How Well Do We Manage the Odontogenic Keratocyst?

*Brian E. Kinard, DMD, *Sung-Kiang Chuang, DMD, MD, †Meredith August, DMD, MD, ‡ and Thomas B. Dodson, DMD, MPH§*

Purpose: To answer the clinical question: Among patients treated for odontogenic keratocysts (OKCs), what is the overall 5-year disease-free rate and what factors are associated with disease recurrence?

Materials and Methods: The investigators implemented a retrospective cohort study and enrolled a sample composed of patients presenting for the evaluation and management of previously untreated OKCs. The predictor variables were grouped into demographic, medical, radiographic, and operative categories. The primary outcome variable was time to lesion recurrence. Data analyses were performed using univariate and bivariate or multivariate Cox proportional hazards models.

Results: The study sample was composed of 31 patients (31 OKCs) with a mean age of 41.0 years. Of the 31 OKCs treated, 19 (61.3%) were treated with decompression with or without residual cystectomy and 12 (38.7%) were treated with enucleation with or without adjunctive therapy. There were 8 recurrences in 8 patients, with a median time to recurrence of 17.8 months (interquartile range, 13.4 to 26.4 months). The 5-year disease-free estimate was 51.2% (95% confidence interval, 37.2%-65.2%). Multiloculated lesions were 33.6 times more likely to recur than unilocular lesions.

Conclusion: This may be the first study looking at disease recurrence after treatment of OKCs using appropriate statistical analyses for a time-dependent outcome (disease recurrence). The risk for recurrent disease is higher in this report than in many other studies and raises the issue that other reports may have underestimated the risk for recurrent disease owing to inappropriate statistical methods for assessing time-dependent outcomes.

J Oral Maxillofac Surg 71:1353-1358, 2013

The odontogenic keratocyst (OKC), also known as the keratocystic odontogenic tumor, is noted for its locally aggressive nature and ability to recur.[1] The authors recognize there is controversy regarding current terminology for these lesions. For the sake of consistency and simplicity, the term *odontogenic keratocyst* is used throughout this document. The current literature cites a broad range of recurrence rates for various surgical treatment options for OKCs (0% to 62%), with most recurrences presenting within 5 years of treatment.[2-4]

In the setting of benign disease, the therapeutic goal is to identify treatments that minimize morbidity and recurrence. For example, resection is associated with a 0% recurrence rate.[2,5-9] In the setting of nonmalignant disease, however, resection to achieve

*Resident, Department of Oral and Maxillofacial Surgery, Emory University School of Medicine, Atlanta, GA.

†Assistant Professor, Department of Oral and Maxillofacial Surgery, Massachusetts General Hospital, Harvard School of Dental Medicine, Boston, MA.

‡Associate Professor, Department of Oral and Maxillofacial Surgery, Massachusetts General Hospital, Harvard School of Dental Medicine, Boston, MA.

§Visiting (Attending) Oral and Maxillofacial Surgeon and Professor; Director, Center for Applied Clinical Investigation, Departments of Oral and Maxillofacial Surgery, Massachusetts General Hospital, Harvard School of Dental Medicine, Boston, MA.

This project was supported in part by the Massachusetts General Hospital Department of Oral and Maxillofacial Surgery Education and Research Fund (to B.E.K.), the Center for Applied Clinical Investigation (to S.-K.C. and T.B.D.), and the Massachusetts General Physicians Organization (to S.-K.C., M.A., and T.B.D.).

Conflict of Interest Disclosures: None of the authors reported any disclosures.

Address correspondence and reprint requests to Dr Dodson: Department of Oral and Maxillofacial Surgery, Massachusetts General Hospital, 55 Fruit Street, Warren Building Suite 1201, Boston, MA 02114; e-mail: tbdodson@partners.org

0278-2391/13/00294-2$36.00/0

http://dx.doi.org/10.1016/j.joms.2013.01.029

a cure may be more morbid than the underlying disease, especially for smaller lesions. Alternatively, enucleation with or without adjunctive treatments, such as peripheral ostectomy or cryotherapy, is a less morbid procedure, but the recurrence rate may be unacceptably high, resulting in multiple episodes of care during the patient's life.[10-14] A treatment that has minimal morbidity but with an acceptable recurrence rate may be decompression, longitudinal irrigation, and residual cystectomy.[15-19] Few studies have compared the success rates for different treatment options within the same patient population.[5,9,20-25]

The purpose of the present study was to address the following clinical question: Among patients with OKCs, what is the overall 5-year disease-free rate and what factors are associated with disease recurrence? The study hypothesis was that in patients treated for OKC, there exists a set composed of at least 1 variable that is associated with disease recurrence that can be modified by the clinician to enhance treatment outcomes. The specific aims of this study were to *1)* design a retrospective cohort study and enroll a sample composed of patients presenting for operative management of OKC, *2)* quantify the number and type of treatment options chosen for each OKC, *3)* estimate the 5-year recurrence rate using appropriate survival analyses, and *4)* identify variables associated with recurrence.

