Ameloblastoma: Epidemiology and Development of New Treatment Options

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Ameloblastoma: Epidemiology and Development of New Treatment Options

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Ameloblastoma:

Epidemiology and Development of New Treatment Options

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	prof.dr. A. Vissink
	prof.dr. H. Rasyid

To my beloved family

“Read with the Name of your Lord Who created [everything].”

– Qur'an, Al-'Alaq (96:1)

Contents

CHAPTER 1

General Introduction

GENERAL INTRODUCTION

Etiology and epidemiology

Ameloblastoma is a benign, gradually developing, locally invasive tumor of epithelial odontogenic origin appearing in the jaw bones. If not appropriately treated, ameloblastoma has a high potential for recurrence[1]. Cusack first discovered the tumor in 1827. Ameloblastoma's name comes from the Old English term “amel,” meaning enamel, and the Greek term “blastos,” meaning germ or bud. Previously, this tumor was also known as adamantinoma, derived from the Greek term “adamantinos” meaning very hard[2,3]. Ameloblastoma is thought to arise from two possible origins: remnants of the tooth germ, such as developing enamel organ, reduced enamel epithelium, and the epithelial lining of odontogenic (dentigerous) cysts; or the basal cells of gingival epithelium[4]. Several etiologies have been hypothesized but have not explicitly been elucidated, with diversifications in the mitogen-activated protein kinase (MAPK), sonic hedgehog (SHH), and WNT/β-catenin pathways being the most common[5]. BRAF V600E gene mutations were the most common in the MAPK pathway. They were commonly identified in mandibular ameloblastomas, while SMO gene mutations were the most common in the non-MAPK pathway and were frequently found in maxillary ameloblastomas[6–8].

Ameloblastoma contributes to about 1 % of all head and neck tumors and 13 to 58% of all odontogenic tumors[9,10]. Ameloblastoma is considered a rare tumor, with an annual incidence of 0.5 cases per million people. Nevertheless, ameloblastoma is the most frequent odontogenic tumor in Africa and China, while it is the second most frequent after odontoma in North America[3]. Most ameloblastoma cases are diagnosed between the ages of 30 and 60, and the peak age of incidence is in the third and the fourth decades of life, with almost equal gender distribution[11,12]. About 80% of ameloblastoma cases occur in the mandible, with the posterior mandible being the most common site, followed by the anterior mandible, posterior maxilla, and anterior maxilla[1,13]. The incidence of ameloblastoma in one or more countries is described in several studies currently. However, there has been no research on the global incidence of ameloblastoma. Furthermore, the latest global review on the biological profile of ameloblastoma was published over two decades ago[12].

Clinical presentation, diagnostic, and current treatment modality

Clinically, the initial manifestations of ameloblastoma are slow-growing and painless swelling, often asymptomatic, showing progressive growth. Symptoms and complications that may occur as tumor size increases include pain, paresthesia, or anesthesia of the affected area, soft tissue invasion, cortical bone expansion, the buccal or lingual plates perforation, dental malocclusion, loosening of the teeth, facial deformity, limited mouth opening, mastication difficulties. This may lead to severe complications such as airway obstruction if tumor growth is not controlled. Radiographically, these tumors present as either a multilocular radiolucent lesion, also known as a honeycomb or soap bubble appearance (Figure 1b), or a unilocular radiolucent lesion. Resorption of dental roots is occasionally discovered[14–18].

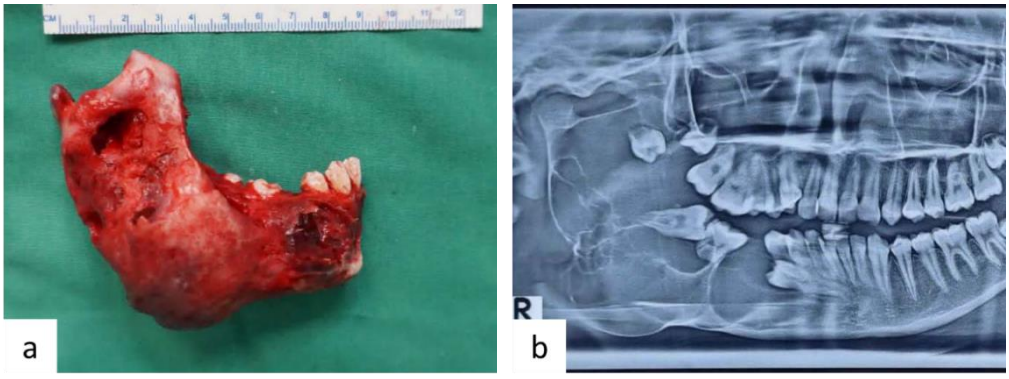

Figure 1. Ameloblastoma. (a) resected part of the mandible containing a tumor, (b) the multilocular (so-called soap-bubble) radiolucency involving the right body and angle of the mandible.

Based on the current 2017 World Health Organization (WHO) classification of odontogenic tumors, ameloblastoma is categorized into three types: ameloblastoma (conventional/ solid/multicystic ameloblastoma), unicystic ameloblastoma, and peripheral/extraosseous ameloblastoma[19]. Histopathologically, the most common pattern of conventional ameloblastoma is the follicular type, consisting of discrete islands of odontogenic epithelium with peripheral columnar cells and a central mass of stellate reticulum (Figure 2a). The second most common pattern is the plexiform type, consisting of anastomosing strands with an inconspicuous stellate reticulum and cyst-like stroma degeneration (Figure 2b). Other histopathological patterns are desmoplastic, acanthomatous, granular, and basaloid. These patterns might be homogenous or mixed. For unicystic ameloblastoma, there are two histopathological patterns, namely the luminal type and the mural type[1,20].

Surgery is the primary treatment of ameloblastomas, which may be divided into conservative and radical approaches. The conservative surgical methods may include enucleation, curettage, marsupialization, or cryosurgery. The conservative approach maintains the patient's normal tissues, reduces facial deformation, involves less time in the operating room, and ensures a good quality of life after the surgery. Still, it is considered to be linked to high recurrence rates, which can be up to 90% and requires repeated resection. Otherwise, the radical surgical approaches consist of marginal (*en bloc*) resection with wide (1-2 cm) bone margins, segmental resection, or total resection (mandibulectomy/maxillectomy). Although the radical approach is thought to be linked to a reduced incidence of recurrence, immediate reconstructive surgery is often required to help with speech and swallowing[11,21–23]. Controversy still exists regarding the choice of treatment approach. In addition to the risk of recurrence and effect on the quality of life after surgery, several factors such as the age of the patient, tumor size and location, and the type of histopathology should also be considered in treatment planning[24,25]. Chemotherapy and radiotherapy are not effective in the management of ameloblastoma. Thus, developing new treatments may be an option to prevent expanded surgery or re-resection for ameloblastoma[26].

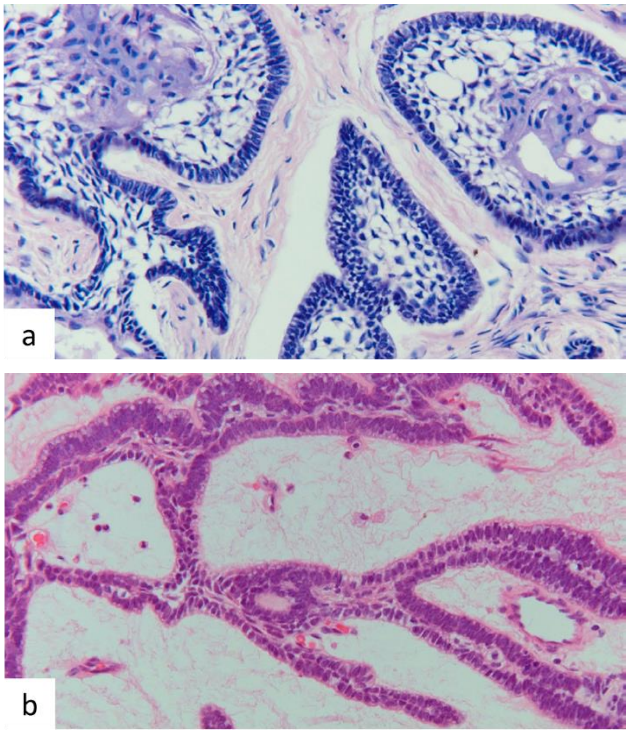

Figure 2. Histopathology of ameloblastoma. (a) follicular: small discrete islands of tumor consist of peripheral layer and central mass, (b) plexiform: anastomosing strands and cords of tumor cells[20].

Development of new treatment options

Recent discoveries of molecular pathways related to ameloblastoma pathogenesis resulted in the development of targeted therapy as a novel therapeutic option for ameloblastoma. This new treatment may reduce the need for extensive and repetitive surgeries[27–29]. Some MAPK-specific and SHH-specific drugs have been used for targeted therapy in several in-vitro studies, which specifically inhibit the function of several gene mutations that play a role in the pathogenesis of ameloblastoma[6,7]. For MAPK-specific drugs, there are vemurafenib and dabrafenib, the mutant BRAF gene inhibitors, and trametinib, which inhibit the mutant MEK gene. Unfortunately, vemurafenib therapy for ameloblastoma has been correlated to resistance mechanisms such as compensatory stimulation of the MAPK pathway via the epidermal growth factor receptor. SHH-specific drugs include arsenic trioxide, KAAD-cyclopamine (chemically-modified derivate of natural cyclopamine), vismodegib, and itraconazole which inhibit mutated SMO gene. Several SHH inhibitors have been suggested, which can be proven effective in targeted therapy for ameloblastoma. Cyclopamine is the most frequently utilized and has shown successful responses in several cancer cells such as gastric, breast, pancreatic cancers, and oral squamous cell carcinoma. However, the primary disadvantage is that it hampers osteoblastic proliferation and differentiation, which is crucial for bone healing[7,11,30].

Several clinical studies using BRAF inhibitors and a combination of BRAF & MEK inhibitors have shown the efficacy of targeted therapy, especially in reducing tumor size in ameloblastoma patients. However, because these studies are still in the form of case reports, the findings do not provide solid clinical evidence. Furthermore, the application of targeted therapy is still limited to adjuvant or neoadjuvant treatment at the current time[29,31–33].

In previous research, we used proteomics and kinase screening to identify the intracellular (cytostatic resistance-related kinases) and the extracellular (tumor-specific surface receptors) targets for osteosarcoma in the extremities[34–36]. Based on this, we have since developed double-targeted nanoliposomes for this osteosarcoma[37]. As adjuvant therapy, we now want to apply this strategy to ameloblastoma, hoping to target and destroy any remaining tumor cells after the resection. For this purpose, we will perform surface proteomic analysis from a human ameloblastoma cell line to investigate the specific and compelling extracellular targets as potential candidates for targeted delivery agents of ameloblastoma.

Aim of study and outlines of the thesis

Given the research context and previously discussed issues, the first part of this thesis aims to evaluate the global incidence of ameloblastoma, provide an update on the global profile of ameloblastoma patients, and assess the outcomes of several surgical treatment approaches for ameloblastoma. Disclosing such information is very important to plan preventive strategies and develop new treatment options that provide the best quality of life for the patients. The second part of this thesis will focus on developing novel treatment strategies for ameloblastoma by performing surface proteomics and screening for effective extracellular targets to develop targeted delivery of therapeutic agents to residual ameloblastoma cells.

In **Chapter 2**, we conducted a systematic literature review and meta-analysis to assess the global incidence of ameloblastoma and provide an update on the global profile of ameloblastoma patients. In **Chapter 3**, we performed a retrospective study to evaluate the incidence, treatment, and complication of ameloblastoma patients in East Indonesia. In **Chapter 4**, we undertook a systematic literature review and meta-analysis to investigate the outcomes of recurrence rates of radical and conservative surgical treatments of intraosseous ameloblastoma. In **Chapter 5**, we conducted a network meta-analysis to assess and compare the efficacy of numerous surgical approaches for solid/multicystic ameloblastoma patients. In **Chapter 6**, we performed proteomic analysis to investigate the specific surface marker of ameloblastoma cells for targeting therapy. **Chapter 7** discusses the results of the topics covered in this thesis, and suggestions for future research are presented. Finally, **Chapter 8** provides an English summary of this thesis.

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CHAPTER 2

Global incidence and profile of ameloblastoma: a systematic review and meta-analysis

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ABSTRACT

Objectives: To evaluate the global incidence of ameloblastoma and to provide a profile of ameloblastoma patients.

Material and Methods: A systematic review and meta-analysis was conducted. Searches were performed in PubMed, Embase, SCOPUS, and Web of Science for articles published from 1969 to 2018 for the global incidence and from 1995 to 2018 for the profile of ameloblastoma patients.

Results: Seven studies on the incidence rate of ameloblastoma were included in the meta-analysis. These studies only covered Europe, Africa, and Australia. The pooled incidence rate was 0.92 per million person-years (95% CI: 0.57-1.49), with significant heterogeneity between studies.

Forty-two articles provided profile data of 6446 ameloblastoma patients. Mean age was 34 years and the peak age incidence in the third decade of life. In Europe and North America, ameloblastoma mostly occurred at an older age when compared to Africa and South America. A slight male preference (53%) was found, and the mandible appeared to be the preferred site. The most common type of ameloblastoma was multicystic. The histopathologic patterns were mostly follicular and plexiform.

Conclusions: This is the first study assessing the global incidence of ameloblastoma. The pooled incidence rate was determined to be 0.92 per million person-years.

Keywords: ameloblastoma, incidence, profile, odontogenic tumor.

INTRODUCTION

Ameloblastoma is a benign odontogenic tumor originating from odontogenic epithelium. It is a locally invasive tumor with a high recurrence rate after removal[1], but metastases are rare[2]. Ameloblastoma was first recognized by Cusack in 1827 and explained by Broca in 1868. It involves 13–58% of all odontogenic tumors[3]. It may arise from remnants of tooth-forming components, such as rests of dental lamina, developing enamel organ and the epithelial lining of odontogenic (dentigerous) cysts, or possibly from the basal epithelial cells of the oral mucosa[4].

At the molecular level, etiopathogenesis of ameloblastoma is multifactorial and involves various cellular pathways and molecular mechanisms. Several types of molecules and gene dysregulations related to sonic hedgehog, WNT/β-catenin, and mitogen-activated protein kinase (MAPK) signaling pathways affect the development and oncogenic transformation of odontogenic epithelium into ameloblastoma[5,6].

According to the current 2005 World Health Organization (WHO) classification of odontogenic tumors, ameloblastoma is divided into four categories: (1) solid/multicystic, in which locally invasive tumor will infiltrate through the medullary spaces and may show multicystic lesions; (2) unicystic, presenting as a cystic intraosseous growth pattern, which is observed clinically and radiographically; (3) peripheral, which is identical to the intraosseous ameloblastoma but appears exclusively in the oral mucosa (extraosseous); (4) desmoplastic, an infiltrative intraosseous tumor characterized by extensive stromal collagenization or desmoplasia, radiographically appearing as a radiolucent-radiopaque lesion mimicking a fibro-osseous lesion[7]. Males and females are equally affected and the mean age of involvement is about 35 years[8]. Children are affected in 8.7 % to 15.0% of the cases[9,10]. The mandible appeared the preferred site (85%), especially the molar-ramus area. Radiographically, these tumors present as multilocular or unilocular radiolucent lesions. The most common histopathologic patterns in ameloblastoma are follicular and plexiform patterns. Other microscopic patterns include acanthomatous, granular and basal cell. These patterns can be uniform or mixed[3].

Surgery is the first choice of treatment of ameloblastoma and can be divided into conservative treatment (enucleation, curettage, and cryosurgery) and radical treatment (marginal or segmental resection)[11].

Many articles describe the incidence of ameloblastoma in one or more countries. However, there is no study at all on the global incidence of ameloblastoma. In addition, the latest large

review on the biological profile of ameloblastoma was published more than 20 years ago, i.e. in 1995[12]. It should be noted that this review listed 56.3% as non-specified cases, making sound conclusions very difficult.

Aims of this study were to evaluate the global incidence of ameloblastoma through a systematic review and meta-analysis based on the articles published from 1969 to 2018 and to provide a global profile of ameloblastoma patients with regard to sex and age distribution, tumor location, tumor types and histopathologic appearance based on the articles published from 1995 to 2018.

MATERIALS AND METHODS

Eligibility Criteria

This present systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[13]. The inclusion criteria were:

1. Studies published from 1969 to 2018
2. English-language and human-species articles
3. Abstracts that discussed the incidence of ameloblastoma
4. Studies reported incidence data and incidence rates separately or when they provided sufficient data to allow calculations.

Articles were excluded for the following reasons:

1. Case reports
2. A number of cases fewer than 10.

Information Sources and Search

Since the global incidence of ameloblastoma has never been accessed so far, we performed a comprehensive search of databases (PubMed, Embase, SCOPUS, and Web of Science) for articles published from January 1969 until March 2018, using the combinations of the following keywords: ameloblastoma and incidence. For the global profile of ameloblastoma patients, we conducted a search for the studies that were published from 1995 to 2018, since the previous review[12] covered the period up until 1995. Comparison of our data with those of before 1995 will elucidate whether trend changes occurred in this period. The search was restricted to English-language articles. In addition, manual searches of the reference lists of the articles

were performed to find other eligible articles that were not available in the electronic databases.

Study Selection, Data Collection, and Data Items

The article selection process was conducted by three independent reviewers (F.N.H., E.V.C., and M.N.H.) blind to each other's activities. The reviewers assessed the selected articles for their relevance and validity. Relevance concerned the measure in which the article applied to the subject. Validity concerned information bias, selection bias, and the quality of analysis. If there was any disagreement between the reviewers, the consensus was reached through discussion. In the first step (screening), the authors excluded studies that did not focus on the incidence of ameloblastoma by screening the titles and abstracts from the search results. In the second step, the authors assessed the full-text articles and excluded studies which did not meet the inclusion criteria. Studies with unavailable full-text or studies with incomplete or unclear data were excluded.

The following data for each study were extracted from full-text articles: author, publication year, country or region of study, study period, sex, age distribution, tumor location, types, the histopathologic pattern, and incidence rate. When multiple articles reporting data from the same study population were encountered, the most comprehensive and accurate data were used. In cases where the articles reported on different timeframes or subgroups (sex, age), all nonoverlapping data were included. The data were recorded in the database. For the global ameloblastoma profile, we calculated the relative frequencies for sex, age, tumor location, tumor types, and histological appearance. Data were then sorted per continent.

Summary Measures and Synthesis of Results

A meta-analysis was performed for the studies that provide the incidence rate of ameloblastoma with pooled incidence rate expressed per 1,000,000 population. To keep the effect of studies with extremely small or extremely large incidence rate estimates on the overall estimate to a minimum, the variance of the study-specific incidence rate was stabilized with the Freeman-Tukey double arcsine transformation before pooling the data with the random-effects meta-analysis model[14]. To indicate the percentage of variance in this meta-analysis that is attributable to study heterogeneity, we calculated the Cochrane Q statistic I^2. All pooled estimates were provided with 95% confidence intervals (95% CIs). For the ameloblastoma profile, the sex distribution of ameloblastoma patients was compared to the

probability of the sex ratio worldwide and per continent based on World Population Prospects, Department of Economic and Social Affairs, United Nations website (https://esa.un.org/unpd/wpp/DataQuery/), by a binomial test. The Chi-square tests were used for the relative frequencies of the age distribution, tumor location, tumor types, and histological appearance. For the statistical analysis, MetaXL program version 5.3 (Ersatz, EpiGear International, Sunrise Beach, Australia) was used. A *p* value less than 0.05 was considered to be statistically significant.

RESULTS

Study Selection

The search strategy yielded a total of 735 articles from all databases and additionally identified through other sources. Of 735 articles, 431 articles were removed after screening for duplication. A total of 205 articles were excluded after reading the titles and abstracts, and the full-text articles of the remaining 99 studies were reviewed independently by three authors for eligibility. At this full-text analysis, 50 studies were excluded because they did not meet our inclusion criteria. A total of 49 studies were processed for final review and meta-analysis. The process of study selection is described in Figure 1.

Synthesis of Results

Incidence rate

Seven studies on the incidence rate of ameloblastoma[15–21] from six countries were available and included in the meta-analysis. These studies covered Europe, Africa, and Australia. Four studies used population-based registries and three studies used hospital-based registries (Table 1).

Johnson et al.[15] reported an incidence rate of ameloblastoma of 2.41 per million population per year in Queensland, Australia in 2011. Shear and Singh[20] reported an incidence rate of ameloblastoma of 1.65 per million population per year in South Africa in 1965-1974. Oomens and Van der Waal[19] reported an incidence rate of ameloblastoma of 1.5 per million population per year in the Netherlands in 1985-2010. Simon et al.[21] performed a prospective study and reported an annual incidence rate of ameloblastoma of 0.68 per million population in Tanzania in 1999-2013. A Swedish study[16] reported an annual incidence rate of 0.60 per million population in 1958-1971. Two studies conducted in Nigeria[17,18] reported an increase

in annual incidence rate of ameloblastoma from 0.35 per million in the period 1980-1995 to 0.76 per million in the period 2009-2012.

