

Marsupialisation for the treatment of unicystic ameloblastoma of the mandible: a long-term follow up of 116 cases

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Received 22 August 2018; accepted 5 June 2019

Available online 21 June 2019

Abstract

Unicystic ameloblastoma is a unique histopathological type of ameloblastoma, and treatment is controversial. Marsupialisation is effective in reducing the size of cystic lesions and their complications. We have retrospectively analysed the clinical, histopathological, and prognostic data of affected patients who were treated by marsupialisation between 2003 and 2013 in three Chinese hospitals. Our aim was to evaluate the effects and prognosis, and the factors associated with outcome. A total of 116 patients with mandibular unicystic ameloblastomas were included, and 74, 26, and 16 patients were histopathologically classified as being luminal, intraluminal, and mural subtypes, respectively. Most responded well to marsupialisation, with an overall recurrence rate of 12%. Resorption of the root ($p < 0.001$), perforation of the cortical bone ($p = 0.005$), and histopathological subtype ($p = 0.013$) were the main factors that predicted the outcome. Perforation of the cortical bone was the only reliable predictor of recurrence ($p < 0.001$). Disease-free survival function curves indicated that patients with the mural subtype were at a higher risk of recurrence than patients with the other two subtypes ($p = 0.003$). Poor outcomes of marsupialisation were treated surgically and, to date, no subsequent recurrences have been reported. Marsupialisation is effective for these patients, with a recurrence rate similar to that of radical treatment. The outcomes can be predicted using characteristics of the lesion such as resorption of the root, perforation of the cortical bone, and histopathological subtypes. However, additional studies are required to corroborate these findings.

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Keywords: Unicystic ameloblastoma; Marsupialization; Histopathological subtype; Recurrence; Prognosis

Introduction

Ameloblastoma is a benign but locally aggressive odontogenic tumour that has a high risk of recurrence. The 4th of the WHO Histological Classification of Head and Neck Tumors simplified and categorised the variants of ameloblastoma into ameloblastoma, unicystic ameloblastoma, and extraosseous/peripheral ameloblastoma.¹ Unicystic ameloblastoma is characterised by a well-defined single

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cavity, and that is further classified into luminal, intraluminal, or mural subtypes, according to their histopathological characteristics. It was previously reported that the unicystic tumour is less aggressive than the ameloblastoma,² but this view has been recently challenged by several studies that reported a high recurrence rate for the unilateral tumour when treated by conservative operation.^{3,4}

The treatment regimens for the unicystic tumour are controversial, and typically grouped into three types: enucleation, marsupialisation, or decompression and radical resection. Conservative treatment has been associated with a poor prognosis, while the various complications associated with radical treatment are an important drawback.⁵ A recent attempt to work out the optimal treatment for the tumour in children showed that the luminal and intraluminal subtypes are less aggressive and respond well to conservative treatment, whereas the plexiform and mural types do not.⁶ However, the specific histopathological subtypes cannot be distinguished before treatment because of their similar clinical and radiological characteristics. It is imperative, therefore, that clinicians identify a treatment that can simultaneously validate the histopathological diagnosis and improve outcomes.

Marsupialisation is a procedure that reduces cystic pressure by maintaining an opening into the oral cavity. As the lesion shrinks it decreases the morbidity of the definitive treatment by, for example, preserving the inferior alveolar nerve,⁷ reducing the risk of pathological fractures, and eliminating the need for a bone graft.⁸ However, the effect of this treatment on mandibular unicystic ameloblastoma is inconsistent, because lesions shrink at different rates, and the recurrence rate ranges from 4.5% to more than 50%.^{9–12} To date, only a few studies have assessed the factors that are associated with the effects and prognosis of marsupialisation.

We have retrospectively analysed cases of mandibular unicystic ameloblastoma that were treated by marsupialisation followed by definitive resection. To establish a rational treatment regimen for specific lesions, we analysed the effects of marsupialisation on these lesions, and identified the clinicopathological characteristics that predict the outcome of treatment and recurrence rates.

