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Clinical factors associated with the recurrence of central giant cell lesions

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KEYWORDS

Central giant cell lesion; central giant cell granuloma; bone disease; clinical features; treatment;
recurrence rate

ABSTRACT

Purpose. Central giant cell lesion of the jaws (CGCLJ) is a destructive condition that shows a varied and unpredictable biological behavior. In the present study, we aimed to evaluate factors associated with the recurrence of CGCLJ.

Methods. Based on the data of a previous systematic review of 2,270 CGCLJ, we used the multiple imputation to deal with the missing data. The dependent variable was the recurrence after the first treatment (yes/no). The dichotomic covariates were sex, upper or lower jaw location, size (up to or larger than 4 cm), pain, cortical bone perforation (yes/no), locularity (uni-/multilocular), tooth displacement (yes/no), treatment type (curettage or enucleation) and root resorption (yes/no).

Results. The final logistic model indicated that the tumors associated with tooth displacement, root resorption, and treated with curettage had a more significant chance of recurrence.

Conclusion. Our study suggests that tooth displacement, root resorption, and the type of treatment are potentially useful in the future construction of an algorithm for patient's treatment.

KEYWORDS

Central giant cell lesion; central giant cell granuloma; bone disease; clinical features; treatment; recurrence rate

INTRODUCTION

Central Giant cell lesion of the jaws (CGCLJ) is a localized destructive benign condition characterized by the proliferation of mononuclear ovoid to spindle-shaped cells intermingled with osteoclast-like giant cells. Despite its benign nature, some lesions are more aggressive and show high recurrence.¹ To date, the varied biological behavior is not associated with microscopic features or molecular alterations.^{2,3}

Chuong et al.⁴ proposed a classification of CGCLJ based on a retrospective clinicopathologic study. The non-aggressive lesions were characterized by the absence or minimal symptoms, slow growth, absence of root resorption or cortical perforation, and low recurrence rate. On the other hand, lesions associated with the presence of pain, rapid growth, root resorption, cortical perforation, and showing recurrence were classified as aggressive. This proposal was slightly modified by Kaban et al.⁵ The aggressive lesions were defined when at least 3 of the following features are present: tumors exhibiting size higher than 5cm, rapid growth, root resorption, tooth displacement, cortical perforation, cortical thinning, or recurrence after curettage. Recurrent tumors or lesions larger than 5cm were defined as aggressive, even when the other features were not present. As 'recurrence' is used in both classifications for the definition of aggressive or non-aggressive lesions, these proposals cannot be used to predict the clinical behavior of the tumors.

We recently performed a systematic review of all available data published on CGCLJ with emphasis on the predictive factors associated with the tumor recurrence⁶. One of the limitations of our study was the missing data because of its retrospective nature⁷ and the lack of multivariate analysis. In the present study, we proposed to analyse the clinico-radiological features that are associated with CGCLJ recurrence after surgery, either by curettage or enucleation.

MATERIAL AND METHODS

Search strategy

The methods used herein are the same as those reported earlier by Chrcanovic et al.⁶

Inclusion Criteria

Publications reporting cases of CGCLJ with enough clinical, radiological, and histological information to confirm the diagnosis were eligible for inclusion. As the objective of the present study was to analyze clinico-radiological features that are associated with recurrence, only those cases that were in the first treatment submitted to surgery, either curettage or enucleation, were included. Even that these CGCLJs were subsequently treated by other methods (which might include drugs), only the first surgical treatment was considered in the present study.

Study selection and data extraction

The methods used herein are the same as those reported earlier by Chrcanovic et al. (2018). The dependent variable was the recurrence after the first treatment (yes/no). The dichotomic covariates were sex, upper or lower jaw location, size (up to or larger than 4 cm), pain, cortical bone perforation (yes/no), locularity (uni-/multilocular), tooth displacement (yes/no), treatment type (curettage or enucleation) and root resorption (yes/no). **Table 1** describes the number of missing data for each one of the covariates. Only patients with information on the dependent variable were included. So, for our study problem, we evaluated 799 patients submitted to curettage or enucleation with or without adjunctive surgical procedure.

Statistical Analyses

Statistical analysis was carried out considering Multiple Imputation (MI) analysis because of the frequency of missing data. The MI by Chained Equations (MICE) package of the R public domain software (The R Foundation for Statistical Computing, Vienna, Austria; <http://www.r-project.org>) was used to make the multiple imputations in the data. The MI technique allows the inclusion of the imputation uncertainty in the results, correcting the biggest problem associated with the single imputation. The MI was carried out in three steps (imputation, analysis, and grouping). Firstly, complete databases are obtained using appropriate imputation techniques. At this step, the covariates were considered for imputation. It was carried out the MI analysis on a dataset from

individual data from a previous systematic review⁶ as recommended by Burgess et al.⁸, applying Rubin's rules.

Unadjusted Odds Ratio (OR) and 95% confidence intervals (95% CI) were estimated for each covariate. Those variables with p-value less than 0.20 were included in the final model. Adjusted OR (95% CI) were estimated for these covariates altogether. Finally, the results found in the binary logistic regression models were combined in a simple and appropriate way to obtain the so-called repeated imputation inference.⁹ Only covariates with a p-value less than 0.05 were retained in the final model. Hosmer & Lemeshow test evaluated the goodness of fit of the final model.