The pooled incidence rate of ameloblastoma was 0.92 per 1,000,000 person-years (95% CI: 0.57-1.49), with significant heterogeneity between-studies, I^2 = 98.64%, Q-statistic = 442.09. df=6, *p*-value < 0.0001 (Figure 2).

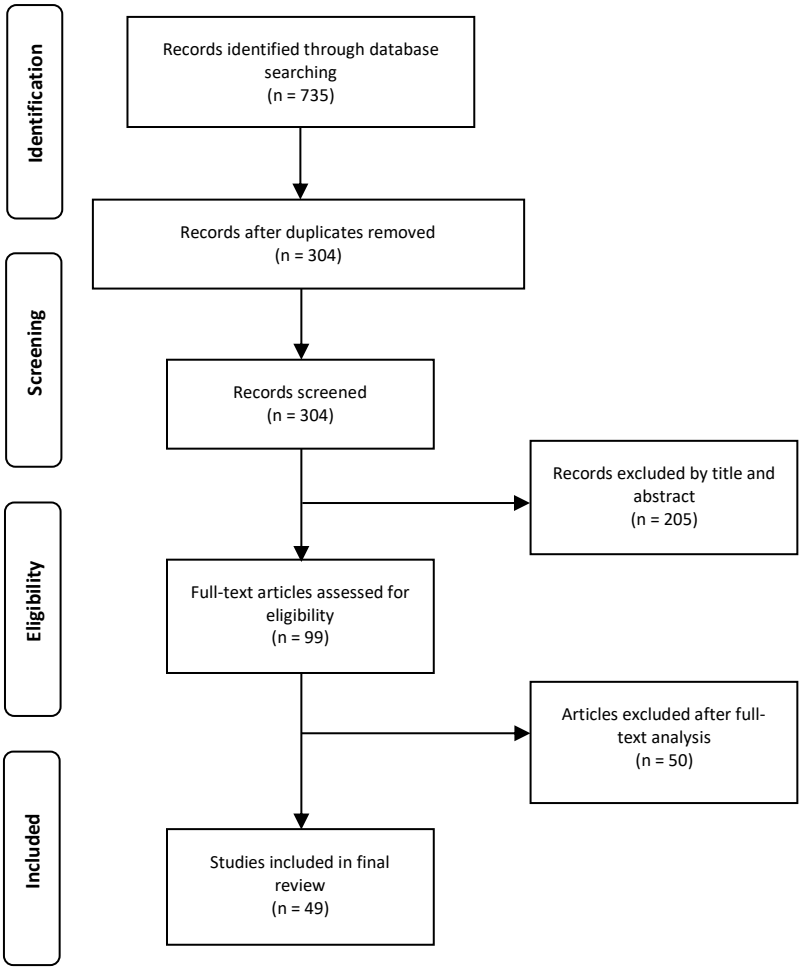

Figure 1. Flowchart of study selection process

Global ameloblastoma profile

A total of 42 articles[3,4,25–34,7,35–44,8,45–54,9,55,56,10,11,22–24] published from 1995 to 2018 with 6446 cases of ameloblastomas were identified, that provided data (sex and age distribution, mean age, tumor location, tumor types, and histological appearance) of ameloblastoma from 27 different countries worldwide.

Table 1. Incidence rates of ameloblastoma

Country	Incidence Rate (incidence/ year/ million population)	No. Cases	Time Period	Study	Type of study/registry
Australia	2.41	11	2011	Johnson NR et al, 2013	Population-based
South Africa	1.65	42	1965-1974	Shear M & Singh S, 1978	Population-based
Netherlands	1.50	591	1985-2010	Oomens MA & van der Waal I, 2014	Population-based
Nigeria	0.76	476	2009-2012	Oginni FO et al, 2015	Hospital-based
Tanzania	0.68	93	1999-2003	Simon EN et al, 2005	Hospital-based
Sweden	0.60	31	1958-1971	Larsson A & Almeren H, 1978	Population-based
Nigeria	0.35	290	1980-1995	Olaitan AA et al, 1998	Hospital-based

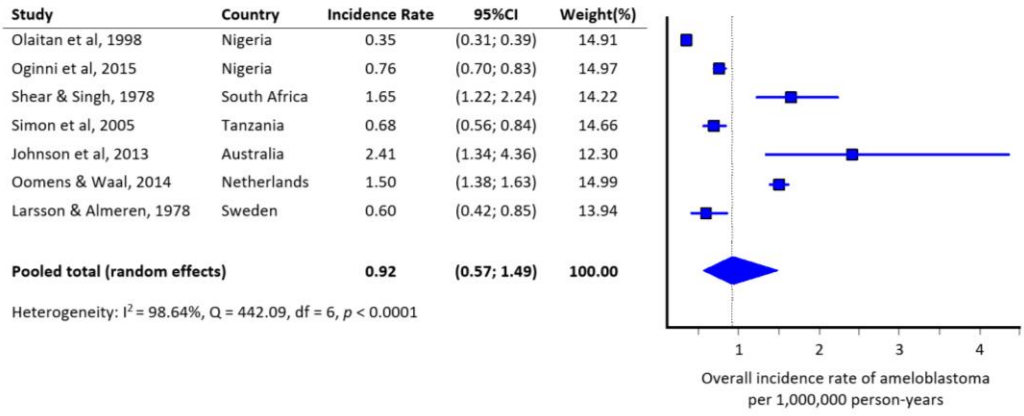

Figure 2. Forest plot showing pooled incidence rate of ameloblastoma

Sex distribution

Among all the cases, 3427 (53.2%) cases were male and 3008 (46.7%) were female with a male/female ratio of 1.14:1 (p < 0.001). The sex of 11 (0.1%) cases were not specified. Male predominance has been reported in Africa (M=650/F=542; p<0.001), North America (M=180/F=124; p<0.001) and Asia (M=2218/F=1915; p<0.001). Australia also reported male predominance, but the difference was not statistically significant (M=26/F=15; p = 0.057). Female predominance has been reported in South America (M=269/F=307; p = 0.111) and Europe (M=84/F=105; p=0.161), but again the difference was not statistically significant. Table 2 shows the sex distribution of ameloblastoma.

Age distribution

Data on the age distribution was retrieved from 28 articles (5389 cases)[3,4,29–31,33,35,36,38,39,43,44,8,45,46,48,49,51,53,55,56,11,22–27]. Overall, the peak incidence of ameloblastoma, worldwide, was in the third decade. In Europe (26.2%) and North America (34.0%), ameloblastoma mostly occurred at an older age (the fifth and sixth decades) while in Africa (32.8%) and South America (29.7%) ameloblastoma mostly occurred at a younger age (the third decade) and in Asia peak incidence was between the third and sixth decade. The difference between age distribution was statistically significant ($\chi^2 = 280.1$; $p < 0.001$). Table 3 shows data on the age distribution. Data on mean age was retrieved from 37 articles (5830 cases)[3,4,25–28,30–35,7,37–41,43–47,8,49–53,55,56,9–11,22–24]. Mean age of all cases was 34.3 years.

Table 2. Sex distribution and tumor location of patients with ameloblastoma (data obtained from 42 articles published from 1995 to 2018)

Continent	Sex distribution			Tumor location				Total number of patients
	Male (%)	Female (%)	Not specified (%)	Maxilla (%)	Mandible (%)	Soft Tissue (Peripheral) (%)	Not specified (%)	
Africa	54.5	45.5	0.0	4.7	93.5	0.5	1.3	1192
Asia	53.7	46.3	0.0	8.6	87.0	0.7	3.7	4133
Australia	63.4	36.6	0.0	19.5	80.5	0.0	0.0	41
Europe	44.4	55.6	0.0	14.8	84.7	0.5	0.0	189
North America	59.2	40.8	0.0	17.8	71.4	10.9	0.0	304
South America	45.8	52.3	1.9	8.2	85.9	0.5	5.4	587
Total	**53.2**	**46.7**	**0.1**	**8.5**	**87.2**	**1.1**	**3.1**	**6446**

Table 3. Age distribution of patients with ameloblastoma (data obtained from 28 articles published from 1995 to 2018)

Continent	Age Distribution						Total number of patients
	≤20 (%)	21-30 (%)	31-40 (%)	41-60 (%)	>60 (%)	NS (%)	
Africa	17.1	32.8	21.4	21.4	7.2	0.0	1051
Asia	21.0	24.2	20.1	25.2	7.9	1.6	3575
Europe	19.8	16.7	13.5	26.2	23.8	0.0	126
North America	9.2	13.6	13.6	34.0	29.6	0.0	250
South America	24.8	29.7	15.8	18.3	9.3	2.1	387
Total	**19.9**	**25.6**	**19.6**	**24.4**	**9.2**	**1.2**	**5389**

* NS: Not specified

Tumor location

Most ameloblastomas were located in the mandible (n=5623, 87.2%), followed by the maxilla (n=549, 8.5%) and peripheral (n=72, 1.1%). In 202 (3.1%) cases, the location was not specified. In all continents, tumors in the mandible outnumbered tumors in the maxilla and other locations ($\chi^2 = 395.3$; $p < 0.001$). Table 2 shows data on tumor location.

Tumor types

We classified ameloblastoma types according to the current 2005 WHO classification of odontogenic tumors. Data on ameloblastoma types were obtained from 29 articles (3637 cases)[3,7,31,33,35,37,39,42,44–47,8,48–56,9–11,23,26–28]. Solid/multicystic type was the most common type of 2462 (67.7%) cases. Unicystic, desmoplastic and peripheral types accounted for 953 (26.2%) cases, 130 (3.6%) cases and 38 (1.0%) cases respectively. The difference between tumor type was statistically significant ($\chi^2 = 584.4$; $p<0.001$). Table 4 shows data on ameloblastoma types.

Table 4. Tumor types of patients with ameloblastoma (data obtained from 29 articles published from 1995 to 2018)

Continent	Solid/ multicystic (%)	Unicystic (%)	Desmoplastic (%)	Peripheral (%)	Others (%)	Not specified (%)	Total number of patients
Africa	60.7	25.5	4.4	0.7	2.3	6.4	435
Asia	64.9	30.4	3.6	1.0	0.1	0.0	2441
Australia	82.9	14.7	0.0	2.4	0.0	0.0	41
Europe	71.4	24.4	0.0	4.2	0.0	0.0	119
North America	57.4	7.4	11.1	0.0	0.0	24.1	54
South America	84.8	11.0	3.3	0.9	0.0	0.0	547
Total	**67.7**	**26.2**	**3.6**	**1.0**	**0.4**	**1.1**	**3637**

Histopathologic appearance

Data on histopathologic appearance was available from 21 articles (2275 cases)[3,7,39–44,48,49,51,54,8,56,9,11,23,24,27,35,37]. The follicular (24.8%) and the plexiform patterns (24.7%) were the two most common histopathologic patterns. Acanthomatous (5.7%), granular cell (2.5%), and basal cell (0.4%) patterns were rare.

In all continents, follicular pattern was the most common histopathologic pattern, except in Asia. In Africa, the most common histopathologic pattern was mixed pattern, followed by the follicular pattern. There was no Australian article on the histopathologic appearance of ameloblastoma. The differences in histological appearance were statistically significant (χ^2=643.1; p< 0.001). Table 5 shows data on the histopathologic features of ameloblastoma.

Table 5. Histopathologic appearance of patients with ameloblastoma (data obtained from 21 articles published from 1995 to 2018)

Continent	Follicular (%)	Plexiform (%)	Acanthomatous (%)	Granular (%)	Basal Cell (%)	Mixed (%)	Cystic (%)	Desmoplastic (%)	Peripheral (%)	Others (%)	Not Specified (%)	Total number of patients
Africa	28.3	10.7	3.0	1.6	0.6	30.5	7.4	4.0	0.8	5.2	7.9	502
Asia	20.4	28.5	5.2	2.8	0.2	3.9	27.9	4.2	1.0	0.2	5.7	1269
Europe	29.8	28.1	3.5	1.7	0.0	12.3	21.0	1.8	1.8	0.0	0.0	57
North America	25.9	14.8	5.6	3.7	7.4	0.0	7.4	11.1	0.0	0.0	24.1	54
South America	33.6	31.3	11.2	3.1	0.0	6.9	8.6	4.3	0.8	0.2	0.0	393
Total	**24.8**	**24.7**	**5.7**	**2.5**	**0.4**	**10.4**	**19.4**	**4.3**	**0.9**	**1.3**	**5.5**	**2275**

* No data from Australia regarding histopathologic appearance

DISCUSSION

Ameloblastoma is an uncommon benign, locally aggressive tumor of odontogenic origin. The present study is the first systematic review and meta-analysis on the global incidence of ameloblastoma according to the literature from 1969 to 2018. We decided to include these studies in a range of time of five decades because we believe the information is valuable in the absence of more recent studies. In addition, we analyzed the profile of ameloblastoma patients with regard to sex and age distribution, tumor location, tumor types, and histopathologic appearance. For this global ameloblastoma profile, we included studies from 1995 until 2018 and compared it to the previous review by Reichart et al[12].

In the present study, 49 articles on the incidence of ameloblastoma from various countries were reviewed. The true incidence is defined as the number of new cases during a specified period in a specified population, so the most reliable data on incidence rate came from population-based studies, but unfortunately, few studies reported population-based incidence rates of ameloblastoma.

Through a systematic review and meta-analysis of the latest literature, we were able to provide a pooled estimate of the incidence rate of ameloblastoma of 0.92 per million population per year. We found heterogeneous incidence rates of ameloblastoma. Differences in incidence rate estimates may be caused by different methodological approaches, by incomplete reporting of cases to cancer registries, the lack of accurate case verification and different diagnostic capabilities. Furthermore, incidence rates were calculated in some articles covering short periods of time may be less reliable.

The global sex distribution from 6446 patients with ameloblastoma was 53% male and 47% female. These findings are consistent with the review by Reichart et al[12]. The mean age of the patients at the time of initial diagnosis was 34.3 years. Reichart et al. reported a mean age of 35.9 years in their review[12]. In the present study, we found the peak age of ameloblastoma incidence in the third decade of life. The peak incidence in Africa and South America was in the third decade, while the peak incidence in Europe and North America was in the fifth and sixth decades. These differences in peak incidence may be based on socioeconomic factors, as Reichart et al. mentioned: in developing countries, ameloblastoma tends to occur at a younger age. Accelerated aging due to poor nutrition and reduced access to the health care system may also play a role[12]. Whether or not ethnic background also contributes to making this difference in the age distribution of ameloblastoma, is unclear[9].

The mandible appeared the preferred site in the present study (87.2%) followed by maxilla (8.5%), which is consistent with the review from Reichart et al.[12]. Soft tissue (extraosseous) lesions were seen in 1.0% of the cases. These sites included gingiva, alveolar process, soft tissue of tuberosity, buccal and mandibular vestibule, retromolar pad, and edentulous areas.

Regarding the tumor types, solid/multicystic ameloblastomas were the most common type (67.7%), followed by unicystic (26.2%), desmoplastic (3.6%), and peripheral (1.0%) ameloblastomas with 1.1% of the cases were not specified. In sharp contrast, in the Reichart study, more than half (56.3%) of the total number of patients were non-specified cases. Apparently, the quality of reporting has drastically improved so that in our study a classification of the tumor type could be attributed to 98.9% of the patients. If we would correct the frequencies reported by Reichart et al. (33.8% solid/multicystic, 6.2% unicystic, 0.6% desmoplastic, and 2.0% peripheral ameloblastomas) by substracting the non-specified cases from the total number of cases, these values would change to 77.2%, 14.1% unicystic, 1.4% desmoplastic and 4.5% peripheral ameloblastomas respectively. Direct comparison of these values would imply differences from 1.1-4.5 times between the tumor types of both studies,

but we strongly feel that this comparison is not allowed or fair due to the large number of non-specified cases in the Reichart study[12].

According to the present review, follicular (24.8%) and plexiform (24.7%) patterns of solid ameloblastomas were the two most common histopathological appearances. The follicular pattern by far is the most common histopathological appearance encountered in most continents with exception of Asia, where the plexiform pattern dominated. The mixed pattern was relatively common (10.4%), while the acanthomatous, granular, and basal cell patterns were rare. The most common mixed pattern was the combination of follicular and plexiform. These results are in line with the review of Reichart et al., except that they found the acanthomatous pattern more often[12].

The potential for histopathological and radiographic confusions between ameloblastoma, odontogenic cysts, and other odontogenic tumors are very likely to occur and can lead to misdiagnosis[57,58]. A comprehensive examination of several aspects such as clinical, radiographic, and histopathological appearances, is mandatory to get the proper diagnosis. Radiographically, 3D imaging like computed tomography, magnetic resonance imaging, and cone-beam computed tomography is considered standard today[59].

In our study, we did not assess the global prevalence of ameloblastoma; our primary focus was the occurrence of the disease. Besides, since none of the cross-sectional studies presented the true prevalence of ameloblastoma, this assessment was not possible to begin with.

Our review has several limitations. We could not assess the study quality because we were not able to estimate the validity of the study results. These studies on the incidence of ameloblastoma were based on various registries. In the case of registry-based studies, validity involves the quality and completeness of the registry whether it is population-based or hospital-based. In this respect, it is important to realize that we did not assess the true underlying ameloblastoma incidence rate since the included reports are only based on incidence rates of ameloblastoma patients who presented to healthcare settings seeking for care. This will most certainly result in an underestimation of the true incidence rate. Unfortunately, estimating the extent of our systematic error is a virtually impossible endeavor due to many country- and patient-specific factors influencing this aspect, thereby making it impossible to determine a generalized and/or country-specific correction factor for this. For a more extensive discussion regarding the complex relationship existing between oral cancer screening (i.e., presentation) and mortality or other outcomes, one is referred to a recent

paper[60]. In addition, the quality of the diagnoses might influence the incidence. When the diagnoses are not accurate or when the histological examination is not available and the diagnosis is made based on the clinical symptoms and signs, the incidence might be overrated. We were also not able to do subgroup analysis because of the small number of the studies and for the sensitivity analysis due to lack of relevant data. The heterogeneity of the included studies may be caused by different methodological approaches, by incomplete reporting of cases to cancer registries, the lack of accurate case verification and different diagnostic capabilities or other unknown factors. Despite these limitations, some important conclusions can be drawn from the meta-analysis as the results of the review are based on the best available evidence.

This is the first study assessing the global incidence of ameloblastoma. The pooled incidence rate was determined to be 0.92 per million person-years, confirming that ameloblastoma is a rare odontogenic tumor. We saw a slight male preference (53%) and the peak age incidence in the third decade of life. The mandible is the preferred site. The most common type of ameloblastoma is solid/multicystic and the most histopathologic patterns are follicular and plexiform. The recent uniform classification such as 2005 WHO classification of odontogenic tumors, should be a reference for histological diagnosis of ameloblastoma. More epidemiological studies on the incidence rate of ameloblastoma are needed, especially in Asia and America, to determine the global incidence of ameloblastoma more accurately.

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CHAPTER 3

The Epidemiology, treatment, and complication of ameloblastoma in East-Indonesia: 6 years retrospective study

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ABSTRACT

Background: Ameloblastoma is a neoplasm classified as a benign epithelial odontogenic tumor of the jaws, grow slowly and are locally invasive. The aim of the present study was to investigate the incidence, treatment, and complication of patients with ameloblastoma in East-Indonesia during six years retrospective study.

Material and Methods: This retrospective study included 84 patients who were diagnosed with ameloblastoma from 2011 to 2016. There were 56 patients with treatment data available. Data from each patient, including gender, age, histologic type, the size of the tumor, radiologic form, tumor location, type of treatment, and complication were reviewed and analyzed retrospectively.

Results: Fourteen patients were diagnosed with unicystic ameloblastoma (25%), thirty-two patients with multicystic follicular ameloblastoma (57%) and ten patients with an unspecified multicystic ameloblastoma (18%). A total of about 35 patients were treated conservatively (62.5%) and 21 patients were treated radically (37.5%). Swelling was present as a pre-operative complication in all 56 cases (100%). There were no complaints concerning speech.

Conclusions: The majority findings of the histologic type were multicystic ameloblastoma and their location were in the mandible. Most ameloblastoma were treated conservatively and reconstructions were made with only titanium plates and not bone graft.

Keywords: Ameloblastoma, epidemiology, east Indonesia.

INTRODUCTION

Ameloblastoma is a neoplasm classified as a benign epithelial odontogenic tumor of the jaws. Ameloblastomas grow slowly and are locally invasive. A vast majority of ameloblastomas are unilateral (95%) and occur in the posterior region of the jaws (85%). Most tumors are located in the mandible (80-93%)[1,2].