Patients and methods

Patients

We report our findings from managing 116 patients with mandibular unicystic ameloblastoma who were treated by marsupialisation between 2003 and 2013. Clinical, histopathological, and follow-up data were obtained from the archives of the following three hospitals in China: First Affiliated Hospital of Huzhou University; Ninth People's Hospital of the College of Stomatology at Shanghai Jiao Tong University School of Medicine; and the Second People's Hospital of Changshu. The diagnosis was confirmed by imaging, and

macroscopic and histopathological findings as described by the 4th edition of the WHO guidelines.¹

All histopathological sections were reviewed by three pathologists in the department of histology and pathology of Ninth People's the Hospital of the College of Stomatology at Shanghai Jiao Tong University School of Medicine. The exclusion criteria were: incomplete data, or records could not be obtained for review; previous treatment before marsupialisation, or patients who did not return to the department for definitive treatment; and the presence of severe systematic disease. The protocol was approved by the Ethics Committees of all three hospitals.

Methods

Marsupialisation was done under general anaesthesia in accordance with the patients' requests and surgical regimen. The typical incisions were located at the minimal depth of the osseous wall, and the cystic lining was removed and sent for histopathological analysis. Affected teeth with more than one-third of the root resorbed or that were obviously loose were usually removed during marsupialisation. The alveolar bones of the tooth sockets were then enlarged and trimmed using a large round burr to provide a window for marsupialisation. Special care was taken to avoid damaging any of the proximal vital structures.

The obturator was positioned to prevent the closure of the surgical site, and the patients were instructed to irrigate the cavity regularly until the definitive operation was done. Patients were monitored radiographically monthly during the initial three months, then every three months for the first year, every six months for the second and third years, and annually subsequently. They were observed for any changes, including bony regeneration and recurrence of the tumour. The size of the lesion was calculated by measuring the maximal width (cm) x height (cm), and the margins of shrinkage were measured during the period preceding the definitive operation.

The duration of marsupialisation was based on how much the lesion shrank. The threshold for definitive intervention was defined as the absence of any further signs of tumour shrinkage over three months, or any signs of growth of the tumour. The definitive intervention comprised curettage, marginal resection, or partial resection according to specific conditions. During curettage, the mandibular bone was excised with at least a 2 mm margin to obviate potential recurrence of the tumour. The remaining affected teeth were simultaneously removed during the definitive operation, based on the degree of shrinkage of the lesion. The teeth that were formerly enveloped, but no longer affected, were preserved to improve functional and cosmetic outcomes.

The effect of marsupialisation was calculated by measuring the change in size of the lesion between the initial and the definitive interventions. The outcomes of marsupialisation were divided into two groups: >30% was deemed to be effective while 30% or less, or no change in size, was deemed to be ineffective.

Table 1
Clinical and radiographic variables and histopathological subtypes.

Variables	Luminal (n = 74)	Intraluminal (n = 26)	Mural (n = 16)	F/ χ^2	p value
Age (years)*	22.1 (9.7)	23.5 (9.9)	21.4 (7.0)	0.291	0.748
Sex (male:female)	40:34	13:13	9:7	0.186	0.911
Site of tumour:				2.580	0.63
Anterior	7 (9.5)	5 (19.2)	3 (18.8)		
Posterior only	47 (63.5)	14 (53.8)	8 (50.0)		
Posterior with ramus	20 (27.0)	7 (27.0)	5 (31.2)		
Size of tumour (cm ²)	29.4 (16.7)	27.3 (12.1)	27.1 (15.4)	0.268	0.766
Resorption of root (yes:no)	16:58	10:16	11:5	14.116	0.001 ^b
Cortical perforation (yes:no)	6:68	6:20	9:7	21.124	<0.001 ^{a,b,c}
Duration of marsupialisation (months) (n = 103)	12.0 (3.4)	15.2 (4.2)	15.9 (2.2)	11.103	<0.001 ^{a,b}
Follow-up (months)	109 (38)	109 (36)	107 (43)	0.018	0.983

Data are mean (SD) or as the number (%).

