for topical 5-FU treatment in patients with OKC.

Patients with OKCs as part of the manifestation of Gorlin syndrome or Nevus Basal Cell Carcinoma Syndrome were not included in this study. Patients with Gorlin syndrome develop multiple OKCs that may be synchronous or metachronous and cause extensive bone destruction in the jaws. The risk of recurrence is reported to be high, although it may be difficult to distinguish recurrence from a new cyst. To date, we have used 5-FU to manage OKCs in 8 patients with Gorlin syndrome, with 2 recurrences subsequently treated with further enucleation and application of 5-

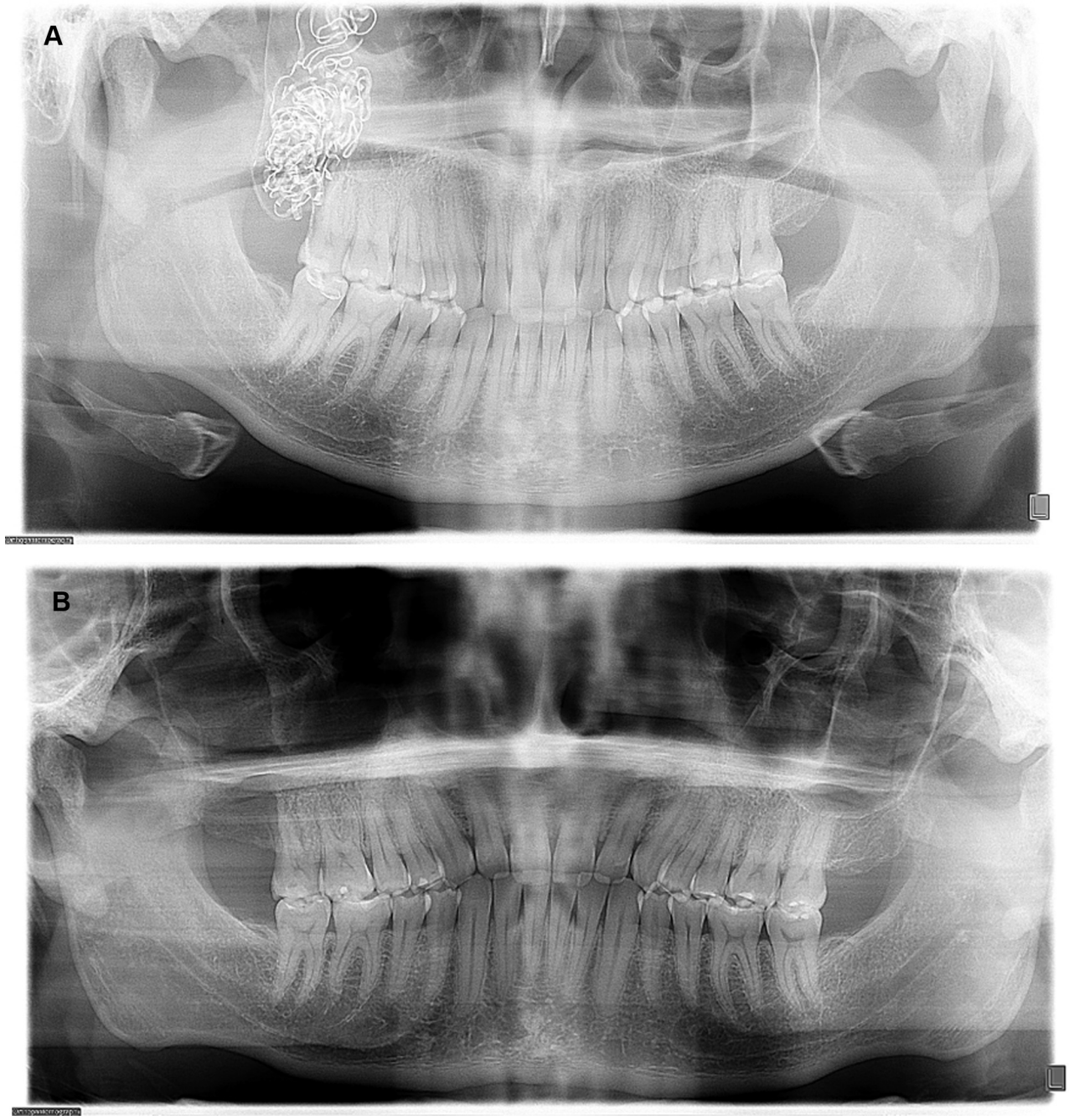

FIGURE 4. Case 1: OPG of a 28M whose right posterior maxillary OKC had been treated with 5-FU. *A*, Immediate postoperative pan showing 5-FU–soaked ribbon; *B*, At 6 months postoperatively showing good bony fill with no radiographic evidence of recurrence. 5-FU, 5-fluorouracil; OKC, odontogenic keratocyst; OPG, orthopantomogram.

Caminiti et al. 5-Fluorouracil in Odontogenic Keratocyst Management. J Oral Maxillofac Surg 2020.

FU. Although these results are promising, further evaluations are required to study the use of 5-FU for treatment of syndromic OKCs.

There are some limitations to be noted in this study. First, it is important to recognize that these follow-up times, especially for OKCs, may be relatively short. Although it should be noted that the follow-up times between the 5-FU and MCS groups were comparable, further follow-up will be required to ascertain the true rates of recurrence after use of topical 5-FU. Nevertheless, we attempted to control for the variability in follow-up times between the 2 groups by conducting a Cox regression analysis. Furthermore, although potential confounders were controlled for in our multivariate analyses, the retrospective nature of this study introduces the potential for incomplete

or imperfect data. Nonetheless, with the positive results of this study, we endeavor to work on establishing the engagement of a multicentered prospective study to overcome these limitations.

Results from this study suggest that when used topically, 5-FU effectively lowers the recurrence rate of OKCs. Comparing to the high recurrence rates reported with MCS of up to 35%, topical 5-FU may prove to be an effective alternative for the treatment of OKCs. 5-FU may be more ideal because of its ready availability, technical ease, shorter operating time, and decreased morbidity compared with MCS. The drug is well known and well studied with a good safety profile. Further high-quality prospective studies with long follow-up times are warranted to make definitive conclusions regarding the effectiveness of this novel technique.

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