A systemic review by MacDonald-Jankowski *et al.*[3] showed that number of ameloblastomas per hospital was significantly higher in Asian or African populations than European or American hospitals. Lu *et al.*[4] studied the Chinese populations and showed a mean age of 31.4 years with a 1.5:1 male: female ratio and 90.8% of the tumors were in mandible. A study by Hatada *et al.*[5] on the Japanese population showed a mean age of 34.7 years with a 1.6:1 male: female ratio and 92.6% was located in the mandible. There was no study found in Indonesian population.

The main goals of ameloblastoma treatment are complete removal of the tumor and restoration of function and aesthetics[6]. Broadly speaking, this can be achieved in two ways with surgical management; through conservative approach or radical approach[6–8]. The conservative approach of treating ameloblastoma includes enucleation and curettage, whereas the radical approach includes resection or excision of a lesion that includes a measurable perimeter of investing bone[7].

The incidence of ameloblastoma, treatment, and complication has not been studied in the Indonesian population especially in East-Indonesia. The purpose of this study was to conduct a retrospective investigation to examine these important topics in East-Indonesia.

MATERIAL AND METHODS

The data was collected for three months in Sulawesi, Indonesia during the period of April 13th - July 8th, 2016. The data was obtained from two hospitals, these were Hasanuddin University Dental Hospital in Makassar and Undata General Hospital in Palu. Patients' files were collected for the period of January 2011 - June 2016, where 84 patients were diagnosed with ameloblastoma. The inclusion criteria of treatment data were diagnosed with ameloblastoma and treated for the same. The exclusion criteria were incomplete patients' files (no treatment mentioned) and histopathological diagnoses other than ameloblastoma.

This study used a questionnaire to gather the data. Unknown data was left blank. Histologic type was confirmed by Pathology Anatomy (PA) result, if it was available in the medical files. The radiologic form was scored by one oral surgeon if radiographs were available.

Hong *et al.* made eight groups: anterior mandible (cuspid to cuspid); left and right posterior mandibles (pre-molar to molar); both rami (third molar to condyle); anterior maxilla (cuspid to cuspid); and both posterior maxilla (premolar to pterygoid plates)[9]. In this study, the groups were used and altered four locations: posterior maxilla; anterior maxilla; posterior mandible; anterior mandible. The cuspids in the maxilla and the mandible indicate the anterior border and posterior border. No difference was made between left and right.

Data from each patient, including gender, age, histologic type, location, the size of tumor, radiologic form, treatment of ameloblastoma, reconstruction, pre-operative, and post-operative complications were collected from medical reports and reviewed and analyzed retrospectively.

A database was created using Microsoft Excel and collected data was analyzed using SPSS v23 for statistical significance. Tests used were chi-square and an independent samples t-test. The significance level was < 0.05.

RESULTS

Eighty-four patients were diagnosed with ameloblastoma between January 2011 and June 2016. Forty-nine patients were treated in Makassar and 35 in Palu. Eighty- four patients were used in epidemiological data in this study including 40 males (48%) and 44 females (52%). The treatment data was not available for all patients, files of 28 patients turned out to be unusable for this study, forty-five cases were obtained from Makassar and 11 from Palu totaling to 56 usable patient files for treatment, which included data of 21 males (37.5%) and 35 females (62.5%).

Epidemiological Data

The mean age was 39.7 years (SD 17.4), with a minimum of five years and a maximum of 85 years. Out of 84 patients, 56 patients had a PA result included in the medical files. Fourteen patients were diagnosed with unicystic ameloblastoma (25%), thirty-two patients with multicystic follicular ameloblastoma (57%) and ten patients with an unspecified multicystic ameloblastoma (18%). The location of tumor according to the four regions showed six cases in

the maxilla, five (10.4%) in posterior and one (2.1%) in anterior, the mandible showed 38 (81.3%) cases in posterior and three (6.3%) cases in anterior. Radiographs were available for 56 patients. Nineteen radiolucencies (34%) were scored as uniloculated and 37 radiolucencies (66%) as multiloculated (Table 1).

Treatment Data

Most patients were treated in 2014 but it is not known why there was such a spike in treatments in that year. The location of the tumor was known for 39 cases, three patients had a tumor in the maxilla. Of the 36 tumors in the mandible, ten tumors had no specified location, three were specified to be in the anterior region, and 23 were in the posterior region (Table 2).

A total of about 35 patients were treated conservatively (62.5%) and 21 patients were treated radically (37.5%). Most patients treated conservatively underwent enucleation and curettage (62.8%), the rest received only enucleation (37.25). Of the patients treated radically, about 10 patients received a marginal resection (47.6%) and 10 patients received segmental resection (47.6%), while only one patient underwent a maxillectomy (4.8%) (Table 2).

Table 1. Disease-related results of patients with ameloblastoma.

	n	(%)
Histologic Type (n =56)		
Unicystic	14	(25)
Follicular Multicystic	32	(57)
Unspecified Multicystic	10	(18)
Tumor Location (n = 48)		
Maxilla (n = 6)		
Posterior	5	(10.4)
Anterior	1	(2.1)
Mandible (n = 42)		
Posterior	39	(81.3)
Anterior	3	(6.3)
Radiolucencies (n = 56)		
Uniloculated	19	(34)
Multiloculated	37	(66)

A total of about five patients were documented to have received a reconstruction after tumor removal (8.9%). One of those reconstructions was an unspecified autogenous bone graft, the remaining four were reconstruction made with titanium plates. The patient with the bone graft had undergone a conservative treatment of enucleation and curettage. Three titanium plate reconstructions were performed after an enucleation.

The follow-up was documented for 56 patients (25%) for a period of up to four years. Six recurrences were noted for these 56 patients (42.8%). Both of the patients who had undergone enucleation experienced a recurrence. Forty percent of the patients that had enucleation and curettage had a recurrence. One patient treated with segmental resection had a recurrence after four years (Table 3).

Table 2. Gender distribution, number of patients treated in each year, location, and type of treatment.

	N	%
Gender		
Male	21	37.5
Female	35	62.5
Patients treated in each year		
2011	5	8.9
2012	9	16.0
2013	9	16.0
2014	19	33.9
2015	12	21.4
2016	2	3.8
Tumor location		
Maxilla	3	5.3
Mandible		
Anterior	3	5.3
Posterior	23	41.1
Unspecified	10	17.9
Unknown	17	30.4
Type of treatments		
Conservative		
Enucleation + curettage	22	39.3
Enucleation	13	23.2
Radical		
Marginal resection	10	17.8
Segmental resection	10	17.8
Maxillectomy	1	1.7

Table 3. Follow-up and recurrences of patients with ameloblastoma.

	Recurrence	No recurrence
Numbers of follow-ups and recurrences after set amount of years		
1 year	2	6
2 years	1	2
3 years	0	2
4 years	1	0
The known recurrence for all patients that had follow-ups, specified for each type of treatment		
Enucleation	2	0
Enucleation + Curettage	4	6
Segmental resection	1	1

Complication

Swelling was present as a pre-operative complication in all 56 cases (100%). Out of 56 patients, the pain was present in eight cases (10%), numbness or an altered feeling was present in two cases (2%), breathing obstruction was present in one case (1%), and swallowing problems were present in two cases (2%). There were no complaints concerning speech (Table 4).

Table 4. Pre-operative complications of patients with ameloblastoma. Some patients had more than one complication

Type of Complications	n (%)
Swelling	56 (100)
Pain	8 (10)
Paresthesia	2 (2)
Breathing Obstruction	1 (1)
Swallowing Problems	2 (2)

DISCUSSION

Patient files in Dental Hospital, especially in Makassar were barely maintained and documented a decade ago, but for the past five years, documentation has improved. This is a promising prospect for future (prospective research) in East-Indonesia. Setting up prospective studies for the treatment of ameloblastoma would most definitely help the continuing development and improvement of local health care.

Patients often wait for seeking medical care until their life is significantly impacted by the tumor[2]. Since ameloblastoma is a slow growing tumor, it can take many years until a patient

seeks medical care, at which point the treatment is much more complicated due to the size of the tumor. The patients in Indonesia showed a mean age of 39.7 years, which is similar to the main age of Caucasians (39.9 years) and Asian (41.2 years) according to Reichart *et al.*[10]. In this study, the mean age was 41.00 for males and 38.64 for females. In the studies of Chukweneke *et al.* and Oomens *et al.* a higher age for males was also found[11,12].

Histologic distribution within this study was 25% unicystic ameloblastoma, about 57% multicystic ameloblastoma and an unspecified multicystic ameloblastoma 18%. These findings are similar to the findings from Gandhi *et al.*[13], which found 23% unicystic ameloblastoma and 77% multicystic ameloblastoma and findings from Saghravanian *et al.*[14], which found 24% with unicystic ameloblastoma, about 73% with multi- cystic ameloblastoma and 3% with extraosseous ameloblastoma.

Radiographically, the currents study had less uniloculated and more multiloculated radiolucencies compared to the finding of Gandhi *et al.* and Bansal *et al.*[13,15]. It seems that the children have a higher percentage of uniloculated radiolucencies and a lower percentage of multiloculated radiolucencies, which is in accordance with a higher percentage of unicystic ameloblastoma and a lower percentage of multicystic ameloblastoma. But it should be stressed that both unicystic and multicystic ameloblastoma could show both uniloculated and multiloculated radiolucencies. In other words, the radiographic appearance is not dependent on the histological type[15–17].

The mean age of unicystic ameloblastoma (49.75 years) in the current study was higher than multicystic ameloblastoma (38.18 years). This difference was not significant. However, in literature, a lower age was found for unicystic ameloblastoma than multicystic ameloblastoma[1,14]. Also, a higher percentage of unicystic ameloblastoma and a lower percentage of multicystic ameloblastoma were found within studies including only children, compared to studies including all ages[10,16,17].

Reconstructions were mostly done with titanium metal plates, which is notable in the modern literature that mainly discusses and offers studies about bone graft. Recent literature on titanium plates is mostly limited to case report[18,19]. Older study shows high rates of complications[20–22], which seems to be confirmed by this study where two out of four patients experienced post-operative complications; one patient had excessive wound bleeding and one patient experienced plate rejection after difficult closure during the surgery. The

ameloblastoma reconstructions are less invasive and less expensive for the patient since no bone has to be grafted, which could explain why it is used so often East-Indonesia.

In East-Indonesia, most patients were treated conservatively (62.5%) despite a majority of patients being diagnosed with multicystic ameloblastoma. There is no ex- planation for this, but it could be that treatment is decided by the size of the tumor and not by the histological type. Patients may also deny radical treatment due to financial factors or reluctance towards the risk of deformities, lip numbness, malocclusion, or poor mastication[23].

The swelling was found in 70% cases in the study of MacDonald-Janskowski *et al.*[3]. In this study, the swelling is the chief complaint. These swellings were larger in size compared with literature and the patients waited longer before seeking medical assistance.

A cultural reason would be that Indonesian people have a higher threshold of seeking medical assistance. The geographical restriction could also apply. On the Sulawesi Island, there are only a few big cities with hospitals and oral surgeons. The infrastructure and distances from their homes to these big cities could be a restricting factor to seek medical assistance.

The present study has several shortcomings. This study was limited to East-Indonesia (Makassar and Palu). Further study related to ameloblastoma is still required in other health centers in Indonesia. However, the number of treated patients is not equally distributed among the hospitals. Most patients are treated at the Dental Hospital Hasanuddin University Makassar and General Hospital Palu. Therefore, our results may not be generalizable to the whole population of Indonesia. Because this study was retrospective, the analysis may include an information bias. However, the results presented in this study are similar to the reports from other studies. Furthermore, the analysis in this report provides important data for improving the treatment plans for ameloblastoma surgery.

In the Indonesian retrospective study regarding ameloblastoma, the majority findings of the histologic type were multicystic ameloblastoma and their location was in the mandible. Most ameloblastomas were treated conservatively in East-Indonesia and reconstructions were mostly made with only titanium plates and not by bone graft, which is an older technique not used much in the Western world anymore. These reconstructions some- times have complications that require more surgery or a longer hospital day.

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CHAPTER 4

Radical vs conservative treatment of intraosseous ameloblastoma: systematic review and meta-analysis

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ABSTRACT

Objectives: The aim of the present study was to assess the outcomes of radical and conservative treatment approaches of solid/multicystic and unicystic ameloblastoma in terms of recurrence rates.

Material and methods: A systematic review and meta-analysis was conducted based on the PRISMA statement. Search was performed using PubMed, Embase, SCOPUS, and Web of Science for articles published from January 1969 until March 2018. Quality assessment of the selected articles was conducted using the Quality Appraisal of Case Series Studies Checklist. The meta-analysis was performed using the MedCalc program.

Results: The search strategy yielded 6984 articles; 20 studies met the eligibility criteria and were included in the meta-analysis. The pooled recurrence rate of solid/multicystic ameloblastomas following radical treatment was 8%, while conservative treatment caused recurrences in 41%. For unicystic ameloblastomas, these values were 3% and 21%, respectively. The risk of recurrences in both types of ameloblastomas following radical treatment was lower than following conservative treatment.

Conclusions: The present study showed statistically significant differences in recurrence favoring radical treatment for both unicystic and solid/multicystic ameloblastoma. The solid/multicystic type showed more recurrences than the unicystic type. Unfortunately, since only retrospective studies were available, the evidence is less strong as wished for.

Keywords: ameloblastoma; recurrence; treatment; solid multicystic ameloblastoma; unicystic ameloblastoma

INTRODUCTION

Ameloblastoma represents about 1% of all tumors and cysts of the jaws, and 13% - 78% of all odontogenic tumors[1]. Ameloblastoma is a locally invasive benign tumor of epithelial origin that may grow from rests of dental lamina, enamel apparatus, the epithelial lining of an odontogenic (dentigerous) cyst, or from the basal epithelial cells of the oral mucosa[2]. It often manifests clinically as a slow-growing, painless swelling, causing expansion of cortical bone, spreading of the lingual and/or buccal plates, and penetration of soft tissue. The diagnosis of ameloblastoma is often delayed, probably because of its slow-growing character[3].

The current classification of the World Health Organization (WHO) in 2005 distinguishes four types of benign ameloblastoma: solid or multicystic, unicystic, peripheral and desmoplastic ameloblastoma[4]. The solid or multicystic ameloblastoma is the most common subtype of ameloblastoma (approximately 80% of cases) and has a predilection for the posterior side of the jaws, especially the body, ramus, and angle of the mandible[5]. Ameloblastoma shows no clear sex predilection and is most commonly diagnosed in adults between the age of 30 and 60 years[6]. Recurrence rates are very high if not treated adequately[7].

Primary treatment of ameloblastoma is surgical and can be separated into conservative and radical methods[5]. Choice of treatment depends on the type of the tumor and its clinical presentation. Unicystic and peripheral ameloblastoma are usually treated conservatively, while solid or multicystic ameloblastoma are often treated radically. Conservative methods such as enucleation and curettage require less operation time, but these methods are assumed to be associated with high recurrence rates and re-resection(s). On the other hand, radical surgery like segmental resection is thought to be associated with lower recurrence rates but often requires plate reconstruction or more extensive reconstructive surgery[8].

Antonoglou and Sandor[9] conducted a systematic review and meta-analysis on the recurrence rates of solid and unicystic ameloblastomas based on studies published from 1977 to 2003 and revealed lower risk of recurrence after radical compared to conservative treatment, but were only able to conclude this for solid or multicystic ameloblastomas, since the very low number of studies evaluating both treatment modalities in unicystic ameloblastomas prohibited sound assessments. Lau and Samman[10] in their review concluded that there is only weak evidence showing that the risk of recurrence of unicystic ameloblastomas in jaw resection is lower compared to enucleation with Carnoy’s solution.

The aim of this present study was to assess the outcomes of radical and conservative treatment approaches of solid or multicystic as well as unicystic ameloblastoma in term of recurrence rates by conducting a systematic review and meta-analysis of the studies published in the last fifty years.

MATERIALS AND METHODS

Protocol and Eligibility Criteria

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[11]. Although the guideline is intended for reviews of prospective randomized controlled studies, this review included retrospective non-randomized studies in the absence of randomized controlled studies of ameloblastoma. The inclusion criteria were:

1. Studies published from 1969 to 2018
2. English-language and human-species articles
3. At least presented one treatment approach (radical or conservative) of ameloblastoma and matching recurrence rate
4. Diagnosis of solid/multicystic or unicystic ameloblastoma obtained after histological examination and matching recurrence rate.

Articles were excluded for the following reasons:

1. Case reports
2. A number of cases fewer than 10.

Information Sources and Search

The electronic literature search was performed using PubMed, Embase, SCOPUS, and Web of Science for articles published from January 1969 until March 2018 (date of the last search: March 14, 2018), with the combination of medical subject heading (MeSH) terms “ameloblastoma treatment” and “ameloblastoma recurrence”. The search was restricted to English-language articles and human species articles. In addition, manual searches of the reference lists of the articles were performed to find other eligible articles that were not available in the electronic databases.

Study Selection, Data Collection, and Data Items

The article selection process was conducted by two independent reviewers (F.N.H. and D.S.N.K.) blind to each other's activities. Disagreements between reviewers regarding the included studies were resolved by discussion. If necessary, a third reviewer (T.F.) was consulted for selection and evaluation of the included studies. In the first step (screening), the authors excluded studies that did not focus on treatment and recurrence of ameloblastoma by screening the titles and abstracts from the search results. In the second step, the authors assessed the full-text articles and excluded studies which did not meet the inclusion criteria. Studies with unavailable full-text or studies with incomplete or unclear data were excluded.

The following data for each study were extracted from full-text articles using a data extraction form and stored in 2016 Microsoft Excel file format: author, publication year, country or region of study, tumor type, the histopathologic pattern, treatment method, recurrences, and post-operative follow up period. When multiple articles reporting data from the same study population were identified, the most comprehensive and recent data were used. For example, numerous articles may report on data from the same registry. In cases where the studies reported on different timeframes or subgroups, all nonoverlapping data were included.

The primary outcome of the study was the recurrence rate of ameloblastoma. The objectives were to provide the pooled recurrence rates following the treatment approaches and to compare the recurrence rate of different treatment approaches (radical versus conservative) in solid/multicystic and unicystic ameloblastoma.

The radical approach includes the following treatment modalities: marginal resection, segmental resection, hemimaxillectomy or hemimandibulectomy, wide margin resection, and total resection. The conservative approach includes: curettage, enucleation, marsupialization alone or followed by enucleation or curettage, enucleation with the application of Carnoy's solution, curettage plus cryotherapy, decompression, other or combination of the previous.

Risk of Bias in the Individual Studies and Across Studies

The analysis of the risk of bias in individual studies was to be assessed using the Quality Appraisal of Case Series Studies Checklist (QACSS) by Institute of Health Economics (IHE), Edmonton, Canada[12]. Funnel plots were created to evaluate the presence of publication bias among the studies comparing radical and conservative treatment.

Summary Measures and Synthesis of Results

Recurrence rates were calculated and pooled for each group of treatment (radical or conservative) separately in solid or multicystic and unicystic ameloblastomas. The relative risk (RR) of ameloblastoma recurrence was used to determine the effect size for the comparison of the recurrence between radical approach and conservative approach in solid or multicystic and unicystic. The corresponding 95% confidence intervals (CIs) were calculated. Heterogeneity among studies was assessed using the Q statistic by Cochran and I^2 index introduced by Higgins and Thompson[13]. The meta-analysis of random effects model was used in cases of statistical evidence of heterogeneity. All statistical analyses were performed using MedCalc program version 15.2 (MedCalc Software, Ostend, Belgium).