* =age at initial presentation.

^a = $p < 0.05$, luminal compared with intraluminal.

^b = $p < 0.05$, luminal compared with mural.

^c = $p < 0.05$ for intraluminal compared with mural.

A retrospective chart was prepared for all patients that included demographic, clinical, and histopathological factors from the documented records. All patients included in the study were followed up with regular outpatient appointments for a minimum of five years. The duration of follow up was calculated from the date of the first treatment to the date of the last assessment available. Operations and follow-up examinations were done by experienced surgeons at the three participating hospitals, and they all used the same systems and regimens to maintain continuity and excellence in care.

Statistical analysis

Variance analysis and chi squared tests were used to compare demographic and radiological factors for the different histopathological groups. Univariate and multivariate logistic regression analyses were used to identify factors associated with the effects of marsupialisation. Cox's proportional hazards models were used to identify factors that were associated with recurrence of disease. A multivariate Cox regression analysis was done, and disease-free survival function curves were plotted to identify factors that were independently associated with the effects of marsupialisation and recurrence of the tumour. Probabilities of less than 0.05 were accepted as significant. SPSS Statistics for Windows (version 17.0, SPSS Inc software was used for statistical analysis.

Results

All patients for whom complete medical data were available during the study period were included in the study, and their demographic and clinical characteristics are highlighted in Table 1 according to the three subtypes. The statistical results for age, sex, site, and size of tumour, and follow-up period were similar for each group. Resorption of the root, perforation of the cortical bone, and duration of marsupialisation

were significantly associated with different histopathological subtypes ($p = 0.001$, $p < 0.001$, and $p = 0.023$, respectively). The longest period of marsupialisation was 25 months, and the shortest seven months. Thirteen of the patients presented with no change in the size of the lesion, and they were promptly treated with definitive procedures three months after their initial treatment. They were therefore not included in the dataset for duration of marsupialisation.

Table 2 shows the results of univariate and multivariate logistic regression analyses of the variables that correlated with the effect of marsupialisation. Seventy-six were classified as effective while 40 were classified as ineffective, with a maximum rate of shrinkage of 96% and a minimum rate of 7.5%. Patients with radiographic signs of resorption of the root and perforation of the cortical bone had a significantly higher chance of experiencing ineffective results after marsupialisation ($p < 0.001$). Histopathologically the mural subtype of unicystic ameloblastoma had the greatest probability of not responding to marsupialisation when compared with the other two subtypes ($p = 0.002$). Multiple logistic regression analysis gave identical results, which indicates that these three variables can be used as base factors to predict the effects of marsupialisation ($p < 0.001$, $p = 0.005$, and $p = 0.013$, respectively).

The clinicopathological characteristics of the 21 patients for whom marsupialisation had no effect or who experienced a recurrence are shown in Table 3. The mean (range) time before recurrence was 39 (8–87) months. There were six recurrences in patients who also had no effect from the initial marsupialisation, five patients who had a secondary recurrence, and two who had a third recurrence. These cases were treated with more radical procedures according to the size of the recurrent lesions, and none of them developed uncontrolled ameloblastoma. Patients with the mural subtype had a greater probability of recurrence than those with luminal or intraluminal subtypes. The function curves for disease-free survival are shown in Fig. 1 ($p = 0.003$).

Table 2

Univariable and multivariable logistic regression analysis of clinical and radiological data for the effect of marsupialisation.