Materials and Methods

STUDY DESIGN AND SAMPLE

To address the research objectives, the investigators designed and implemented a retrospective cohort study. The study cohort was derived from the population of patients presenting to the Department of Oral and Maxillofacial Surgery at the Massachusetts General Hospital from February 2001 to April 2011 for the evaluation and management of OKC.

Patients eligible for study inclusion had 1 OKC lesion present that had not been treated previously. Patients were excluded if they were diagnosed with nevoid basal cell carcinoma syndrome or presented with lesions that had been previously treated, if data collection was incomplete, or patient records were not available for review. This project was reviewed and approved by the Partners Healthcare Human Studies investigational review board (protocol 2009-9-001606; MGH).

STUDY VARIABLES

The predictor variables were composed of a set of heterogeneous variables grouped into demographic, medical, radiographic, and operative categories. Demographic and medical variables included age, gender, and American Society of Anesthesiologist (ASA) health status (I to V). The radiographic variables were location of the lesion (maxilla or mandible), association with impacted teeth, evidence of cortical perforation, locularity (unilocular or multilocular radiographic appearance), and radiographic size of the lesion. The radiographic size of each lesion was recorded as the largest diameter of the lesion in any dimension estimated using panoramic radiographs taken before treatment. The operative variable was treatment categorized as enucleation without adjuvant therapy, enucleation with adjuvant therapy (including Carnoy solution, cryotherapy, or peripheral ostectomy), and decompression and longitudinal irrigation with or without subsequent residual cystectomy. Owing to subgroups with small samples, the operative variables were recoded to *1)* decompression with or without residual cystectomy and *2)* enucleation with or without adjuvant therapy. In the study unit, patients undergoing decompression treatment had a stent placed into the lesion at time of biopsy. The goal was to maintain the stent for 12 months and irrigate it twice daily with 0.12% chlorhexidine and saline. At the end of the 12 months, the stent was removed and any residual lesion was excised and submitted for histologic evaluation.[16,20]

The primary outcome variable was the disease-free interval, defined as the time from the date of operation to the date of diagnosis of a recurrent lesion or the last visit if there was no recurrence. For patients who underwent decompression and longitudinal irrigation, the date of operation was defined as the date the decompression stent was removed if no residual cystectomy was completed or the date of the residual cystectomy. Commonly, stent removal and residual cystectomy were performed in the same operation. In other cases, the definitive treatment was stent removal only.

STATISTICAL ANALYSIS

The charts were reviewed and information was collected and recorded on a standard data collection form by 1 researcher (B.E.K.). The data were entered into an Excel spreadsheet (Microsoft 2007, Redmond, WA). The Excel spreadsheet was transformed into a statistical database for use with SAS 9.3 (SAS Institute, Cary, NC). Potential significant predictors and prognostic variables were considered factors for the outcome of time to recurrence based on univariate Cox regression analyses. The biologic variables of age and gender, the operative variable, and nearly statistically significant variables ($P \leq .15$) identified using univariate Cox regression analyses were used to build the multivariate Cox proportional hazards regression model to identify variables associated with time to disease recurrence. In the multivariate model, statistically significant variables were set at $P \leq .05$. Statistical and survival methodologies were based on Kaplan-Meier analysis and Cox proportional hazards models were used to assess recurrence risks and time-to-recurrence survival analysis.[26,27]

Table 1. DESCRIPTIVE STATISTICS

Sample size (n)	
Patients	31
OKCs	31
Demographic variables	
Age (yr)	41.0 ± 21.6
Men	20 (64.5%)
Health status variables	
ASA classification	
I	15 (48.4%)
>I	16 (51.6%)
Operative variables—treatment	
Decompression ± residual cystectomy	19 (61.3%)
Enucleation ± adjuvant therapy	12 (38.7%)
Radiographic risk factors	
Location of lesion	
Mandible	22 (71.0%)
Associated with impacted teeth	
Yes	16 (51.6%)
Largest diameter (cm)	3.9 ± 1.9
Evidence of cortical perforation	
Yes	21 (67.7%)
Locularity	
Unilocular	17 (54.8%)
Multilocular	14 (45.2%)
Outcome variable	
Lesion recurrence	8 (25.8%)
Mean duration of follow-up	14.5 ± 14.7
Median duration of follow-up (interquartile range)	10.9 (1.12-22.5)
Mean time to recurrence	22.3 ± 14.5
Median time to recurrence (interquartile range)	17.8 (13.4-26.4)

Abbreviations: ASA, American Society of Anesthesiology; OKC, odontogenic keratocyst.