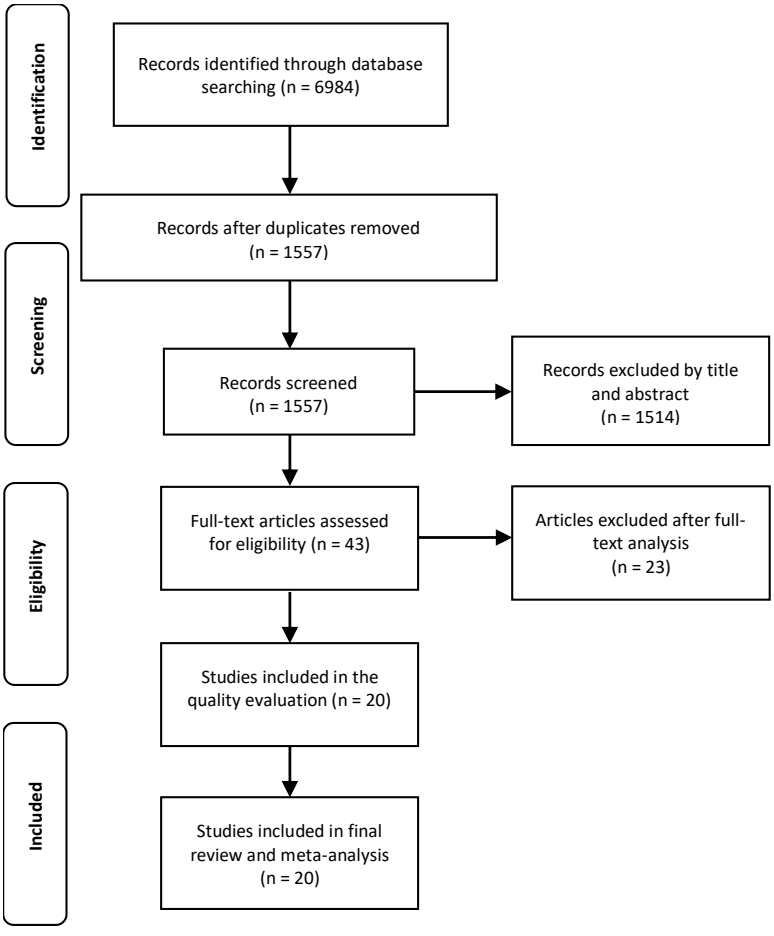


Figure 1. Flowchart of the study selection process

RESULTS

Study Selection and Characteristics

The search strategy yielded a total of 6984 articles from electronic databases. Of 6984 articles, 5427 articles were removed after screening for duplication. A total of 1514 articles were excluded after reading the titles and abstracts, and the full-text articles of the remaining 43 studies were reviewed independently by two authors for eligibility. At this full-text analysis, 23 studies were excluded because they did not meet our inclusion criteria. The reasons for the exclusion of the articles are shown in Supplementary table 1. A total of 20 studies[1,5–8,14–28] with 1069 cases of ameloblastoma and 218 recurrences from 15 different countries were included and were processed for final review and meta-analysis. The process of study selection is described in Figure 1. The minimum follow-up time in the study was 1 month and the maximum was 25 years. The characteristics of studies included in the review were summarized in Table 1.

Risk of Bias Within and Across Studies

Two studies met 50% of the criteria of QACSS[16,26], four studies met 51-60% of the criteria[1,7,22,24], nine studies met 61-70% of the criteria[6,14,15,17–21,28], and five studies met >70% of the criteria[5,8,23,25,27]. The details of quality assessment according to the criteria of QACSS were presented in Table 2.

Risk of bias across studies was graphically evaluated with the funnel plot. The forest plot comparing radical and conservative treatment in solid or multicystic ameloblastoma showed some indication of publication bias, as small studies favoring radical treatment were over-represented (Figure 2A). For unicystic ameloblastoma, the funnel plot was symmetrical and thus suggest the absence of the publication bias (Figure 2B).

Synthesis of Results

Solid or multicystic ameloblastoma

Fifteen studies with 364 solid or multicystic ameloblastomas reported a recurrence following radical treatment. There was significant heterogeneity among the studies (I^2= 56.9%; p= 0.003), although the Higgins Index showed intermediate results. The pooled recurrence rate for 15 studies with solid or multicystic ameloblastomas in radical treatment was 8% (95% CI, 4-13) (Figure 3A).

A total of 341 solid or multicystic ameloblastomas in eleven studies reported a recurrence following conservative treatment. No significant heterogeneity was detected among the studies (I^2=29.9%; p= 0.161). The pooled recurrence rate was 41% (95% CI, 34-48) (Figure 3B).

Ten studies with 534 solid or multicystic ameloblastomas reported the recurrence following either radical or conservative treatment. There was a low degree of heterogeneity among the studies (I^2= 3%; p= 0.41). Relative risks were calculated to determine the effect size. The estimated combined relative risk was 0.35 (95% CI, 0.23-0.52; p < 0.00001), meaning that the risk of recurrence for solid or multicystic ameloblastomas following radical treatment was lower than following conservative treatment (Figure 2C).

Only 10 articles specified the treatment modality of solid/multicystic ameloblastoma in the radical approach, and 7 articles did so for the conservative approach. Unfortunately, the strong diversity in approaches (Supplementary table 2) prohibited stratification of results for treatment modality.

Unicystic ameloblastoma

Twelve studies with 109 unicystic ameloblastomas reported a recurrence following radical treatment. No significant heterogeneity was detected among the studies (I^2= 0%; p= 0.980). The pooled recurrence rate was 3% (95% CI, 1-7) (Figure 3C).

A total of 255 unicystic ameloblastomas in fifteen studies reported the recurrence following conservative treatment. No significant heterogeneity was detected among the studies (I^2=0%; p= 0.462). The pooled recurrence rate for unicystic ameloblastomas in conservative treatment was 21% (95% CI, 16-26) (Figure 3D).

Eight studies with 240 unicystic ameloblastomas reported the recurrence following both types of treatment (radical and conservative). The forest plot showed a low degree of heterogeneity among the studies (I^2= 0%; p= 0.94). The comparison of radical versus conservative treatment demonstrated that radical treatment is associated with lower risk of recurrence (95% CI, 0.12-0.82; p= 0.02) (Figure 2D).

Only 7 articles specified the treatment modality of unicystic ameloblastoma in the radical approach, and 11 articles did so for the conservative approach. Again, the strong diversity in approaches (Supplementary table 3) prohibited stratification of results for the treatment modality.

Table 1. Summary of studies included in the review

No.	Author and publication year	Country of study	Total cases	Included cases	Type/ Histological pattern	Treatment type (approach)	Treatment & Recurrence						Follow up Time
							Radical	Recurrence	Rec. rate	Conservative	Recurrence	Rec. rate	
1	Bataineh, 2000 [7]	Jordan	23	23	Multicystic	Segmental resection (radical)	9	0	0.0				10 years
					Unicystic	Segmental resection (radical)	14	0	0.0				
2	Becelli et al., 2002 [24]	Italy	60	60	Multicystic	Marginal resection (radical)	27	0	0.0				2-10 years
						Segmental resection (radical)	15	0	0.0				
					Unicystic	Marginal resection (radical)	18	0	0.0				
3	Bianchi et al., 2013 [6]	Italy	31	31	Multicystic	Segmental resection (radical)	27	0	0.0				18-120 months (Mean: 53.6 months)
					Unicystic	Segmental resection (radical)	4	0	0.0				
4	Chapelle et al., 2004 [25]	Netherlands	19	19	Multicystic	Marginal resection (radical)	2	0	0.0				Mean: 8.8 years
						Segmental resection (radical)	2	0	0.0				
						Enucleation + Carnoy's Solution (conservative)				4	1	25.0	
						Enucleation (conservative)				6	3	50.0	
					Unicystic	Enucleation + Carnoy's Solution (conservative)				4	0	0.0	Mean: 10.6 years
						Enucleation (conservative)				1	0	0.0	
5	Darshani Gunawardhana et al., 2010 [26]	Sri Lanka	286	147	Multicystic	Enucleation (conservative); marginal, segmental & total resection (radical)	27	2	7.4	56	20	35.7	NA
					Unicystic	Enucleation (conservative); marginal, segmental & total resection (radical)	21	0	0.0	43	12	27.9	
6	Fregnani et al., 2010 [27]	Brazil	121	120	Multicystic	Segmental resection (radical)	47	8	17.0				Mean: 9.7 years
						Curettage + Cryotherapy (conservative)				47	14	29.8	
						Curettage (conservative)				19	3	15.8	
					Unicystic	Curettage (conservative)				7	2	28.6	
7	Hasegawa et al., 2013 [28]	Japan	23	23	Multicystic	Enucleation after Marsupialization (conservative)				6	4	66.7	8-130 months
						Enucleation + Curettage (conservative)				7	2	28.6	
						Enucleation (conservative)				10	4	40.0	
8	Hertog et al., 2012 [14]	Netherlands	35	35	Follicular	Radical Surgery (radical); Enucleation (conservative)	2	0	0.0	8	7	87.5	Mean: 8.3 years
					Plexiform	Radical Surgery (radical); Enucleation (conservative)	3	0	0.0	8	4	50.0	
					Mixed	Radical Surgery (radical); Enucleation (conservative)	1	0	0.0	6	3	50.0	
					Unicystic	Radical Surgery (radical); Enucleation (conservative)	1	0	0.0	6	3	50.0	
9	Hong et al., 2007 [15]	Korea	239	234	Multicystic	Resection with bone margin (radical)	32	5	15.6				1-22 years (Mean: 8 years)
						Segmental resection (radical)	18	1	5.6				
						Conservative (conservative)				104	40	38.5	

					Unicystic	Resection with bone margin (radical)	10	0	0.0			
						Segmental resection (radical)	3	0	0.0			
						Conservative (conservative)				67	11	16.4
10	Junquera et al., 2003 [1]	Spain	22	16	Multicystic	Marginal resection (radical)	1	1	100.0			2-23 years
						Segmental resection (radical)	4	1	25.0			
						Disarticulation (radical)	1	0	0.0			
						Enucleation + Curettage (conservative)				5	2	40.0
					Unicystic	Enucleation + Curettage (conservative)				5	2	40.0
11	Krishnapillai & Angadi, 2010 [16]	India	73	73	Multicystic	Wide margin resection (radical)	46	7	15.2			10 months - 16 years
					Unicystic	Enucleation/ Curettage (conservative)				27	2	7.4
12	Lee et al., 2004 [17]	Hong Kong	29	29	Unicystic	Resection (radical)	5	0	0.0			2-12.5 years (Median 6 years 9 months)
						Enucleation (conservative)				2	2	100.0
						Enucleation + Carnoy's Solution (conservative)				22	4	18.2
13	Leider et al., 1985 [18]	USA	33	22	Unicystic	Enucleation/ Curettage (conservative)				22	4	18.2	2-25 years (Mean: 6 years)
14	Migaldi et al., 2008 [19]	Italy	24	19	Multicystic	Radical surgery (radical); Conservative surgery (conservative)	12	3	25.0	6	4	66.7	2-146 months (Mean: 57 months)
					Unicystic	Conservative surgery (conservative)				1	0	0.0	
15	Nakamura et al., 2002 [20]	Japan	78	75	Follicular	Radical surgery (radical); Enucleation + Curettage after Marsupialization, Enucleation + Curettage (conservative)	12	1	8.3	7	4	57.1	Unicystic: 4 months - 9.5 years (Mean: 21.3 months); Solid: 3 - 22 months (Mean: 11.7 months)
					Plexiform	Radical surgery (radical); Enucleation + Curettage after Marsupialization, Enucleation + Curettage (conservative)	12	1	8.3	11	4	36.4	
					Follicular + Plexiform (Mixed)	Radical surgery (radical); Enucleation + Curettage after Marsupialization, Enucleation + Curettage (conservative)	5	1	20.0	4	2	50.0	
					Unicystic	Radical surgery (radical); Enucleation + Curettage after Marsupialization, Marsupialization (conservative)	13	0	0.0	11	2	18.2	
16	Olaitan & Adekeye, 1997 [21]	Nigeria	21	21	Unicystic	Marginal resection (radical)	5	1	20.0			1 month - 13 years; Median: 8.3 years
						Full-thickness resection (radical)	5	0	0.0			
						Enucleation (conservative)				11	2	18.2
17	Ooi et al., 2014 [8]	Singapore	30	30	Multicystic	Segmental resection (radical)	24	0	0.0			12-128 months (Mean: 59 months)
					Unicystic	Segmental resection (radical)	6	0	0.0			
18	Robinson & Martinez, 1977 [22]	USA	20	15	Unicystic	Enucleation (conservative)				15	3	20.0	Mean: 106.2 months

19	Singh et al., 2015 [5]	Australia	41	40	Multicystic	Radical surgery (radical); Conservative treatment (conservative)	29	1	3.4	5	3	60.0	Mean: 51 months
					Unicystic	Radical surgery (radical); Conservative treatment (conservative)	2	0	0.0	4	2	50.0	
20	Zhang et al., 2010 [23]	China	37	37	Multicystic	Segmental resection (radical)	6	0	0.0				3 months - 6 years
						Curettage, Curettage + Cautery or Decompression (conservative)				22	9	40.9	
					Unicystic	Segmental resection (radical)	2	0	0.0				
						Curettage, Curettage + Cautery or Decompression (conservative)				7	1	14.3	
	Total			1069			473	33	7.0	596	185	31.0	

a. Rec. rate: Recurrence rate
b. NA: Not available

Table 2. Quality assessment of individual study

Study/Criteria	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12
Bataineh, 2000	Yes	No	Unclear	Yes	No	Unclear	Yes	Yes	Yes	Yes	Yes	No
Becelli et al, 2002	Yes	No	Unclear	Yes	No	Unclear	Yes	Yes	Yes	Yes	Yes	No
Bianchi et al, 2013	Yes	No	Unclear	Yes	Partial	Unclear	Yes	Yes	Yes	Yes	Yes	No
Chapelle et al, 2004	Yes	Yes	Unclear	Yes	Partial	Unclear	Yes	Yes	Yes	Yes	Yes	No
Darshani G et al, 2010	Yes	No	Unclear	Yes	Yes	Unclear	Yes	Unclear	No	No	Yes	No
Fregnani et al, 2010	Yes	No	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Hasegawa et al, 2013	Yes	Yes	Unclear	Yes	Partial	Unclear	Yes	Yes	Yes	No	Yes	Partial
Hertog et al, 2012	Yes	No	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No
Hong et al, 2007	Yes	No	Unclear	Yes	Partial	Unclear	Yes	Yes	Yes	Yes	Yes	Partial
Junquera et al, 2003	Yes	No	Unclear	Yes	Partial	Unclear	Yes	Yes	Yes	No	Yes	No
Krishnapillai & Angadi, 2010	Yes	No	Unclear	Yes	No	Unclear	Yes	Yes	No	No	Yes	Partial
Lee et al, 2004	Yes	No	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No
Leider et al, 1985	No	Yes	No	Yes	Partial	Unclear	Yes	Yes	Yes	Yes	Yes	No
Migaldi et al, 2008	Yes	No	Unclear	Yes	Partial	Unclear	Yes	Yes	Yes	Yes	Yes	Partial
Nakamura et al, 2002	Yes	No	Unclear	Yes	Partial	Unclear	Yes	Yes	Yes	Yes	Yes	No
Olaitan & Adekeye, 1997	Yes	No	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No
Ooi et al, 2014	Yes	No	Unclear	Yes	Partial	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Robinson & Martinez, 1977	Yes	No	No	Yes	Partial	Unclear	Partial	Yes	Yes	Yes	Yes	No
Singh et al, 2015	Yes	No	Unclear	Yes	Partial	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Zhang et al, 2010	Yes	No	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Partial

Notes:

Q1: Was the hypothesis/ aim/ objective of the study clearly stated?

Q2: Were the cases collected in more than one center?

Q3: Were patients recruited conse-cutively?

Q4: Were the characteristics of the patients included in the study described?

Q5: Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?

Q6: Did patients enter the study at a similar point in the disease?

Q7: Was the intervention of interest clearly described?

Q8: Was follow-up long enough for important events and outcomes to occur?

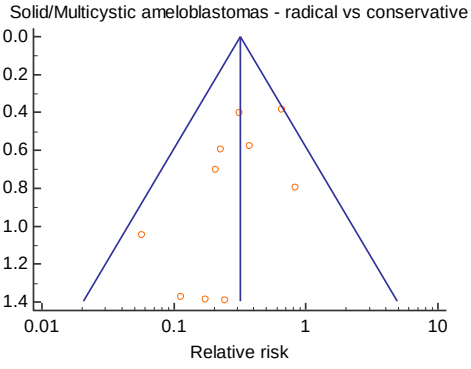
Q9: Were losses to follow-up reported?

Q10: Were the adverse events reported?

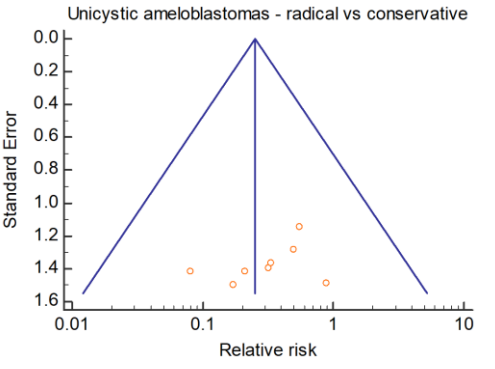
Q11: Were the conclusions of the study supported by the results?

Q12: Were both competing interests and sources of support for the study reported?

A



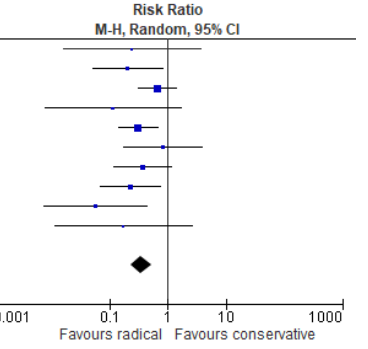
B



C

Study or Subgroup	Radical Events	Radical Total	Conservative Events	Conservative Total	Weight	Risk Ratio M-H, Random, 95% CI
Chapelle K et al, 2004	0	4	4	10	2.2%	0.24 [0.02, 3.72]
Darshani Gunawardhana KS et al, 2010	2	27	20	56	8.4%	0.21 [0.05, 0.82]
Fregnani ER et al, 2010	8	47	17	66	26.4%	0.66 [0.31, 1.40]
Hertog D et al, 2012	0	6	14	22	2.3%	0.11 [0.01, 1.67]
Hong J et al, 2007	6	50	40	104	24.2%	0.31 [0.14, 0.69]
Junquera L et al, 2003	2	6	2	5	6.6%	0.83 [0.18, 3.96]
Migaldi M et al, 2008	3	12	4	6	12.3%	0.38 [0.12, 1.16]
Nakamura N et al, 2002	3	29	10	22	11.6%	0.23 [0.07, 0.73]
Singh T et al, 2015	1	29	3	5	3.8%	0.06 [0.01, 0.45]
Zhang J et al, 2010	0	6	9	22	2.2%	0.17 [0.01, 2.61]
Total (95% CI)		**216**		**318**	**100.0%**	**0.35 [0.23, 0.52]**
Total events	25		123			

Heterogeneity: Tau² = 0.02; Chi² = 9.31, df = 9 (P = 0.41); I² = 3%
Test for overall effect: Z = 5.11 (P < 0.00001)



D

Study or Subgroup	Radical Events	Radical Total	Conservative Events	Conservative Total	Weight	Risk Ratio M-H, Random, 95% CI
Darshani Gunawardhana KS et al, 2010	0	21	12	43	11.5%	0.08 [0.00, 1.29]
Hertog D et al, 2012	0	1	3	6	14.1%	0.50 [0.04, 6.17]
Hong J et al, 2007	0	13	11	67	11.6%	0.21 [0.01, 3.38]
Lee PK et al, 2004	0	5	6	24	11.9%	0.32 [0.02, 4.94]
Nakamura N et al, 2002	0	13	2	11	10.3%	0.17 [0.01, 3.23]
Olaitan & Adekeye, 1997	1	10	2	11	17.7%	0.55 [0.06, 5.18]
Singh T et al, 2015	0	2	2	4	12.4%	0.33 [0.02, 4.85]
Zhang J et al, 2010	0	2	1	7	10.5%	0.89 [0.05, 16.36]
Total (95% CI)		**67**		**173**	**100.0%**	**0.32 [0.12, 0.82]**
Total events	1		39			

Heterogeneity: Tau² = 0.00; Chi² = 2.28, df = 7 (P = 0.94); I² = 0%
Test for overall effect: Z = 2.37 (P = 0.02)

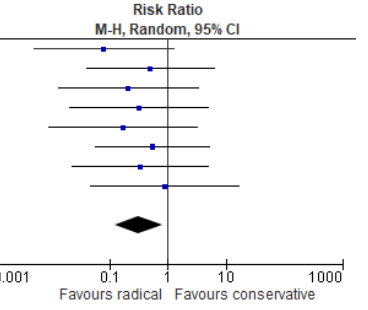
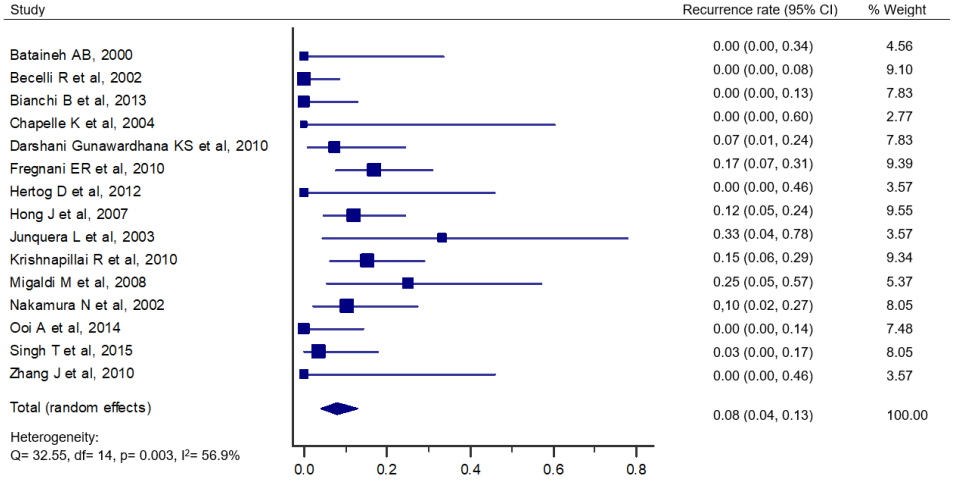
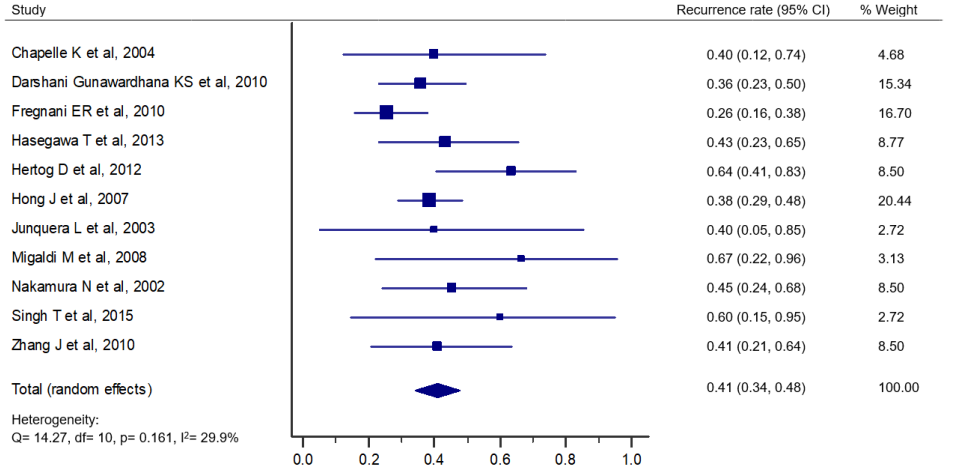


Figure 2. Funnel plots of the studies reporting the relative risk of the treatment: (A) solid/multicystic ameloblastoma and (B) unicystic ameloblastoma. Forest plots of random effects comparing the recurrence rates between the radical and the conservative approach: (C) solid/multicystic ameloblastoma and (D) unicystic ameloblastoma.