Variables	B value	OR	95% CI	p value
Univariable logistic regression analysis				
Sex				
Male		1		
Female	0.058	1.06	(0.492 to 2.283)	0.882
Site of tumour:				
Anterior		1		0.650
Posterior only	−0.160	0.852	(0.272 to 2.675)	0.784
Posterior with ramus	−0.533	0.587	(0.162 to 2.130)	0.418
Size of tumour (cm ²)				
<25		1		0.262
25–50	−0.508	0.602	(0.255 to 1.421)	0.247
>50	0.528	1.696	(0.489 to 5.879)	0.405
Resorption of root:				
Yes		1		
No	−2.618	0.073	(0.026 to 0.207)	<0.001*
Cortical perforation:				
Yes		1		
No	−2.588	0.075	(0.019 to 0.292)	<0.001*
Duration of marsupialisation (months)				
<12		1		0.089
12–18	0.416	1.516	(0.481 to 4.778)	0.028
>18	0.241	1.273	(0.220 to 7.362)	0.370
Histopathological subtype:				
Luminal		1		0.001*
Intraluminal	0.334	1.397	(0.427 to 4.567)	0.431
Mural	3.533	34.219	(3.658 to 320.043)	<0.001
Multivariate logistic regression analysis				
Resorption of root:				
Yes		1		
No	−2.549	0.078	(0.025 to 0.245)	<0.001*
Cortical perforation:				
Yes		1		
No	−2.283	0.102	(0.021 to 0.494)	0.005*
Histopathological subtype:				
Luminal		1		0.026*
Intraluminal	−0.41	0.663	(0.185 to 2.373)	0.528
Mural	2.97	19.493	(1.885 to 201.551)	0.013*

B = partial regression coefficient; HR = hazard ratio.

* p < 0.05.

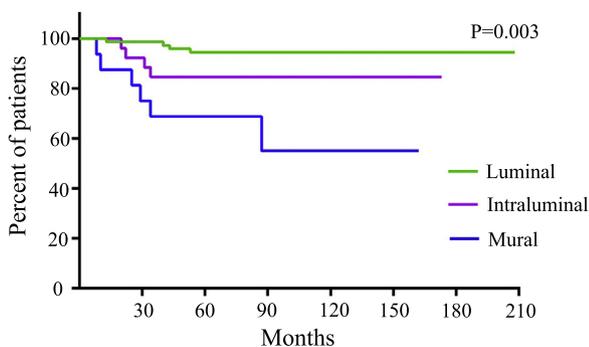


Fig. 1. Disease-free survival function curves according to the histopathological subtype.

Cox proportional hazards models were used to identify the factors associated with recurrence of disease (Table 4). According to the results of the univariate Cox regression analysis, the risk of recurrence correlated significantly

with resorption of the root ($p=0.009$), cortical perforation ($p<0.001$), and the effects of marsupialisation ($p=0.004$). Both mural and intraluminal subtypes had greater risks of recurrence than the luminal subtype, but the observations were significant only for the mural subtype ($p=0.001$ and $p=0.112$, respectively). The results of the multivariate Cox regression analysis showed that perforation of cortical bone was the only reliable predictor for recurrence in affected patients ($p<0.001$), irrespective of the other factors.

Discussion

A number of previous studies have focused on elucidating the treatment regimens for unicystic ameloblastoma, but the results remain controversial.^{13,14} The aim of this study was to pursue a conservative approach that could remove the lesion while prioritising the patient's quality of life. Marsupialisation is a widely-accepted procedure for the treatment

Table 3

Clinicopathological characteristics of cases without effect of marsupialisation or with recurrence.