RESULTS

In the final model, the tumors associated with tooth displacement, root resorption, and treated with curettage had a more significant chance of recurrence (**Table 2**). Hosmer & Lemeshow tests indicated the adequacy of the final model.

DISCUSSION

Patients with CGCLJs show a broad spectrum of tumor aggressiveness, varying from an indolent course to lesions growing fast and showing recurrence. Although the classifications proposed by Chuong et al.⁴ and Kaban et al.⁵ are academically relevant, as recurrence is one of the parameters used to separate aggressive from non-aggressive lesions, they cannot be used to predict patient's outcome after surgical treatment (enucleation or curettage). We have recently performed a systematic review of 2,270 cases of central giant cell lesions reported in the literature⁶. Cortical bone perforation and tooth resorption were associated with an increased recurrence rate. However, the high frequency of missing data was one of the limiting factors in the statistical analysis. Therefore, in the present study, we used the MI analysis to help us with missing data and fixed effect linear models to identify the best clinical and radiological parameters to be used as a predictive factor for recurrence. Based on the estimation results of a simulation study conducted by Burgess et al.⁸ with

fixed effect linear models and a 50% percent of missing data in the explanatory variables, the statistical analyses of our study was systematically performed, combining meta-analysis and the MI through Rubin's rules.

Tooth displacement, root resorption, and curettage were the only factors associated with recurrence. Also, no interaction between these variables was found ($p>0.05$). Tooth displacement and root resorption have already been used, among other clinico-radiological factors, in the classification of aggressive and non-aggressive CGCLJ lesions.^{4,5} Our data confirm that these variables are probably relevant in the prediction of tumor recurrence and can be useful in the construction of a treatment algorithm for patient's management. Although some other clinical factors, such as cortical thinning and pain, are also proposed to be used in the classification of aggressive or non-aggressive lesions, they did not impact recurrence in our analysis. However, a significant number of missing data could have affected the analysis of the results somehow. The association between curettage and recurrence is expected to occur as it has been demonstrated in the literature that more conservative treatment is associated with a high recurrence, especially for more aggressive tumors.⁶

Recently, different molecular profiles of CGCLJ were reported.² Based on the genetic profiles, there are at least four subgroups of lesions (*TRPV4*, *KRAS*, *FGFR1*, wild-type lesions), but the clinical significance of this genetic classification is still unknown. Although the impact of these molecular alterations in the clinical behavior of these lesions has not been established yet, the molecular heterogeneity may also contribute to the clinico-radiological variations of the tumors.

The present results must be interpreted taking into consideration some limitations. There was a significant percentage of missing data for each covariate, limiting the study. To circumvent this problem, the MI method was employed in this study, which is suggested by many authors¹⁰ and classic books of missing data (see, e.g., Little and Rubin¹¹). It is possible to combine the MI and meta-analysis with a significant level of missing data via meta-analysis and Rubin's rules procedure (see, Burgess et al.⁸). Moreover, the short follow-up period on some of the published cases used in the analysis could have led to an underestimation of the actual recurrence rate.⁶ As the objective of the

present study was to analyze clinico-radiological features that predict recurrence after surgical treatment, the predictor variables that were associated with recurrence cannot be extrapolated to other non-surgical treatment forms.

In conclusion, our study suggests that tooth displacement, root resorption, and the type of treatment are potentially useful in the future construction of an algorithm for the treatment of patients with CGCL. Prospective studies are necessary to confirm the relevance of our findings in the clinical classification of CGCL aggressiveness.

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Declaration of conflicting interests

There are no conflicts of interest to declare.

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TABLES

Table 1. Description of missing data for each covariate in the group of patients treated by enucleation or curettage.

Variables	Valid	Missing	%
Sex	788	11	1.4
Upper or lower jaw	797	2	0.3
Size (up to or larger than 4cm)	342	457	57.2
Pain	385	414	51.8
Locularity	341	458	42.7
Tooth displacement	293	506	36.7
Root resorption	319	480	39.9
Treatment type	799	0	0
Cortical bone perforation	309	490	61.3
Recurrence after first treatment	799	0	0

Table 2. Covariates associated with lesion recurrence.

Covariates	Unadjusted OR (95% CI)	P value	Adjusted Odds Ratio (95% CI)	P value
Sex				
Male	1	0.248		
Female	0.802 (0.552-1.163)			
Upper or lower jaw				
Upper jaw	1	0.307		
Lower jaw	1.234 (0.817-1.862)			
Size				
Up to 4cm	1	0.012		
Larger than 4cm	2.160 (1.200-3.888)			
Pain				
Yes	1.391 (0.788-2.456)	0.252		
No	1			
Locularity				
Yes	0.951 (0.508-1.781)	0.865		
No	1			
Tooth displacement				
Yes	4.263 (2.105-8.633)	<0.001	3.820 (1.850-7.890)	<0.001
No	1		1	
Root resorption				
Yes	3.669 (2.161-6.229)	<0.001	3.160 (1.790-5.580)	<0.001
No	1		1	
Treatment type				
Curettage	1.405 (0.968-2.039)	0.074	1.790 (1.140-2.800)	0.012
Enucleation	1		1	
Perforation				
Yes	3.222 (1.790-5.801)	<0.001		
No	1			