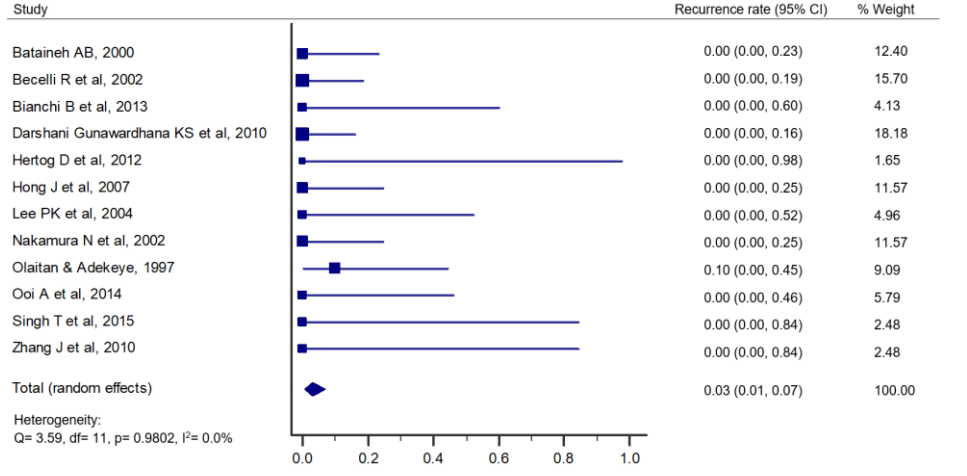
A


Study
Recurrence rate (95% CI)
% Weight
Bataineh AB, 2000 0.00 (0.00, 0.34) 4.56
Becelli R et al, 2002 0.00 (0.00, 0.08) 9.10
Bianchi B et al, 2013 0.00 (0.00, 0.13) 7.83
Chapelle K et al, 2004 0.00 (0.00, 0.60) 2.77
Darshani Gunawardhana KS et al, 2010 0.07 (0.01, 0.24) 7.83
Fregnani ER et al, 2010 0.17 (0.07, 0.31) 9.39
Hertog D et al, 2012 0.00 (0.00, 0.46) 3.57
Hong J et al, 2007 0.12 (0.05, 0.24) 9.55
Junquera L et al, 2003 0.33 (0.04, 0.78) 3.57
Krishnapillai R et al, 2010 0.15 (0.06, 0.29) 9.34
Migaldi M et al, 2008 0.25 (0.05, 0.57) 5.37
Nakamura N et al, 2002 0,10 (0.02, 0.27) 8.05
Ooi A et al, 2014 0.00 (0.00, 0.14) 7.48
Singh T et al, 2015 0.03 (0.00, 0.17) 8.05
Zhang J et al, 2010 0.00 (0.00, 0.46) 3.57
Total (random effects) 0.08 (0.04, 0.13) 100.00
Heterogeneity:
Q= 32.55, df= 14, p= 0.003, I²= 56.9%
0.0
0.2
0.4
0.6
0.8

B


Study
Recurrence rate (95% CI)
% Weight
Chapelle K et al, 2004 0.40 (0.12, 0.74) 4.68
Darshani Gunawardhana KS et al, 2010 0.36 (0.23, 0.50) 15.34
Fregnani ER et al, 2010 0.26 (0.16, 0.38) 16.70
Hasegawa T et al, 2013 0.43 (0.23, 0.65) 8.77
Hertog D et al, 2012 0.64 (0.41, 0.83) 8.50
Hong J et al, 2007 0.38 (0.29, 0.48) 20.44
Junquera L et al, 2003 0.40 (0.05, 0.85) 2.72
Migaldi M et al, 2008 0.67 (0.22, 0.96) 3.13
Nakamura N et al, 2002 0.45 (0.24, 0.68) 8.50
Singh T et al, 2015 0.60 (0.15, 0.95) 2.72
Zhang J et al, 2010 0.41 (0.21, 0.64) 8.50
Total (random effects) 0.41 (0.34, 0.48) 100.00
Heterogeneity:
Q= 14.27, df= 10, p= 0.161, I²= 29.9%
0.0
0.2
0.4
0.6
0.8
1.0

C


Study
Recurrence rate (95% CI)
% Weight
Bataineh AB, 2000 0.00 (0.00, 0.23) 12.40
Becelli R et al, 2002 0.00 (0.00, 0.19) 15.70
Bianchi B et al, 2013 0.00 (0.00, 0.60) 4.13
Darshani Gunawardhana KS et al, 2010 0.00 (0.00, 0.16) 18.18
Hertog D et al, 2012 0.00 (0.00, 0.98) 1.65
Hong J et al, 2007 0.00 (0.00, 0.25) 11.57
Lee PK et al, 2004 0.00 (0.00, 0.52) 4.96
Nakamura N et al, 2002 0.00 (0.00, 0.25) 11.57
Olaitan & Adekeye, 1997 0.10 (0.00, 0.45) 9.09
Ooi A et al, 2014 0.00 (0.00, 0.46) 5.79
Singh T et al, 2015 0.00 (0.00, 0.84) 2.48
Zhang J et al, 2010 0.00 (0.00, 0.84) 2.48
Total (random effects) 0.03 (0.01, 0.07) 100.00
Heterogeneity:
Q= 3.59, df= 11, p= 0.9802, I²= 0.0%
0.0
0.2
0.4
0.6
0.8
1.0

D

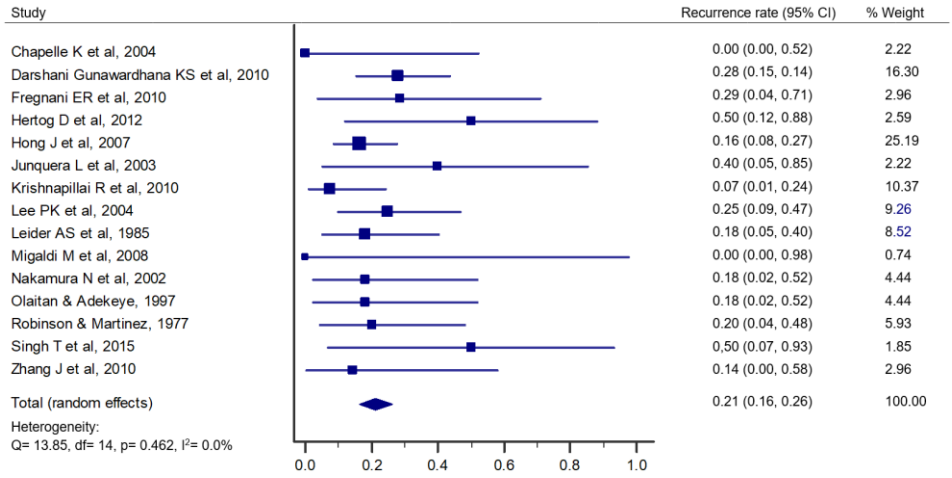


Figure 3. Forest plots of meta-analysis summarizing the recurrence rates of solid/multicystic ameloblastoma: (A) the radical approach and (B) the conservative approach, and of unicystic ameloblastoma: (C) the radical approach and (D) the conservative approach.

DISCUSSION

Although ameloblastoma is considered a benign tumor, it is locally invasive and has a high rate of recurrence if not adequately removed[7,20]. Management of ameloblastoma is still controversial. Various treatment methods of ameloblastoma have been suggested in relation to many factors, such as the tumor type and clinical presentation. Unicystic ameloblastomas are usually treated conservatively with curettage, enucleation, and cryosurgery while solid or multicystic ameloblastomas are usually treated with radical surgery that often requires plate reconstruction or more extensive reconstructive surgery[15,27,28].

In the present study, we performed a systematic review and meta-analysis to assess the recurrence rates of radical and conservative treatment approaches of solid or multicystic and unicystic ameloblastoma. Of the 43 articles submitted to full-text analysis, 20 studies met the eligibility criteria and were included in this final review. All the included studies were retrospective without mention of randomization. Only a few studies were found with the high level of scientific evidence based on the criteria of QACSS. This may be explained by the difficulty of conducting randomized controlled trials on the treatment of ameloblastoma due to several factors such as the heterogeneity in the treatment procedures, the difference in the quality of operating techniques, lack of resources (time, costs, number of patients), and problems with ethics.

We found the pooled recurrence rate for solid ameloblastomas was 8 % after radical, and 41% after conservative treatment. For unicystic ameloblastomas, these values were 3% and 21% respectively. The risk of recurrence following radical compared to conservative treatment in solid or multicystic type was lower. These results are consistent with the previous systematic review by Antonoglou and Sandor[9].

The meta-analysis also showed the lower risk of recurrence of unicystic ameloblastomas in radical treatment compared to conservative treatment. To the best of our knowledge, this present study is the first review to assess the comparison between radical versus conservative treatment of unicystic ameloblastomas using the risk ratio of recurrence.

The pooled recurrence rates in solid or multicystic ameloblastomas compared to unicystic ameloblastomas were higher following conservative as well as following radical treatment. This may indicate that the solid or multicystic type behaves more aggressive than the unicystic type. These results are in line with several other reviews[29–31]. Therefore, the treatment of ameloblastoma especially for solid or multicystic type should consist of segmental resection with adequate margins.

Even though our results favor radical treatment for both unicystic and solid or multicystic ameloblastomas, appropriate and careful consideration of several factors such as age and clinical presentation is required in determining the treatment option for the patient to get the best result while preventing over-treatment. In children, for instance, a conservative approach may be preferred in order to not impair facial growth and to avoid psychological, functional, and aesthetic effects after the surgery. In this case, the conservative treatment with decompression or enucleation with the application of Carnoy's solution might be a good alternative[10,31]. One important component in postoperative follow-up is whether the patient has any complications or not. Unfortunately, we could not address this issue in the present study because of the lack of studies containing information on complications.

This study has several limitations. Several parameters we would have liked to include were not or inadequately reported in the studies. For example, we could not consider the quality of life in the included studies. Also, we could not assess the adequacy of follow-up time or the description of follow-up period of the study included which can affect the validity of the study. Moreover, we could not assess when a recurrence occurred after treatment of ameloblastoma since only very limited information could be extracted from the included studies. Finally, only retrospective series case studies were available and analyzed in this study, and this design is

considered to have a low level of scientific evidence based on the criteria of QACSS. However, despite the fact that this is the only design found on the topic, we are nevertheless convinced that important conclusions on the treatment and recurrence rates of ameloblastoma can be drawn from the present systematic review and meta-analysis as the results of the review are based on the best available evidence. Further larger and prospective studies with greater methodological aspects and rigor in data collection, analysis, and reporting, as well as long-term postoperative follow-up periods with information on complications, are needed.

CONCLUSION

The present systematic review and meta-analysis showed statistically significant results favoring radical treatment for both unicystic and solid or multicystic ameloblastoma. The solid or multicystic ameloblastoma may behave more aggressively than the unicystic ameloblastoma based on the recurrence rates. The evidence of the results is limited since only retrospective studies were available.

Acknowledgements

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Supplementary Information

Supplementary table 1. Articles excluded and the reasons for their exclusion.

Articles excluded	Reason for exclusion
Arotiba et al. (1997)	No data about histopathological type
Chana et al. (2004)	
Chung et al. (1969)	
Franca et al. (2012)	
Fung (1978)	
Hammarfjord et al (2013)	
Hatada et al. (2001)	
Pandya et al. (1972)	
Potdar et al. (1969)	
Sehdev et al. (1974)	
Keszler et al. (1996)	No data about recurrence rate
Chawla et al. (2013)	No data regarding histopathological type in the treatment approach
Pinsolle et al. (1995)	
Sampson & Pogrel (1999)	
Takata et al. (1999)	
Vayvada et al. (2006)	
Adebayo et al. (2005)	No data regarding histopathological type in the treatment approach and recurrence
Akinosi et al. (1969)	
Chidzonga et al. (1996)	
Milman et al. (2016)	
Siar et al. (2012)	
Curi et al. (1997)	Study with the same population as another study included
Al-Khateeb & Ababneh (2003)	Study with the same population as another study included and treatment of children and adolescents only

Supplementary table 2. Treatment modality of solid/multicystic ameloblastoma.

Study	Total cases	Included cases	Solid/ Multicystic cases	Treatment Modality & Recurrence																														
				Radical Treatment									Conservative Treatment																						
				MR	Rec	%	SR	Rec	%	D	Rec	%	E	Rec	%	E+ Carn	Rec	%	C	Rec	%	M+E+ C	Rec	%	E+C	Rec	%	M+E	Rec	%	C+ Cryo	Rec	%
Bataineh, 2000	23	23	9				9	0	0.0																									
Becelli et al., 2002	60	60	42	27	0	0.0	15	0	0.0																									
Bianchi et al., 2013	31	31	27				27	0	0.0																									
Chapelle et al., 2004	19	19	14	2	0	0.0	2	0	0.0				6	3	50.0	4	1	25.0																
Darshani Gunawardhana et al., 2010[b]	286	147	83										56	20	35.7																			
Fregnani et al., 2010	121	120	113				47	8	17.0										19	3	15.8										47	14	29.8
Hasegawa et al., 2013	23	23	23										10	4	40.0										7	2	28.6	6	4	66.7			
Hertog et al., 2012[a]	35	35	28										22	14	63.6																		
Hong et al., 2007[b]	239	234	154	32	5	15.6	18	1	5.6																									
Junquera et al., 2003	22	16	11	1	1	100	4	1	25.0	1	0	0.0													5	2	40.0						
Krishnapillai et al., 2010	73	73	46	46	7	15.2																												
Nakamura et al., 2002[a]	78	75	51																			14	8	57.1	8	2	25.0						
Ooi et al., 2014	30	30	24				24	0	0.0																									
Zhang et al., 2010[b]	37	37	28				6	0	0.0																									
Total	1077	923	653	108	13	12.0	152	10	6.6	1	0	0.0	94	41	43.6	4	1	25.0	19	3	15.8	14	8	57.1	20	6	30.0	6	4	66.7	47	14	29.8

Rec, Recurrence; %, Recurrence rate; MR, Marginal Resection; SR, Segmental Resection; D, Disarticulation; E, Enucleation; Carn, Carnoy's solution; C, Curettage; M+E+C, Enucleation and Curettage after Marsupialization; M+E, Enucleation after Marsupialization; Cryo, Cryotherapy.

[a] Not specifying the modality of radical treatment.

[b] Not specifying the modality of conservative treatment.

Supplementary table 3. Treatment modality of unicystic ameloblastoma.

Study	Total cases	Included cases	Unicystic cases	Treatment Modalilty & Recurrence																																
				Radical Treatment									Conservative Treatment																								
				MR	Rec	%	SR	Rec	%	FR	Rec	%	M	Rec	%	E	Rec	%	E+ Carn	Rec	%	C	Rec	%	E/C	Rec	%	M+ E+C	Rec	%	E+C	Rec	%			
Bataineh, 2000	23	23	14				14	0	0.0																											
Becelli et al., 2002	60	60	18	18	0	0.0																														
Bianchi et al., 2013	31	31	4				4	0	0.0																											
Chapelle et al., 2004	19	19	5													1	0	0.0	4	0	0.0														
Darshani Gunawardhana et al., 2010 [a]	286	147	64													43	12	27.9																	
Fregnani et al., 2010	121	120	7																			7	2	28.6											
Hertog et al., 2012 [a]	35	35	7													6	3	50.0																	
Hong et al., 2007 [b]	239	234	80	10	0	0.0	3	0	0.0																											
Junquera et al., 2003	22	16	5																														5	2	40.0
Krishnapillai et al., 2010	73	73	27																						27	2	7.4								
Lee et al., 2004 [a]	29	29	29													2	2	100	22	4	18.2														
Leider et al., 1985	33	22	22																						22	4	18.2								
Nakamura et al., 2002 [a]	78	75	24										3	0	0.0													8	2	25.0					
Olaitan & Adekeye, 1997	21	21	21	5	1	20.0				5	0	0.0				11	2	18.2																	
Ooi et al., 2014	30	30	6				6	0	0.0																											
Robinson & Martinez, 1977	20	15	15													15	3	20.0																	
Zhang et al., 2010 [b]	37	37	9				2	0	0.0																											
Total	1157	987	357	33	1	3.0	29	0	0.0	5	0	0.0	3	0	0.0	78	22	28.2	26	4	15.4	7	2	28.6	49	6	12.2	8	2	25.0	5	2	40.0		

Rec, Recurrence; %, Recurrence rate; MR, Marginal Resection; SR, Segmental Resection; FR, Full-thickness Resection; M, Marsupialization; E, Enucleation; Carn, Carnoy's solution; C, Curettage; M+E+C, Enucleation and Curettage after Marsupialization.

[a] Not specifying the modality of radical treatment.

[b] Not specifying the modality of conservative treatment.

CHAPTER 5

A network meta-analysis assessing the effectiveness of various radical and conservative surgical approaches regarding recurrence in treating solid/multicystic ameloblastomas

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ABSTRACT

Multiple treatment approaches have been undertaken to reduce the incidence of recurrence in solid/multicystic ameloblastoma (SMA), both conservative and radical. A network meta-analysis (NMA) was conducted to assess and compare the effectiveness of these various treatment approaches concurrently. This study was reported based on the Preferred Reporting Items for Systematic Reviews for Network Meta-Analysis (PRISMA-NMA) statement. PubMed (MEDLINE), ScienceDirect, Scopus, and Web of Science were searched until August 10, 2021. The NMA was conducted using the STATA program. Of 1153 records identified in the search, seven observational studies with 180 patients were included. Six different treatment approaches were identified. Segmental resection ranked highest for reducing the recurrence rate with the highest SUCRA score (77.7), followed by curettage with cryotherapy (66.9) and marginal resection (49.3). Network inconsistencies and publication bias appeared to be absent. According to the Confidence in Network Meta-Analysis (CINeMa) method, the evidence's certainty was low for all comparisons due to imprecision and within-study bias. In conclusion, this study is the first NMA in the field of ameloblastoma. Segmental resection seemed to be the most effective treatment approach for minimizing recurrence in SMA patients. Nevertheless, weak certainty of evidence makes that the results must be regarded with caution.

Keywords: ameloblastoma; treatment; recurrence; network meta-analysis; multicystic ameloblastoma

INTRODUCTION

Ameloblastoma is a rare benign odontogenic tumor of epithelial origin that makes up around 10% of all tumors in the jaws. Despite being considered benign, ameloblastoma has a locally invasive development. Around 70% of cases progress to malignancy, and up to 2% of cases spread to other organs[1,2]. Ameloblastoma is classified into three types according to the 2017 World Health Organization (WHO) classification of benign epithelial odontogenic tumors: ameloblastoma (solid/multicystic/conventional ameloblastoma), unicystic ameloblastoma, and peripheral ameloblastoma[3].

Solid/multicystic ameloblastoma (SMA) is the most prevalent type and appears more aggressive than other types based on recurrence rates[4,5]. SMAs mostly occur in the posterior mandible of patients aged 30-40 years, without gender or ethnicity preference[6,7]. The most common histopathological pattern of SMA is follicular, followed by plexiform and other rare patterns: acanthomatous, desmoplastic, basaloid, and granular[8].