Age / sex	Tumour site	Tumour size (cm ²)	HP subtype	Effect of MS	Second operation	Treatment interval (months)	Recurrence	Onset of recurrence and treatment					
								First (month)	Treatment	Second (month)	Treatment	Third (month)	Treatment
24/M	P	29.7	L	Poor	Curettage	10	Yes	40	Marginal resection	-	-	-	-
16/M	P	70.3	M	None	Radical mandibular resection + fibular flap	3	No	-	-	-	-	-	-
17/F	P	14	IL	Poor	Curettage	10	Yes	22	Marginal resection	-	-	-	-
15/F	A	82.5	L	None	Curettage	4	Yes	13	Curettage	64	Hemimandibulectomy + fibular flap	-	-
23/F	P	32.9	IL	None	Curettage	2	No	-	-	-	-	-	-
15/M	P+R	70.3	L	None	Partial mandibulectomy + fibular flap	3	No	-	-	-	-	-	-
18/M	P	17.9	L	None	Curettage	1	No	-	-	-	-	-	-
34/M	A	16.7	M	Poor	Curettage	15	Yes	29	Curettage	49	Curettage	87	Partial mandibulectomy + free iliac flap
21/F	P	30.5	IL	None	Curettage	3	Yes	20	Marginal resection	40	Partial mandibulectomy + DCIA	-	-
34/M	P	23.2	M	None	Marginal resection	1	Yes	34	Marginal resection	-	-	-	-
12/M	P	25.2	L	None	Curettage	2	Yes	53	Curettage	-	-	-	-
19/F	P+R	19.9	M	None	Curettage	3	-	-	-	-	-	-	-
26/M	P+R	35.5	IL	Partial	Curettage	18	Yes	31	Curettage	-	-	-	-
25/F	P	13.1	M	Partial	Curettage	13	Yes	87	Curettage	-	-	-	-
31/M	P	21.7	L	Partial	Curettage	13	Yes	43	Curettage	-	-	-	-
23/M	P	22.2	L	None	Curettage	3	-	-	-	-	-	-	-
15/F	P+R	16.4	M	Poor	Curettage	16	Yes	25	Marginal resection	-	-	-	-
29/F	P+R	55.3	M	None	Curettage	1	Yes	8	Partial mandibulectomy + free iliac flap	38	Hemimandibulectomy + DCIA	-	-
52/M	P	22.2	IL	Apparent	Curettage	14	Yes	34	Curettage	-	-	-	-
26/F	P	32	M	None	Marginal resection	3	No	-	-	-	-	-	-
28/M	A	22.3	M	None	Curettage	2	Yes	10	Marginal resection	19	Curettage	81	Partial mandibulectomy + DCIA

M = male; F = female; HP = histopathological; M = marsupialisation; P = posterior only; A = anterior; R = ramus; L = luminal; IL = intraluminal; M = mural.

Table 4
Univariate and multivariate Cox regression analysis of clinical and radiological data to recurrence.

Variables	B Value	HR	95% CI	p value
Univariate logistic regression analysis				
Sex:				
Male		1		
Female	−0.135	0.873	(0.303 to 2.518)	0.802
Site of tumour:				
Anterior		1		0.522
Posterior only	−0.670	0.512	(0.136 to 1.930)	0.323
Posterior with ramus	−0.856	0.425	(0.086 to 2.106)	0.295
Size of tumour (cm ²):				
<25		1		0.729
25–50	−0.325	0.723	(0.218 to 2.401)	0.596
>50	0.344	1.410	(0.299 to 6.644)	0.664
Resorption of root:				
Yes		1		
No	−1.466	0.231	(0.077 to 0.689)	0.009*
Cortical perforation:				
Yes		1		
No	−2.329	0.097	(0.033 to 0.291)	<0.001*
Duration of marsupialisation (months):				
<12		1		0.404
12–18	1.1	3.003	(0.606 to 14.890)	0.178
>18	−12.637	–	–	0.987
Histopathological subtype:				
Luminal		1		0.003*
Intraluminal	1.124	3.076	(0.769 to 12.305)	0.112
Mural	2.172	8.775	(2.469 to 331.183)	0.001
Effect of marsupialisation:				
Effective		1		
Ineffective	1.704	5.459	(1.722 to 17.532)	0.004*
Multivariable logistic regression analysis				
Cortical perforation:				
Yes		1		
No	−2.329	0.097	(0.033 to 0.291)	<0.001*

B = partial regression coefficient; HR = hazard ratio.

of large mandibular cystic lesions, and has the benefit of relieving symptoms while improving the experience for the patient.^{15,16} The contraindications are based primarily on the unpredictability and variability in its effects, and in the recurrence rates of the lesions treated. We analysed the positive effects of marsupialisation and identified factors that are potentially associated with outcomes of treatment and the risk of recurrence to try and predict indications for this conservative treatment.