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Results

During the study interval, 46 patients with 69 OKCs were evaluated and treated at the study institution. Patients were excluded from the sample if they had *1)* nevoid basal cell carcinoma syndrome (n = 1) or *2)* previously treated lesions (n = 14). The final sample was composed of 31 patients with 31 previously untreated lesions (Table 1). The sample's mean age was 41.0 ± 21.6 years and 64.5% were men. Fifteen patients (48.4%) were classified as ASA I, 14 (45.2%) as ASA II, and 2 (6.5%) as ASA III. Owing to the small subgroups, ASA status was recoded to ASA I (n = 15, 48.4%) and higher than ASA I (n = 16, 51.6%). Twenty-two lesions (71.0%) were located in the mandible, 16 lesions (51.6%) were associated with impacted teeth, and 21 (67.7%) had radiographic evidence of cortical perforation. The largest radiographic diameter of the defects averaged 3.9 ± 1.9 cm. Seventeen lesions (54.8%) were unilocular.

Table 2. KAPLAN-MEIER SURVIVAL ESTIMATES

	Lesions			
Time (mo)	At Risk (n)	Recurrence (n)	Disease Free (%)	95% CI for Survival
0	31	0	100.0	100.0-100.0
12	15	2	90.7	84.2-97.3
24	8	3	68.2	55.8-80.7
36	4	2	51.2	37.2-65.2
48	1	0	51.2	37.2-65.2
60	1	0	51.2	37.2-65.2

Abbreviation: CI, confidence interval.

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Eleven patients (35.5%) had enucleation without adjunctive treatment, 1 patient (3.2%) had enucleation with adjuvant therapy, 2 patients (6.5%) were treated with decompression and irrigation, and 17 patients (54.8%) were treated with decompression and irrigation, which was later followed by cystectomy. Because of the small number of patients in the subgroups, treatment was recoded into a binary variable: decompression with or without residual cystectomy and enucleation with or without adjuvant therapy. Nineteen patients (61.3%) were treated with decompression with or without residual cystectomy and 12 (38.7%) were treated with enucleation with or without adjunctive therapy.

The overall mean follow-up time was 14.5 ± 14.7 months (median, 10.9 months; interquartile range, 1.12 to 22.5 months). Eight patients (25.8%) developed recurrent lesions. The mean time to recurrence was 22.3 ± 14.5 months and the median time to recurrence was 17.8 months (interquartile range, 13.4 to 26.4 months). Table 2 presents the Kaplan-Meier survival estimates. Based on Kaplan-Meier analyses, the 5-year estimate of disease-free lesions was 51.2%.

Table 3 presents the univariate Cox proportional hazards analysis, which suggested that a multilocular lesion is 4.7 times more likely to recur than a unilocular lesion. The multivariate Cox proportional hazards model (Table 4) indicated that younger patients have an increased risk for recurrent lesions and multiloculated lesions are 33.6 times more likely to recur compared with uniloculated lesions.

Discussion

The purpose of this study was to quantify the overall 5-year disease-free rate and factors associated with

Table 3. UNIVARIATE COX PROPORTIONAL HAZARDS ANALYSES: FACTORS ASSOCIATED WITH TIME TO RECURRENCE

	Hazard Ratio	95% CI	*P* Value
Demographics			
Age (reference, increasing yrs)	0.97	0.93-1.02	.3
Sex (reference, male)	1.2	0.3-5.6	.8
Health status variables			
ASA classification I (reference, >I)	0.5	0.16-2.01	.3
Operative variables			
Decompression (reference, enucleation)	0.9	0.2-3.8	.9
Radiographic risk factors			
Location of lesion			
Mandible (reference, maxilla)	0.3	0.03-3.3	.3
Associated with impacted teeth			
Yes (reference, no)	1.5	0.4-5.9	.6
Largest diameter (cm) (reference, increasing size)	1.1	0.9-1.4	.3
Evidence of cortical perforation			
Yes (reference, no)	1.9	0.4-8.3	.4
Locularity			
Multilocular (reference, unilocular)	4.7	0.9-23.8	.06

Abbreviations: ASA, American Society of Anesthesiology; CI, confidence interval.