The main treatment is surgery, which may be classified into two modalities: radical and conservative. Radical surgical approaches include *en bloc* or marginal and segmental resections with wide (1-2 cm) safety bone margins. Conservative surgical approaches consist of enucleation, curettage, and marsupialization, followed by additional treatment, such as peripheral ostectomy, cryotherapy, or Carnoy's solution[9–11]. Our previous systematic review and meta-analysis discovered that the radical approach is the treatment of choice for SMA patients due to a reduced recurrence rate[5]. However, it usually requires reconstructive procedures and greatly affects the patient's quality of life after surgery. Contrarily, conservative therapy can minimize operating time while maintaining the patient's quality of life, however, associated with a high incidence of recurrence[12,13].

Besides our previous study[5], there have also been several systematic reviews and meta-analyses that compare radical treatment versus conservative treatment in SMA patients[6,7,14–16]. Still, no studies have compared several (more than two) approaches of each modality simultaneously and specifically due to the limitations of conventional meta-analysis methods that can only compare a pair of interventions. In recent years, a popular and increasingly recognized technique has been developed to overcome this problem, which is an advanced form of paired meta-analysis called network meta-analysis (NMA)[17].

NMA is the best method of compiling evidence and selecting the most valuable treatment from many studies that compare numerous interventions. It can estimate direct and indirect

comparative efficacies and provide a ranking among all interventions. Moreover, integrating both direct and indirect evidence can produce more precise estimates[17–20]. Hence, by implementing this new method in the present study, we aim to evaluate the efficacy of various radical and conservative surgical approaches in terms of recurrence rate for the treatment of SMA patients.

MATERIAL AND METHODS

Protocol registration

This NMA was conducted according to PRISMA for Network Meta-analyses (PRISMA-NMA) Guidelines[21]. The protocol was registered on PROSPERO (ID: CRD42021271539).

Research question and eligibility criteria

We planned to investigate and answer the following research question: "Which radical and conservative treatment approach results in lower recurrence rates in SMA patients?". The following eligibility criteria were used: Participants(P): Human patients with primary SMA. Interventions(I): Radical surgical approaches (segmental resection, marginal resection) and conservative surgical approaches (enucleation, curettage, the combination between them, and with or without adjuvant therapy). Comparators(C): All interventions (surgical approaches) will be compared with each other. Outcome(O): Recurrence rate. Study design(S): Randomized/non-randomized controlled trials and observational studies that compared at least two interventions (surgical approaches). Case reports and reviews were excluded.

The exclusion criteria were: recurrent SMA treatment; former marsupialization or decompression, irradiation, or prior therapy at a different facility than the one where the research was conducted; unicystic, peripheral, and metastasizing ameloblastomas; a follow-up duration is not stated; non-English languages studies; in vitro and animal studies, reviews, case reports, and case series with fewer than 10 participants.

Searches and information sources

PubMed (MEDLINE), Scopus, ScienceDirect, and Web of Science databases were used to search the articles published up to August 2021 (date of the last search: August 10, 2021), utilizing a combination of search phrases: "ameloblastoma", "radical OR conservative", and "recurrence OR relapse". Furthermore, manual searches of the articles' reference list were conducted to

locate more relevant publications not found in the databases. The details of the search strategy are presented in Supplementary Table 1.

Study selection, data selection process, and data items

Two independent reviewers (F.N.H. & M.N.H.) conducted the article selection process blinded to each other. Disagreements among the reviewers were settled through discussion. A third reviewer (T.F.) was consulted if necessary. The search histories were saved and exported to the reference management program (Mendeley Desktop, Version 1.19.8). Duplicate records were removed afterwards.

In the first stage of screening process, titles and abstracts from remaining records were screened for possible inclusion. In the second stage, the full text of the articles was screened for final inclusion. Studies with no full-text available or data that was incomplete or ambiguous were omitted.

Author, publication year, study country or region, study design, demographic data of participants, tumor and histopathologic type, treatment modality, recurrences linked to the treatment method, and post-operative follow-up period were extracted from full-text articles using a data extraction form and stored in Microsoft Excel program for each study. We also checked for information regarding adjuvant therapy given to primary SMA patients in all included studies, but none provided such information.

Interventions of interest

The interventions of interest were the first and primary surgical treatments of SMA patients, divided into radical and conservative approaches. The radical approach consists of segmental resection, marginal resection, hemimandibulectomy, or total mandibulectomy. The conservative approach includes enucleation, enucleation plus curettage, enucleation with Carnoy's solution, enucleation plus cryotherapy, enucleation plus peripheral ostectomy, curettage, curettage plus cryotherapy, other or a combination of the previous.

Outcome of interest

The primary outcome of interest was a recurrence, defined as ameloblastoma coming back at the original site or a distant location.

Quality assessment

Risk of bias in non-randomized studies-of exposure (ROBINS-E)[22] tool was used to assess the risk of bias within studies. This tool sets seven domains of bias: confounding, measurement of the exposure, selection of participants, post-exposure interventions, missing data, measurement of the outcome, and selection of the reported result. The assessment was graded as low risk, medium risk (some concerns), or high risk. For the overall risk of bias results, the studies were classified as low risk if all domains are at low risk except for concerns in the confounding domain, as medium risk if at least one domain is at some concerns but no domains are at high risk, and as high risk if at least one domain is at high risk of bias. The results were displayed as the risk of bias graph and summary using RevMan 5.4 program (Review Manager. The Cochrane Collaboration, 2020).

To assess the certainty of evidence in network meta-analysis, the Confidence in Network Meta-Analysis (CINeMA) web tool was employed, which evaluated the following aspects: within-study bias, indirectness, imprecision, heterogeneity, incoherence, and reporting bias. For each comparison, the confidence level was rated as high, moderate, low, or very low[23–25].

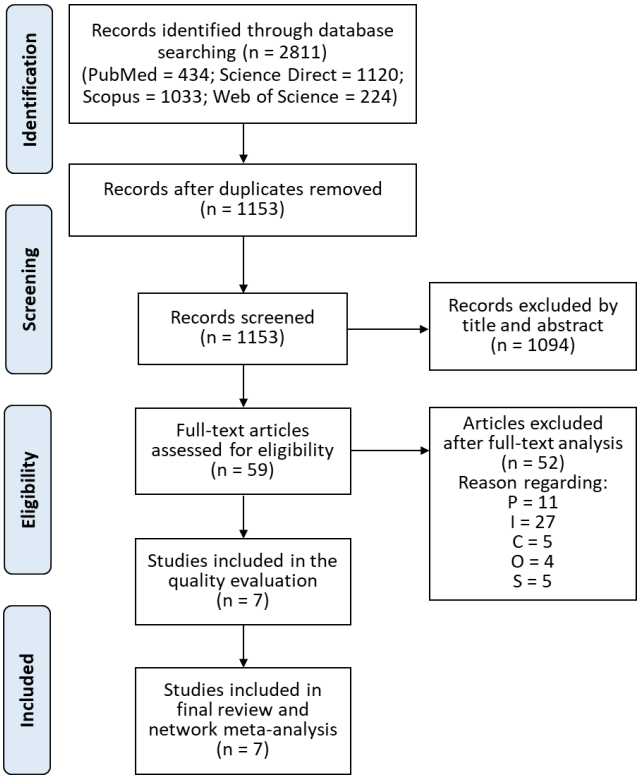

Figure 1. The study selection process diagram.

Strategy for data synthesis

A network meta-analysis was conducted using mvmeta and network packages in Stata program (Stata SE. Version 16.0. StataCorp LLC. College Station, TX, USA)[26]. We estimated the odds ratios (ORs) with 95% confidence intervals (CIs) for each comparison and displayed the results in the interval plot or network league table. The geometry of the treatment network was shown visually via the network map or diagram.

Inconsistency was assessed through two stages. The first is to test overall inconsistency globally using the design-by-treatment interaction model, calculated using the Wald test. The second is to use the loop-specific approach, which evaluates inconsistencies separately in each closed loop of network interventions. The inconsistency factor (IF) is assessed in each loop as the absolute difference between direct and indirect estimations for one of the loop's comparisons. A 95% CI and a z-test for IF were also calculated. Loops with statistically significant inconsistency are those in which the lower CI limit of the IF does not reach zero. If inconsistencies are detected, sensitivity and meta-regression analyses are used to explore potential inconsistency causes[20,26–28].

We evaluated the potential publication bias using a net funnel plot[29]. The surface under the cumulative ranking (SUCRA) curve was used to rank the treatment approach and plotted the results in rankogram to identify which treatment approach is the best[30].

RESULTS

Study selection and characteristics

A total of 2811 records were found in multiple databases throughout the search. We screened 1153 records by titles and abstracts after eliminating duplicates. A total of 59 articles were considered for full-text screening, with 23 of them being eliminated later. The reasons for article exclusion are listed in Supplementary Table 2. Subsequently, seven studies[31–37] with 180 SMA patients and 38 recurrences from several countries in Europe, Asia, North America, and South America were included in the quality evaluation and incorporated in the review and network meta-analysis. Figure 1 depicts the study selection procedure. All studies included were retrospective cohort studies. The mean age of patients was approximately 36.8 years. The follicular pattern was the most common histopathological subtype (37%), followed by the plexiform pattern (34.7%). There were several surgical approaches to radical treatment, such

as segmental resection (SR) and marginal resection (MR); as well as conservative treatment options such enucleation, enucleation and curettage (ENCU), enucleation with the Carnoy's solution (ECS), and curettage with cryotherapy (CCR). Table 1 summarizes the characteristics of the studies that were included.

Table 1. The characteristics of the studies that were included.

Study & Country	Number of SMA	Age of patients	Treatment approach	Recurrence	Histopathological subtype (recurrence)	Follow-up period
Chapelle et al. 2004[31] Netherlands	14	Median: 43 years (17-77)	Segmental resection = 2 Marginal resection = 2 Enucleation + Carnoy's solution = 4 Enucleation = 6	0 0 1 3	Follicular = 7 (2) Plexiform = 2 (0) Follicular + Plexiform = 5 (2)	Mean: 8.8 years (1-20 years)
Curi et al. 1997[32] Brazil	36	Mean: 31 years	Marginal resection = 5 Curettage + Cryotherapy = 31	2 9	NA	Mean: 62 months (14 months – 18 years)
Hasegawa et al. 2013[33] Japan	17[a]	Mean: 38.8 years	Enucleation + Curettage = 7 Enucleation = 10	2 4	Follicular (3) Plexiform (2) Desmoplastic (1)	8 - 130 months
Hong et al. 2007[34] South Korea	51[b]	Mean: 34.5 years	Segmental resection = 19 Marginal resection = 32	1 5	Follicular = 15 (3) Plexiform = 21 (0) Acanthomatous = 9 (2) Granular cell = 5 (1) Desmoplastic = 1 (0)	More than 1 year
Junquera et al. 2003[35] Spain	12	Mean: 44.5 years	Segmental resection = 5 Marginal resection = 2 Enucleation + Curettage = 5	1 1 2	Follicular = 5 (1) Plexiform = 4 (1) Acanthomatous = 1 (1) Granular cell = 1 (1) Desmoplastic = 1 (0)	2 - 23 years
Nakamura et al. 2002[36] Japan	40[a]	Mean: 34.1 years	Segmental resection = 25 Marginal resection = 4 Enucleation + Curettage = 11	3 0 2	Follicular = 13 (2) Plexiform = 16 (1) Follicular + Plexiform = 8 (2) Desmoplastic = 3 (0)	More than 5 years
Petrovic et al. 2018[37] USA	10	Median: 61.5 years (19-81)	Segmental resection = 9 Marginal resection = 1	2 0	Follicular = 7 (1) Plexiform = 1 (0) Acanthomatous = 1 (1) Granular cell = 1 (0)	Mean: 69.2 months (1-196 months)
Total	180		180	38		

[a] Treatment with marsupialization was excluded.
[b] Conservative treatment was excluded because the approach was not specified.
SMA: solid/multicystic ameloblastoma.
NA: Not available

Risk of bias in individual studies

For the overall risk of bias, all the studies had a medium risk of bias. Regarding the domain assessment, all the studies had some concerns in confounding and post-exposure intervention domains. They had a low risk of bias at missing data and measurement of the exposure and outcome domains. Two studies had some concerns about selecting participants, and three had concerns about selecting the reported result. Figure 2 shows the risk of bias graph and summary of the studies that were included.

Network geometry and inconsistency

Ten direct pairwise comparisons of treatment approaches were available in the network map. The most common comparators were MR, SR, and enucleation, respectively. The number of studies in each treatment comparison were SR vs. MR (5), MR vs. ENCU (2), SR vs. ENCU (2), MR vs. CCR (1), MR vs. ECS (1), enucleation vs. ENCU (1), SR vs. enucleation (1), enucleation vs. ECS (1), SR vs. ECS (1), and MR vs. enucleation (1). Furthermore, 15 indirect pairwise comparisons were made. The network map of treatment approach comparisons is shown in Figure 3. For inconsistency in the network, five closed loops were identified, including the treatment approaches of ECS, enucleation, ENCU, MR, and SR. These loops had acceptable IF values, and the overall *p*-value for network inconsistency was 0.96, which meant no violation of the consistency assumption for direct and indirect estimates (Supplementary Table 3).

Figure 2. Risk of bias graph & risk of bias summary of individual studies.

Network meta-analysis outcome

The network league of treatment approach comparisons is presented in Table 2. Compared to enucleation only, the odds ratio (OR) of recurrence rate for SR, CCR, MR, ENCU, and ECS were 0.22 (95% confidence interval (CI), 0.03 – 1.43), 0.24 (95% CI, 0.01 – 3.98), 0.39 (95% CI, 0.05 – 2.95), 0.47 (95% CI, 0.09 – 2.59), and 0.48 (95% CI, 0.05 – 5.05) respectively. Compared to ECS, OR of SR, CCR, MR, and ENCU were 0.45 (95% CI, 0.03 – 6.31), 0.50 (95% CI, 0.02 – 13.96), 0.81 (95% CI, 0.05 – 12.12), and 0.97 (95% CI, 0.07 – 13.67) consecutively. Compared to ENCU, OR of SR, CCR, and MR were 0.46 (95% CI, 0.12 – 1.81), 0.51 (95% CI, 0.04 – 6.60), and 0.83 (95% CI, 0.16 – 4.37) respectively. Compared to MR, OR of SR and CCR were 0.56 (95% CI, 0.14 – 2.20) and 0.61 (95% CI, 0.09 – 4.31). Comparison of SR with CCR had an OR of 0.91 (95% CI, 0.08 – 9.86).

Based on SUCRA values, SR had the highest mean rank (2.1) for lowering the recurrence rate (SUCRA score 77.7) in the rankogram, followed by CCR (SUCRA score 66.9) and MR (SUCRA score 49.3). The SUCRA value and the rankogram for the ameloblastoma treatment approach network are shown in Table 3 and Figure 4. The relative ranking of treatments using the multidimensional scaling (MDS) approach showed the same results that segmental resection was the best treatment approach to reduce the incidence of recurrence (Supplementary Figure 1).

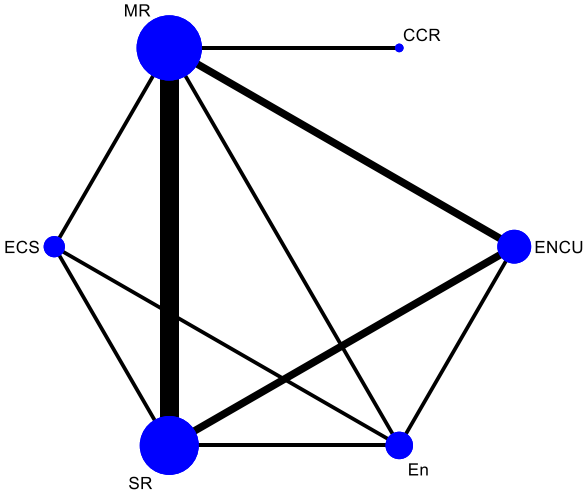

Figure 3. Network map of treatment approach comparisons. The size of the nodes describes the total sample size of treatment approaches. The thickness of the lines correlates to the number of studies that are compared. CCR = Curettage + Cryotherapy, ECS = Enucleation + Carnoy's solution, En = Enucleation, ENCU = Enucleation + Curettage, MR = Marginal resection, SR = Segmental resection.

Table 2. Network league of treatment approach comparisons for recurrence outcome using Odds Ratio (OR) to measure the effect size.

SR					
0.91 (0.08,9.86)	CCR				
0.56 (0.14,2.20)	0.61 (0.09,4.31)	MR			
0.46 (0.12,1.81)	0.51 (0.04,6.60)	0.83 (0.16,4.37)	ENCU		
0.45 (0.03,6.31)	0.50 (0.02,13.96)	0.81 (0.05,12.12)	0.97 (0.07,13.67)	ECS	
0.22 (0.03,1.43)	0.24 (0.01,3.98)	0.39 (0.05,2.95)	0.47 (0.09,2.59)	0.48 (0.05,5.05)	En

*CCR = Curettage + Cryotherapy, ECS = Enucleation + Carnoy's solution, En = Enucleation, ENCU = Enucleation + Curettage, MR = Marginal resection, SR = Segmental resection.

Publication bias and evidence's certainty

Publication bias or risk of bias across studies was unlikely to be detected, as indicated by the symmetrical funnel plot (Supplementary Figure 2). The certainty of the evidence was low for all comparisons due to imprecision and within-study bias. The imprecision occurs because the confidence intervals of all pairwise treatment comparisons include a value of one, which indicates no difference in effect between the two treatments. Supplementary Table 4 shows the confidence ratings for the treatment approach comparisons.

DISCUSSION

To our knowledge, this is the first NMA of ameloblastoma treatment. Our prior systematic review found a higher recurrence rate in SMA patients with the conservative treatment approach than with the radical approach[5]. Nevertheless, even within conservative and radical treatments, approaches vary widely. By using the NMA method, we wanted to analyse in more detail what the best treatment modality of those various approaches (four types of conservative and two types of radical treatment) was in reducing the recurrence rate of SMA. Of 1153 records identified in the search, seven observational studies with 180 patients were included. We found that based on the network league and rankogram results, segmental resection ranked highest for reducing the recurrence rate with the highest SUCRA score (77.7), followed by curettage with cryotherapy (66.9) and marginal resection (49.3). Enucleation appeared the worst to reduce the recurrence rate in SMA patients. However, the confidence interval of all treatment approach comparisons includes one, which means the results are not statistically significant. This, coupled with the low certainty of the evidence, makes the results obtained need to be interpreted with caution.

SR is a radical surgical approach with discontinuity of the jawbone. This approach is usually accompanied by immediate or delayed bone repair with tissue grafts and prosthesis rehabilitation to aid speech and mastication in post-operative patients[10,34,38,39]. The results of this present study are in line with several reviews that state that SR is the preferred treatment for preventing SMA recurrence[40–42]. The meta-analysis of Almeida et al.[6] also showed that SR appeared to be better than MR at reducing recurrence rates for SMA patients. However, the results were not statistically significant owing to a scarcity of samples or studies.

Considering the results of the SUCRA scores and the relative ranking of treatments, the best treatment approach after SR is CCR, a combination of conservative surgical modalities. Cryotherapy is an additional treatment approach that uses freezing to eradicate remaining tumor cells by inducing cellular necrosis while preserving the inorganic osseous structure[43–45]. These results indicate that the combination of conservative treatments still has the potential to be used in SMA patients, especially for those in which treatments are not possible or have contraindications for getting radical treatment. Examples are elderly patients who are physically weak and vulnerable[46,47], or pediatric patients who require consideration of several other factors such as the occurrence of dysfunction, deformity, impaired growth of the face, as well as psychological effects after surgery[48,49]. These results also show that combining several conservative treatment approaches is still better at reducing the recurrence rate than using a single conservative approach. This is consistent with several reviews which state that using a single conservative approach such as simple enucleation is not recommended for SMA patients. Although this procedure has a low morbidity rate and provides outstanding aesthetic and functional outcomes, its drawback is the high recurrence rate (60-80%)[42,50].

The high rate of ameloblastoma recurrence after treatment is still a major issue today. This recurrence rate is correlated to several factors, including the type of genetic mutation, the ameloblastoma variant based on its histopathology, and the treatment method[12,51,52]. SMA, the most common and aggressive variant of ameloblastoma, was significantly correlated with recurrence, especially for the follicular pattern with acanthomatous and basal cell alterations[53].

This NMA includes seven studies that matched the eligibility criteria, all of which were retrospective cohort studies. The rare incidence of ameloblastoma (with a 0.9 per million annual incidence rate)[54] with slow-growing characteristics accompanied by the recommendation for a post-treatment follow-up period of more than five years, makes it

difficult for researchers to conduct prospective studies or randomized clinical trials (RCT) on the treatment of ameloblastoma. Not surprisingly, until now, there has not been a single RCT in this field.