Previous reports of patients with unicystic ameloblastoma who were treated with marsupialisation were limited by shortcomings and errors. They contain a catalogue of failures in their methods that are related to short, infrequent, or unreported periods of follow up, small groups of patients, and variations in treatments that render their results invalid or inadequate.¹⁷ We therefore applied strict practices to guarantee the reliability of our results, including standardised treatment, strict inclusion and exclusion criteria, and a relatively large number of patients. Additionally, clinical data for all the patients from before and after the operation were obtained and analysed thoroughly. The long follow-up period enabled us to track shrinkage of lesions and diagnose recurrences rapidly while they were still small, which ensured

better outcomes for the subsequent interventions. Finally, the use of logistic and Cox's regression analyses and disease-free survival curves provided us with more accurate risk assessments for outcome and prognosis than are commonly reported with simple proportionate data.

Previous studies have found that the radiological presence of root resorption in these tumours indicates a potentially poor prognosis.¹⁸ The relation between the radiological boundary and proliferation of the tumour has been further investigated through a retrospective analysis of 178 cases.¹⁹ Our data indicate that such a tumour with the characteristics of resorption of the root, perforation of the cortical bone, or a mural histopathological subtype, can indicate their underlying aggressive biological potential, which would result in a poor results from marsupialisation. As a result, lesions with any of the three factors outlined above may not be appropriate candidates for marsupialisation as the initial treatment.

Marsupialisation does not eliminate the risk of recurrence. Recurrences can take more than 20 years to become apparent, and the lesions that recur are often associated with osseous perforation or adhesion of soft tissues.^{20,21} The overall recurrence rate during follow up in this study was 12%, which is in agreement with the results of previous reports.^{4,6} Our results

showed that perforation of the cortical bone was the only factor that predicted recurrence, which indicated that aggressive biological characteristics may be crucial for the prognosis of the tumour.

The possible adverse outcomes of marsupialisation are, first, that the tumour cells can to a certain extent invade the cancellous bone. While shrinkage of the tumour is evident, the removal of satellite tumour tissue can be inadequate, which leads to recurrence beyond the margin of the main lesion. Secondly, multiple operations may result in implantation of tumour cells, which can cause or accelerate recurrence of the tumour. For recurrent cases, a more aggressive surgical approach that prioritises the elimination of tumour cells should be considered, particularly for conditions that recur more than once.

There were certain limitations to this study. First, the excised tumour tissue obtained from marsupialisation is equivalent to an incisional biopsy so the histopathological diagnosis of the small quantity of tissue may not reflect the specific subtype of unicystic ameloblastoma, as the pattern of mural invasion may not be present across the entire circumference of the cyst. The risk for sampling errors, therefore, particularly in large tumours, should not be underestimated.²² Secondly, although it has been reported that TP53 and IL-1 α expression¹² or raised hydrostatic pressure²³ are related to the invasiveness of an ameloblastoma, the potential mechanisms of the biological behaviour of marsupialisation are still not clear. Meanwhile, treatments such as enucleation, followed by the dredging method or Carnoy's solution, have been proposed for these tumours,^{24–26} but neither technique was assessed in this study. Future studies should use these techniques, which may improve the prognosis and lower recurrence rates.

Conclusion

The data from this study show that marsupialisation is an effective treatment for reducing the size of a unicystic ameloblastoma, and the overall recurrence rate with the treatment currently being used was only 12%. Resorption of the root, cortical perforation, and the histopathological subtype were predictive of the effects of marsupialisation, while cortical perforation alone was able to predict the risk of recurrence after treatment. Balanced critical judgement is essential when selecting a treatment regimen, and further validation through large-scale, multicentre, randomised controlled trials is required to optimise treatment.

Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patients' permission

We have obtained ethics committees' approval. Patients' consent was not required.

Funding

This work was supported by the Huzhou Welfare Technology Applied Research Program. [grant number 2017GY41].

Acknowledgements

We would like to thank Mr Kaveh Shakib, Head of department, Consultant oral and maxillofacial surgeon, Honorary senior lecturer, Royal Free London NHS Trust, London, UK, for providing language help and writing assistance.

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