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Table 4. MULTIVARIATE ANALYSIS: FACTORS ASSOCIATED WITH TIME TO RECURRENCE

	Hazard Ratio	95% CI	*P* Value
Age (reference, increasing yrs)	0.96	0.93-0.98	<.01
Sex (reference, male)	2.1	0.7-6.2	.17
Treatment: enucleation ± adjuvant therapy (reference, decompression ± residual cystectomy)	0.08	0.01-1.19	.06
Locularity: multilocular (reference, unilocular)	33.6	1.2-975.8	.04

Note: Although not all these factors were statistically significant, the hazard ratios suggested that for the variable age, for every unit increase in years, lesions were 0.96 times less likely to recur. Lesions treated with enucleation with or without adjuvant therapy were 0.08 times less likely to recur than lesions that were decompressed with or without residual cystectomy. Stated more simply, decompression with or without residual cystectomy was 12.8 times (ie, 1/0.08) more likely to recur than lesions that were enucleated, after adjusting for locularity. Multilocular lesions were 33.6 times more likely to recur than unilocular lesions.

Abbreviation: CI, confidence interval.

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persistent remission of disease in patients presenting with OKCs in a statistically rigorous and appropriate manner. The study hypothesis was that in patients treated for OKC, there exists a set composed of at least 1 variable that is associated with disease recurrence that can be modified by the clinician to enhance treatment outcomes. The specific aims of this study were to design a retrospective cohort study and enroll a sample composed of patients presenting for operative management of OKC to *1)* quantify the number and type of treatment options chosen for each OKC, *2)* estimate the 5-year recurrence rate using appropriate time-to-recurrence survival statistics, and *3)* identify variables associated with recurrence.

The key findings of this study were that 8 patients (25.8%) had a recurrent lesion at the end of the study period, with a mean time to recurrence of 22.3 months and a median time to recurrence of 17.8 months. The Kaplan-Meier 5-year estimate for disease recurrence was 51.2%.

Multivariate analysis showed that younger patients had an increased risk for recurrent disease compared with older patients ($P < .01$). This is consistent with data reported by Forsell,[28] yet inconsistent with those reported by Habibi et al[21] who found that age had no statistically significant influence on recurrence.

Enucleation with or without adjuvant therapy was associated with a nearly statistically significant ($P = .06$) decreased risk for recurrent disease compared with decompression with or without secondary cystectomy. This finding is inconsistently reported in the literature with a wide range of statistical significance.[9,18,21,22,25]

Multilocular lesions were 33.6 times more likely to recur than unilocular lesions ($P = .04$). This finding has been reported by many other studies at levels of near statistical significance.[16,18,20,29]

The mean follow-up period was 14.5 months (standard deviation, 14.7 months). This follow-up period is among the shortest follow-up periods reported in the current literature. However, the failure of previous studies to use time-to-event analysis likely overreports the follow-up periods. This duration of follow-up is biased toward a small number by the fact that a large proportion of lesions recurred very soon after treatment. In addition, the duration of follow-up was long enough to detect a high frequency

of recurrent OKC lesions. Some may argue that the duration of follow-up was insufficient. If the authors reported that there were no recurrent lesions, then this would be a valid criticism. In fact, the authors identified 8 recurrent lesions over the 10 years of the study. The authors hypothesize that the estimates of recurrent disease in this sample (49% at 5 yr) may be a low estimate of the true rate of recurrence.

A weakness of this study is the small sample owing to the rareness of this lesion, resulting in nonsignificant results for some study variables that may be important prognostic variables. The small sample increases the risk for type II errors (ie, a statistically significant variable is deemed nonsignificant owing to a small sample). The other potential limitation consists of the highly correlated independent (predictor) variables (eg, locularity of the lesion) that might dilute the *P* values to assess the significance of the primary treatment-effect estimate.

In previous OKC studies, investigators used frequencies or percentages (ie, number of patients with recurrent OKC divided by the total number of patients treated) to estimate treatment effect. Although this is a straightforward computation, it is the incorrect statistic to estimate the rate of recurrent disease. This computational method weights patients with follow-up periods of 1 day the same as patients who are disease-free for 5-years. As such, it tends to overestimate success rates. Even in this study, the raw frequency estimate of disease recurrence was 8 of 31 (25.8%), but the statistically correct method (ie, Kaplan-Meier analysis) results in a 5-year estimate of disease recurrence at 48.8%. In addition, failing to report correctly the follow-up time (ie, mean vs median) overestimates the duration of follow-up. In this study, the mean follow-up time was 22 months, but the median was 17 months. Studies in which patients are followed over time to determine treatment success (eg, cancer survival or implant survival) use survival analyses or time-to-event analyses to estimated success. These methods (ie, Kaplan-Meier survival analyses) adjust for the duration of follow-up. In reviewing the English-language literature on OKCs from January 1980 through February 2012, the authors could not identify any studies that used survival analyses to report their outcomes. The authors believe this is the first study reporting outcomes after the treatment of OKC lesions using appropriate statistical methods.[26,27,30,31]

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