Table 3. The SUCRA value of each ameloblastoma treatment approach with regard to the recurrence rate.

Treatment	SUCRA	PrBest	MeanRank
En	17.3	1.2	5.1
CCR	66.9	37.4	2.7
ECS	45.1	17.3	3.7
ENCU	43.7	4.9	3.8
MR	49.3	4.2	3.5
SR	77.7	35.0	2.1

*CCR = Curettage + Cryotherapy, ECS = Enucleation + Carnoy's solution, En = Enucleation, ENCU = Enucleation + Curettage, MR = Marginal resection, SR = Segmental resection.

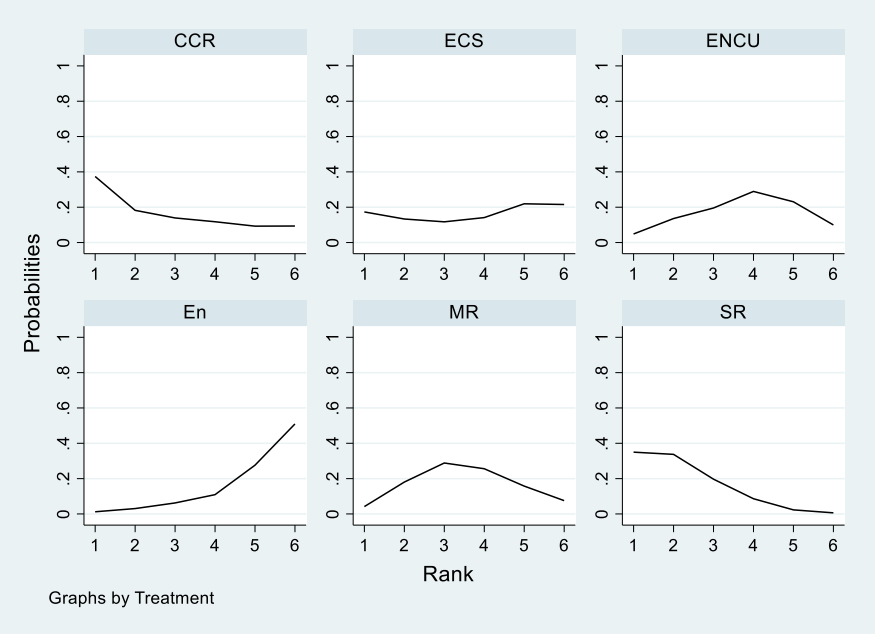

Figure 4. Rankograms for the ameloblastoma treatments network showing the probability of every treatment being in a particular order. CCR = Curettage + Cryotherapy, ECS = Enucleation + Carnoy's solution, En = Enucleation, ENCU = Enucleation + Curettage, MR = Marginal resection, SR = Segmental resection.

Several limitations were found in this present study. Firstly, our review includes only a small number of studies with relatively small sample sizes yielding many analyses having low confidence in their results. Secondly, only retrospective cohort studies were included and analyzed in this study, the design of which provides a low degree of scientific evidence based on the Oxford Centre for Evidence-Based Medicine's standards[55,56]. Furthermore, we could

not account for any confounding factors within studies that may have affected the outcome with that design. Lastly, only English-language literature was searched.

Conclusions

Our network meta-analysis showed SR seemed to be the best treatment approach for reducing recurrence in SMA patients. If radical treatment is not feasible for the patient, conservative treatment with multiple approaches, such as CCR, is indicated. However, the certainty of confidence in the results is still considered weak. Therefore, further studies with optimal methodological standards and long post-operative follow-up duration are needed to strengthen the evidence.

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Supplementary Information

Supplementary Table 1. Search strategy and search results details.

Database	Search Query	Date	Number of Results
PubMed (Medline)	ameloblastoma AND (radical OR conservative OR resection) AND (recurrence OR relapse) ("ameloblastoma"[MeSH Terms] OR "ameloblastoma"[All Fields] OR "ameloblastomas"[All Fields]) AND ("radical"[All Fields] OR "radical s"[All Fields] OR "radicals"[All Fields] OR ("conservancies"[All Fields] OR "conservancy"[All Fields] OR "conservancy s"[All Fields] OR "conservation"[All Fields] OR "conservational"[All Fields] OR "conservations"[All Fields] OR "conservative"[All Fields] OR "conservatively"[All Fields] OR "conservatives"[All Fields] OR "conserve"[All Fields] OR "conserved"[All Fields] OR "conserves"[All Fields] OR "conserving"[All Fields]) OR ("resect"[All Fields] OR "resectability"[All Fields] OR "resectable"[All Fields] OR "resectates"[All Fields] OR "resected"[All Fields] OR "resecting"[All Fields] OR "resection"[All Fields] OR "resectional"[All Fields] OR "resectioned"[All Fields] OR "resectioning"[All Fields] OR "resections"[All Fields] OR "resective"[All Fields] OR "resects"[All Fields])) AND ("recurrance"[All Fields] OR "recurrence"[MeSH Terms] OR "recurrence"[All Fields] OR "recurrences"[All Fields] OR "recurrencies"[All Fields] OR "recurrency"[All Fields] OR "recurrent"[All Fields] OR "recurrently"[All Fields] OR "recurrents"[All Fields] OR ("recurrence"[MeSH Terms] OR "recurrence"[All Fields] OR "relapse"[All Fields] OR "relapses"[All Fields] OR "relapsing"[All Fields] OR "relapsed"[All Fields] OR "relapser"[All Fields] OR "relapsers"[All Fields]))	10-Aug-21	434
ScienceDirect	ameloblastoma AND (radical OR conservative OR resection) AND (recurrence OR relapse)	10-Aug-21	1120
Scopus	ameloblastoma AND (radical OR conservative OR resection) AND (recurrence OR relapse)	10-Aug-21	1033
Web of Science	ameloblastoma AND (radical OR conservative OR resection) AND (recurrence OR relapse)	10-Aug-21	224
		TOTAL	2811

Supplementary Table 2. The reasons for the excluded studies.

Reason for exclusion	Articles excluded
No data about the histopathological type	Saraiya 2020; Adeel et al. 2018; Hammarfjord et al. 2013; Chaine et al. 2009; Chana et al. 2004; Arotiba et al. 1997; Olaitan & Adekeye 1996; Olaitan et al. 1993; Muller & Slootweg 1985; Holland & Mellor 1991; Adekeye 1980
Failure to differentiate histopathological type regarding treatment used	Goh et al. 2021; Hresko et al. 2021; Okechi et al. 2020; Menon et al. 2019; Au et al. 2019; Laborde et al. 2017; Milman et al. 2016; Franca et al. 2012; Li et al. 2012; Dandriyal et al. 2011; Rastogi et al. 2010; Escande et al. 2009; Sammartino et al. 2007; Adebayo et al. 2005; Hatada et al. 2001; Sampson & Pogrel 1999; Chidzonga et al. 1996; Pinsolle et al. 1995; Ueno et al. 1989; Sehdev et al. 1974
Not specifying the treatment approach	Goh et al. 2021; Hresko et al. 2021; Singh et al. 2015; Ghandhi et al. 2006;
Only one type of treatment used	Haq et al. 2016; Ooi et al. 2014; Carneiro et al. 2014; Bianchi et al. 2013; Bataineh 2000; Vedtofte et al. 1978
Recurrence is unclear regarding the type of treatment	Vongsa et al. 2013; Zhang et al. 2010; Molla et al. 1991
Recurrence is unclear regarding the treatment of the primary tumor	Hertog et al. 2012; Fregnani et al. 2010
Possibility of duplicate data	Hertog et al. 2012; Olaitan et al. 1993
Case reports or fewer than 10 cases	Singh et al. 2014; Andrade et al. 2013; Carneiro et al. 2014; Huang et al. 2007; Zwahlen & Gratz 2002;
Follow-up is not specified or unclear	Okechi et al. 2020; Giraddi et al. 2018; Vongsa et al. 2013; Franca et al. 2012; Gunawardhana et al. 2010; Vayvada et al. 2006; Arotiba et al. 1997; Chidzonga et al. 1996; Sehdev et al. 1974

Supplementary Table 3. Network inconsistency.

chi2(3) = 0.33
Prob > chi2 = 0.9547

Loop	IF	seIF	z_value	p_value	CI_95	Loop_Heterog_tau2
C-D-E	0.858	2.340	0.367	0.714	(0.00,5.45)	0.000
D-E-F	0.687	2.550	0.269	0.788	(0.00,5.68)	0.000
B-E-F	0.687	2.695	0.255	0.799	(0.00,5.97)	0.000
C-D-F	0.443	2.164	0.204	0.838	(0.00,4.68)	0.000
C-E-F	0.304	1.661	0.183	0.855	(0.00,3.56)	0.000
B-D-E	.	.	.	.		0.000
B-D-F	.	.	.	.		0.000

Notes: B = Enucleation + Carnoy's solution, C = Enucleation, D = Enucleation + Curettage, E =Marginal resection, F = Segmental resection.

Supplementary Table 4. Confidence assessments in network meta-analysis of treatment approach comparisons.

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
CCR:MR	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias", "Imprecision"]
ECS:En	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias", "Imprecision"]
ECS:MR	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias", "Imprecision"]
ECS:SR	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias", "Imprecision"]
En:ENCU	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias", "Imprecision"]
ENCU:MR	2	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias", "Imprecision"]
ENCU:SR	2	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias", "Imprecision"]
En:MR	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias", "Imprecision"]
En:SR	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias", "Imprecision"]
MR:SR	5	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias", "Imprecision"]
CCR:ECS	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias", "Imprecision"]
CCR:ENCU	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias", "Imprecision"]
CCR:En	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias", "Imprecision"]
CCR:SR	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias", "Imprecision"]
ECS:ENCU	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias", "Imprecision"]

Notes: CCR = Curettage + Cryotherapy, ECS = Enucleation + Carnoy's solution, En = Enucleation, ENCU = Enucleation + Curettage, MR = Marginal resection, SR = Segmental resection.

Supplementary Table 5. SUCRA values for the ameloblastoma treatments network. (A) estimated probabilities; (B) predictive probabilities.

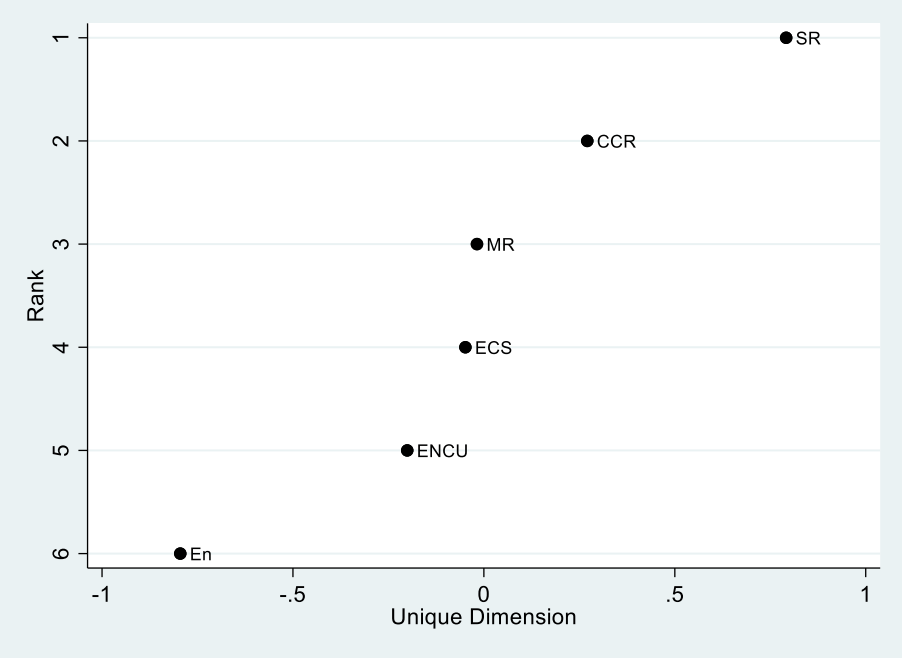
A

Treatment	SUCRA	PrBest	MeanRank
En	17.3	1.2	5.1
CCR	66.9	37.4	2.7
ECS	45.1	17.3	3.7
ENCU	43.7	4.9	3.8
MR	49.3	4.2	3.5
SR	77.7	35.0	2.1

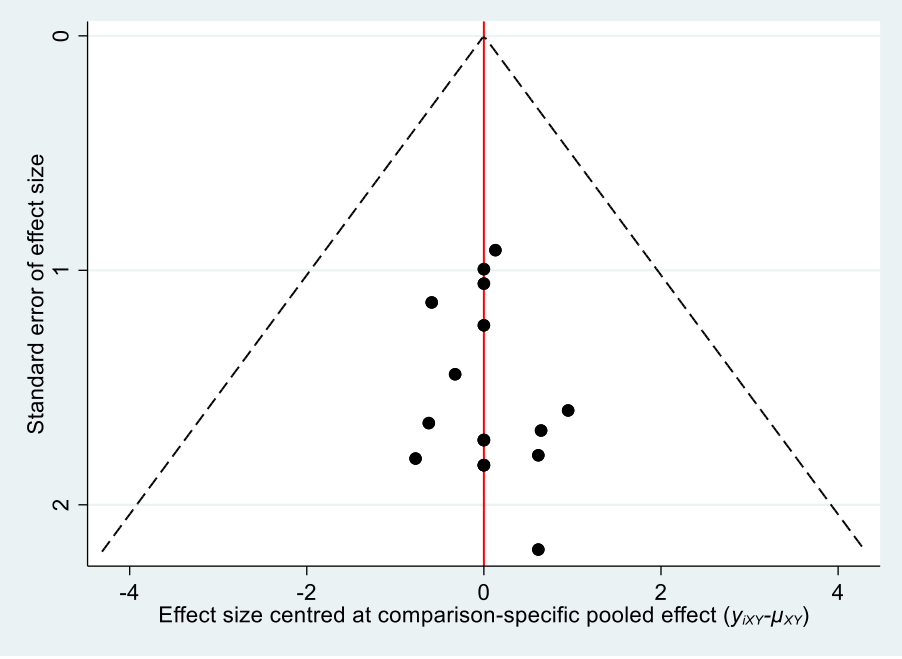
B

Treatment	SUCRA	PrBest	MeanRank
En	17.3	1.2	5.1
CCR	66.9	37.4	2.7
ECS	45.1	17.3	3.7
ENCU	43.7	4.9	3.8
MR	49.3	4.2	3.5
SR	77.7	35.0	2.1

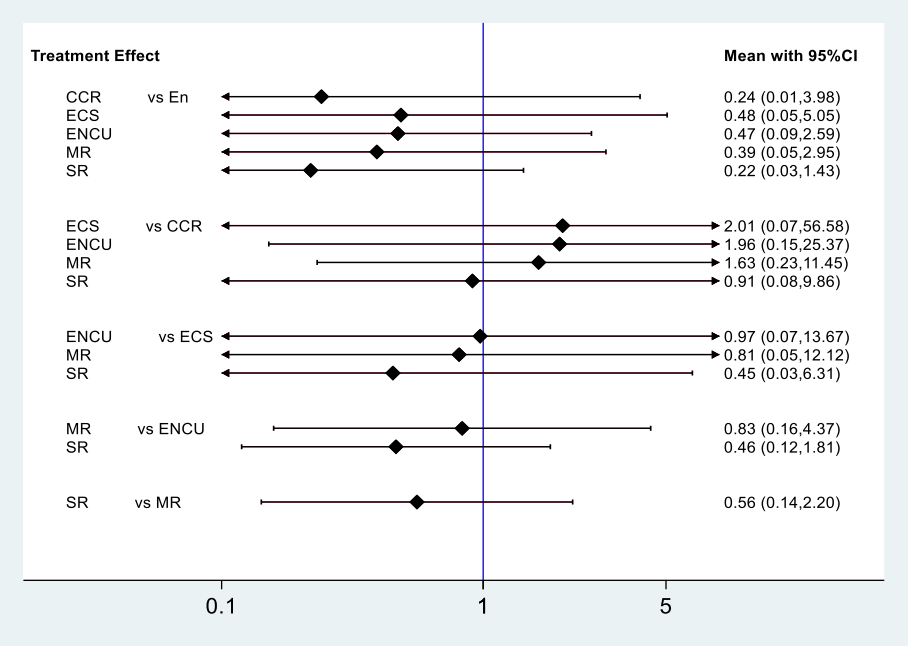
Notes: CCR = Curettage + Cryotherapy, ECS = Enucleation + Carnoy's solution, En = Enucleation, ENCU = Enucleation + Curettage, MR = Marginal resection, SR = Segmental resection.



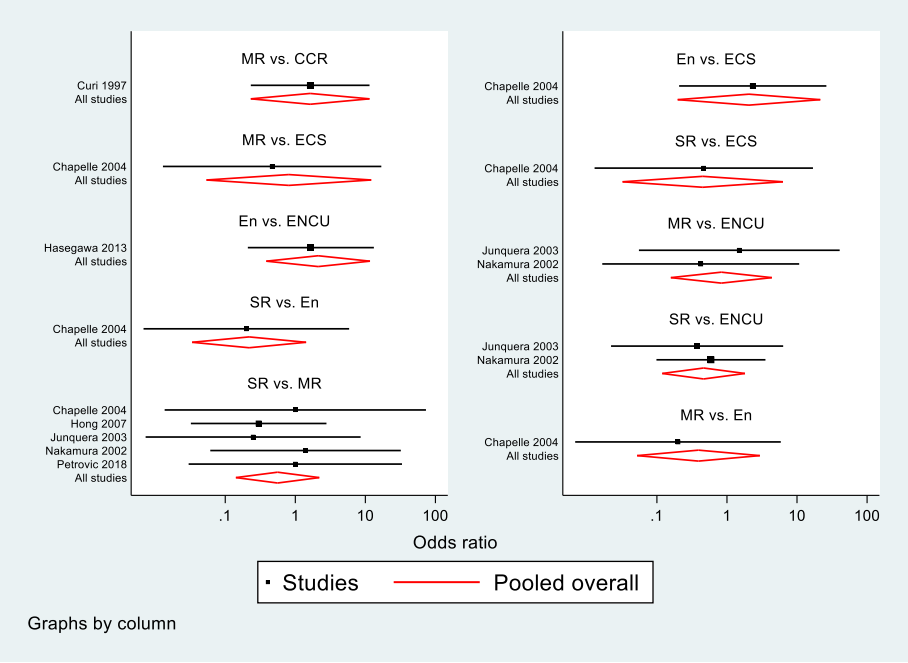
Supplementary Figure 1. Relative ranking of treatments for the ameloblastoma network based on the multidimensional scaling (MDS) approach. Notes: Larger values of the dimension correspond to higher ranks. CCR = Curettage + Cryotherapy, ECS = Enucleation + Carnoy's solution, En = Enucleation, ENCU = Enucleation + Curettage, MR = Marginal resection, SR = Segmental resection.



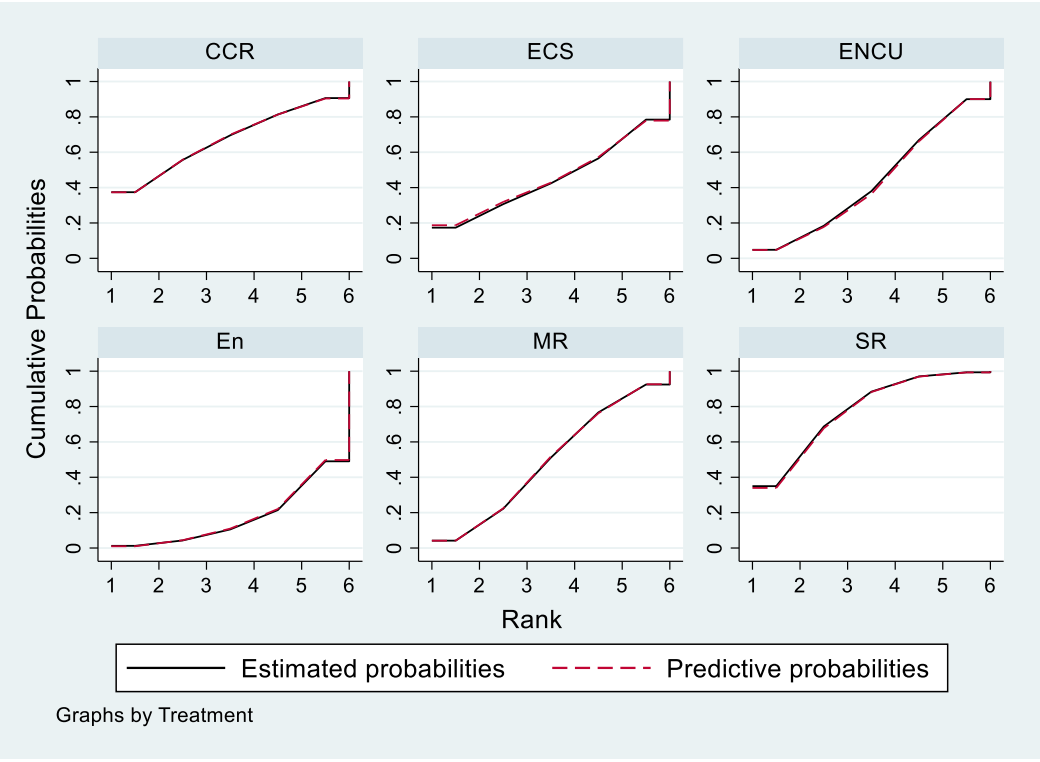
Supplementary Figure 2. Comparison-adjusted funnel plot of the ameloblastoma treatments network.



Supplementary Figure 3. Interval plot of treatment approach comparisons for recurrence outcome using Odds Ratio (OR) to measure the effect size. Notes: CCR = Curettage + Cryotherapy, ECS = Enucleation + Carnoy's solution, En = Enucleation, ENCU = Enucleation + Curettage, MR = Marginal resection, SR = Segmental resection.



Supplementary Figure 4. Network forest plots of treatment approach comparisons. Notes: CCR = Curettage + Cryotherapy, ECS = Enucleation + Carnoy's solution, En = Enucleation, ENCU = Enucleation + Curettage, MR = Marginal resection, SR = Segmental resection.



Supplementary Figure 5. Cumulative probability curves for the ameloblastoma treatments network show that each treatment's estimated and predictive probabilities are up to a specific rank. Notes: CCR = Curettage + Cryotherapy, ECS = Enucleation + Carnoy's solution, En = Enucleation, ENCU = Enucleation + Curettage, MR = Marginal resection, SR = Segmental resection.

CHAPTER 7

General Discussion & Future Perspectives

GENERAL DISCUSSION

This thesis provides an epidemiological evaluation focusing on the incidence and profile of ameloblastoma patients worldwide and in eastern Indonesia. It also evaluates the outcomes of various ameloblastoma treatment approaches. Finally, the preparation of a novel treatment strategy by conducting proteomics analysis to explore suitable surface receptors that can improve the selective delivery of targeted medicines to residual ameloblastoma cells is described.

Incidence & biological profile of ameloblastoma

Ameloblastoma is the most prominent odontogenic tumor of interest among oral and maxillofacial clinicians due to its incidence and clinical profile[1]. In terms of incidence among all odontogenic tumors, ameloblastoma appears to be more common in Asian and African countries. In contrast, it is the second most common in North America after odontoma. The data source is one of the causes of this disparity. Odontogenic lesions are identified and treated in maxillofacial departments in Asian and African countries, whereas patients in Europe and North America can be treated in hospitals and dentistry schools. Odontomas, in particular, are frequently diagnosed based on clinical and radiographic examinations without histological evaluation, leading to an underestimate of their incidence[2].

We discovered in **Chapter 2** that the annual global incidence rate of ameloblastoma is 0.92 per million people, indicating that it is a rare odontogenic tumor. These results were obtained from population- and hospital-based studies and only involved Africa, Australia, and Europe. No studies were available regarding the incidence rate of ameloblastoma in Asia and America. Several countries in Asia and America, such as India and Brazil, have published many studies on ameloblastoma with many patients. However, most of these studies only focus on the clinicopathological aspect without reporting the incidence rate based on the population of the study country.

Ameloblastoma incidence data are frequently collected from pathology department records of the health services and reported as the relative incidences of the total number of odontogenic tumors documented in that health services[3]. There are numerous drawbacks in hospital-based studies, particularly in developing (low and middle-income) countries, which can affect this relative incidence rate, as follows: (1) Several people in the communities having odontogenic tumors may not have gone to the hospital at all for various reasons; (2) Some

of the referred patients may have been unable to cover the charges; (3) Some who reported to the hospital declined to undertake adequate investigations, and hence the definitive diagnosis could not be established by the physicians; and (4) in a few situations, the diagnosis may have been technically unattainable, in which case they were excluded from the study. Given the above considerations, the ameloblastoma incidence rate may be slightly higher[4].

Evaluation of biological features or profiles in neoplasm research may yield valuable and significant information that may aid in identifying the etiology of the tumors and understanding the underlying mechanisms. The most recent extensive review on the biological features of ameloblastoma was published in 1995, more than 20 years ago[5]. Based on that review and the results of our study in **Chapter 2**, the global trend for sex distribution in ameloblastoma remained unchanged, indicating males had a higher incidence than females (male/female ratio of 1.14:1). In **Chapter 3**, we got contradictory results. Females are more affected by ameloblastoma than males. However, this cannot be used as a reference because our study was limited to eastern Indonesia, especially in only two hospitals (Makassar and Palu).

Similarly, the global trend of ameloblastoma concerning the site of occurrence did not change. The mandible is still the most common location for ameloblastoma, especially in the posterior part. The occurrence location of ameloblastoma is related to its genetic mutation. Several studies have found that BRAF gene mutations, especially BRAF V600E, the most common gene mutation in ameloblastoma (43-82%), mainly occurred in the mandible[6–9]. The etiology of genetic mutations in ameloblastoma is still unclear. However, this may be related to cancer's general etiology, such as the patient's lifestyle and exposure to carcinogens. Guan et al. found that mutation signatures in mandibular ameloblastoma were associated with smoking and chewing tobacco habits[10].

We discovered the worldwide average age of ameloblastoma patients at the initial diagnosis was 34.3 years. Reichart et al.[5] in 1995 and Small & Waldron[11] in 1955 showed average ages of 35.9 and 38.9 years in their study, respectively. The findings of this thesis and these reviews show a trend of the average age of ameloblastoma patients becoming younger over time. This trend can be attributed to the acceleration of the aging process, possibly due to cumulative exposure to environmental and lifestyle risk factors, such as bad eating habits, especially in developing countries[12].

Regarding the pathological features of ameloblastoma, the trend appears unchanged when comparing this thesis's results with other studies. Follicular and plexiform are still the two most common histopathological appearances. What should be noted is that many studies related to the profile of ameloblastoma have not reported the patient's pathological picture. In addition to the patient's radiographic examinations and clinical manifestations, the practitioner must conduct a pathological analysis to diagnose ameloblastoma accurately[13]. **Chapters 2** and **3** contain a more detailed discussion of the epidemiological profile of ameloblastoma.

Recurrences

The high recurrence rate of some neoplasms, particularly ameloblastoma, remains a concern that needs to be addressed. Ameloblastoma has a relatively high recurrence rate among all odontogenic tumors, varying between 5% and 30%[14]. There are numerous risk factors for recurrence in ameloblastoma, involving primary treatment modalities, histologic features, gene mutation profile, and tumor size[7,15–18]. In **Chapter 4**, we found that the risk of recurrence was higher with conservative treatment modalities compared with radical treatment for both multicystic and unicystic ameloblastomas. The recurrence rate is lower in unicystic ameloblastoma than multicystic/solid ameloblastoma. These findings align with several related systematic reviews[19–23]. Accordingly, radical surgery is recommended as the treatment of choice to reduce the recurrence rate in ameloblastoma patients.

There are many different modalities for this radical surgery. Thus, in **Chapter 5,** we conducted a network meta-analysis for the first time in this field to determine which treatment modality, both in radical and conservative management, had the lowest postoperative recurrence rate in patients with conventional ameloblastoma. The network meta-analysis method, known as Bayesian meta-analysis, is newly developed and popular today[24]. This method can analyze the evidence of more than two interventions or exposures simultaneously, which is impossible when using standard or conventional meta-analysis methods. This technique can also calculate direct and indirect comparative effectivities and rank all treatment modalities[24–27]. In our network meta-analysis study, even in treatment rank, we found segmental resection is the best to reduce the recurrence. Still, all modalities have no significant difference, so the results should be interpreted cautiously. Utilizing segmental resection still has a chance to relapse, so we need additional treatment to cure the tumor fully.

There is a relationship between recurrence risk and mutational status. The group of ameloblastomas with numerous gene alterations had the highest recurrence rate.

Ameloblastomas with BRAF mutations had a much-decreased risk of recurrence, but tumors with SMO gene alterations appear to have a higher risk of recurrence[7,9]. A study by Yang et al. found an association between tumor size and ameloblastoma recurrence. They discovered that ameloblastomas bigger than 6 cm in diameter and engagement of soft tissues or surrounding anatomical structures are related to early recurrence regardless of surgical approach[17]. These findings are consistent with a study by Au et al., which reported that for every 10-mm increase in tumor diameter, the recurrence risk increased 1.26-fold[15]. In contrast, Fregnani et al.[28] found that tumor size in ameloblastoma was not associated with recurrence. Differences in sample size and length of follow-up may explain these disparities.

The length of follow-up is essential in evaluating the recurrence of ameloblastoma patients. However, there are still several studies that do not report in detail regarding how long the follow-up time is. The majority of ameloblastomas recur after 5-10 years of surgery, either with radical or conservative approaches. Late recurrences have also lasted up to 20 years[15,29]. Coupled with the slow-growing nature of this ameloblastoma[18], sufficient and long-term (at least ten years) clinical and radiological follow-up after surgery is necessary.

Optimizing ameloblastoma treatment

The current optimal treatment for reducing the recurrence of ameloblastoma patients is radical surgery with wide margins from the tumor site. However, even in this way, there is still a chance that ameloblastoma will recur. The recurrence can be caused by remnants of tumor cells that have not been removed. One strategy that has the potential to overcome this problem is to use targeted therapy as an adjuvant treatment given immediately after surgery. For this strategy to be implemented, the first thing that needs to be done is to find reliable and validated specific biomarkers of ameloblastoma. Targeted therapies, which use specific molecules such as genes and proteins for therapeutic reasons, are gaining popularity in treating tumors and malignancies. In the current era of targeted medicine, applying proteomics approaches, which supplement other "omics" techniques such as genomics and transcriptomics, enables gathering a large amount of information about the structure and function of specific proteins[30]. This has led to identifying proteins that play critical roles in biological processes in tumor cells that can be used as viable targets for targeted therapy.

In **Chapter 6**, we conducted proteomic analysis on surface proteins of the ameloblastoma cell line by combining cell surface isolation, gel-electrophoresis and in-gel trypsin digestion, and nano-liquid chromatography-tandem mass spectrometric (nano LC-MS/MS) analysis.

Ultimately, we discovered several surface proteins that could serve as candidate biomarkers for the targeted treatment of ameloblastoma. We used surface receptors as extracellular targeting agents because, based on the previously mentioned in the introduction section, several studies related to ameloblastoma targeted therapy are currently limited to intracellular targeting. Furthermore, membrane proteins play many essential functions in the biological processes of tumors and most research into therapeutic targets for some diseases[31].

Nonetheless, membrane proteins have some drawbacks. Because membrane proteins are usually low in abundance, intracellular proteins with high abundance may overshadow the number of membrane proteins, making identification and quantification more difficult. Moreover, they are less detectable in research using two-dimensional gel-electrophoresis for protein separation[31,32]. However, we overcome these drawbacks by isolating surface proteins with biotinylation techniques and separating them using Sodium Dodecyl Sulfate-Polyacrylamide Gel-Electrophoresis[33,34] prior to nano LC-MS/MS analysis.

In this thesis, we discovered ameloblastoma surface biomarkers utilizing the AM-1 cell line instead of primary tumor tissues. The use of primary tumor cells has numerous advantages, including a precise molecular phenotype and the preservation of essential functions and markers observed in-vivo. We need to culture the cells to identify surface markers. Because primary ameloblastoma cells in culture have a short lifespan, it is difficult or impossible to culture them without an immortalization technique. On the other hand, using cell lines is also not without limitations. The immortalization procedure involving a virus and cell culture may alter the cell phenotype. However, the AM-1 cell line can still be used as an alternative model because it has almost the same behavior as ameloblastoma cell in-vivo[35–37].

To minimize toxicity in tumor-targeted treatments, delivered drugs should ideally target tumor-specific cell receptors highly expressed on tumor cell surfaces but low-expressed on healthy cells. Thus, comparative surface proteomic analysis between tumor cells and appropriate control tissues is recommended to search for surface biomarker candidates for ameloblastoma-targeted therapy. However, the origin of ameloblastoma is still unclear, making selecting the suitable control tissue for this tumor study difficult. Several studies regarding the molecular aspects of ameloblastoma used normal oral mucosa and dental follicle as control tissues[38–46]. We chose dental follicle as a control tissue in our study and successfully isolated the surface protein from several dental follicle samples. However, we have not included it in our proteomic analysis due to various limitations. As an alternative, we compared our results with the normal oral mucosa protein dataset from the public database.

FUTURE PERSPECTIVES

Epidemiological data could be used to design and evaluate programs for preventing disease, patient treatment, and training health personnel. Hence, the first part of this thesis intended to assess the global incidence, obtain the international biological profile of ameloblastoma patients, and evaluate the effects of several treatment approaches for this tumor regarding recurrence. Population-based research provided the best reliable data on incidence rates, although few studies reported population-based incidence of ameloblastoma and only came from a few countries. Thus, in the future, more population-based studies on the incidence will be required to strengthen the worldwide database on the incidence of ameloblastoma.

Identification of risk factors is crucial in developing ameloblastoma prevention and treatment strategies. In this thesis, we found that ameloblastoma patients who get radical treatment have a lower risk of recurrence when compared to those who get conservative treatment. Thus, the type of therapy is one of the risk factors for ameloblastoma recurrence. From the previous discussion, we know several other risk factors of recurrences, such as tumor size, gene mutation, and histologic type. However, in other studies, some of these variables are not included in risk factors, which is still controversial. Therefore, more research is needed on the risk factor of ameloblastoma recurrence with a more rigid method, more significant sample, and a long follow-up period to determine the objective risk factors. In addition, the study needs to be carried out by multi-country and continents to examine whether there are differences in risk factors from each country or continent.

Compared to a single-center study, multi-center research or national registries allows for sharing resources between centers, forming cooperative networks, and expanding sample size, reproductivity, and applicability. We did a retrospective study regarding the epidemiology, treatment, and complication of ameloblastoma in two healthcare centers in East Indonesia. Similar research, combined with the previous topic of incidence and biological profile, needs to be done more broadly and involves more health centers, especially in Indonesia. In addition, clinical research related to complications and quality of life in ameloblastoma patients is still lacking. So, this research topic can be a good thing to do in the future, especially in multi-center research.

We discovered several surface biomarkers in this thesis that can potentially become receptor candidates for ameloblastoma-targeted therapy. However, these findings are still in the biomarker discovery stage and require further verification. An extensive biomarker

development pipeline comprises the following six steps: candidate exploration, qualification, verification, study assay optimization, biomarker validation, and commercialization[47]. Of necessity, we still need to perform a surface proteomics comparison between ameloblastoma cells and control tissue, in this case, the dental follicle, which we have prepared beforehand to make the outcomes more convincing. Several methods can be used to verify candidate surface biomarkers in the future, such as fluorescence-activated cell sorting (FACS) or flow cytometry, immunohistochemistry, and tissue microarrays (TMAs). FACS analysis is one way to validate mass spectrometry results and ensure high levels of cell surface localization of candidate proteins in ameloblastoma cells vs. low levels in controls. The immunohistochemistry on TMAs can be performed by comparing ameloblastoma patient samples with normal dental follicles as a control to assess expression levels, verify the subcellular localization, and asses the clinical relevance of these candidate biomarkers.

The swift advancement of nanotechnology in the development of nano drug products offers enormous potential for enhancing medications for tumors and cancer in the future. Nanoparticles in cancer therapy enable controlled medication delivery, increasing a drug's efficacy towards cancer while decreasing side effects. Nanomaterials in forms such as micelles, liposomes, dendrimers, and nanoemulsions with a base of organic, inorganic, lipid, protein, glycan substances, and synthetic polymers, can be constructed to create a variety of configurations regarding the nature of the particle sought, the administration route, and the part to be encapsulated[48,49]. As mentioned in the introduction, developing double-targeted therapy that combines intracellular (e.g., cytostatic resistance-related kinases) and extracellular (tumor-specific surface receptors) targets using nanoliposome technology for ameloblastoma is a promising future approach. Specific to intracellular targets, it is important to consider each ameloblastoma patient's specific gene mutations before therapy. As previously stated, SMO gene mutations are more likely to result in high recurrence rates than BRAF gene mutations in ameloblastoma, indicating that targeting the SMO gene may be more effective. Personalized medicine approaches can be employed to determine the specific mutation in the ameloblastoma before resection and allow for selecting an appropriate targeted treatment strategy. In cases where the tumor has a BRAF mutation, targeted treatment may not be necessary, while SMO-mutated tumors should get this targeted therapy.

Furthermore, nanotechnology has a wide range of applications, especially in regenerative medicine and bone tissue engineering. Nanotechnology plays a role in bone tissue engineering by (1) delivering bioactive molecules, growth factors, and genetic material, (2) mediating cell

labeling and targeting, and (3) enhancing physicochemical interactions, biocompatibility, mechanical stability, and cellular attachment/survival through nano-based scaffold setup and modification[50]. This concept is suitable for applying to ameloblastoma patients who require reconstruction and rapid tissue regeneration after radical surgery. Finally, the application of nanotechnology by combining double-targeted therapy to eradicate residual tumor cells with regenerative medicine could become a novel treatment strategy for ameloblastoma patients in the future.

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CHAPTER 8

Summary

SUMMARY

Ameloblastoma, as stated in the general introduction, is one of the most common epithelial odontogenic benign tumors in the jaws that is locally invasive and has a high recurrence rate if not treated adequately. Several studies published over many years report the incidence of ameloblastoma in many nations. Nevertheless, no study has been conducted on the global incidence of ameloblastoma. The latest international study of ameloblastoma's biological profile has also been published over twenty years. Therefore, In **Chapter 2**, we undertook a systematic review and meta-analysis to examine worldwide incidents across five decades and present an updated profile of ameloblastoma patients throughout the previous 26 years. We discovered that the global incidence rate was 0.92 per million person-years. The mandible was the favored location, with a slight male preference. The average age was 34, with the highest incidence occurring in the third decade of life. When compared to Africa and South America, ameloblastoma was more common in older people in Europe and North America. Solid/multicystic ameloblastoma was the most prevalent type, and follicular and plexiform histopathologic patterns predominated. However, the pooled incidence only included Europe, Africa, and Australia. Therefore, more epidemiological research on the incidence rate is warranted to more precisely ascertain the global incidence of ameloblastoma.

Further, we would like to discover more about the incidence of ameloblastoma in the Indonesian population. In **Chapter 3**, we conducted a retrospective study to assess the incidence, treatment, and complication profiles of ameloblastoma patients in East Indonesia. The mean age was 39.7 years, and most tumors were located in the posterior part of the mandible. The most common type was multicystic ameloblastoma; most cases were treated conservatively. For patients receiving radical treatment, reconstructions were done without bone grafts and only with titanium plates. We discovered that the most typical pre-operative complication is swelling. However, the scope of this research was restricted to just two healthcare centers in East Indonesia. There is still a need for more research on ameloblastoma in other Indonesian healthcare facilities.

As was already stated, if this tumor is not treated correctly, it will likely relapse. To our knowledge, surgery is the primary therapy for ameloblastoma, and there are two types of surgical methods: radical and conservative. For this reason, we examined how the surgery method affected the recurrence frequency in ameloblastoma patients. In **Chapter 4**, we performed a systematic review and meta-analysis to evaluate the results of radical and

conservative treatment methods for solid/multicystic and unicystic ameloblastoma concerning recurrence rates. We discovered that after radical therapy, the pooled recurrence rate of solid/multicystic ameloblastomas was 8%, compared to 41% after conservative treatment. These percentages were 3% and 21% for unicystic ameloblastomas, respectively. Following radical treatment, the risk of recurrences for both types of ameloblastomas was significantly lower than for conservative patients. The solid/multicystic variety revealed more recurrences than the unicystic type, but it is essential to remember that this research only included retrospective observational studies, which makes the evidence weaker than ideal. Additionally, we could not evaluate the included studies' appropriate follow-up periods and consider the quality of life. It is also necessary to conduct more extensive, prospective studies that are more methodologically rigorous in their data gathering, analysis, and reporting processes and have long postoperative follow-up intervals that include information on complications.

Given that both treatment modalities comprise a variety of approaches, the findings of **Chapter 4** prompted us to determine which radical and conservative treatment strategy results in lower recurrence rates in ameloblastoma patients. In **Chapter 5**, for the first time in the ameloblastoma research field, we conducted a network meta-analysis (NMA) to evaluate and compare the efficacy of these various treatment modalities simultaneously for solid/multicystic ameloblastoma. The NMA method can analyze outcomes from multiple interventions or exposures at once and provide a ranking of all interventions, which is not feasible when using conventional meta-analysis techniques. According to the results, segmental resection ranked highest for lowering the recurrence rate, followed by curettage with cryotherapy and marginal resection. However, the evidence's certainty was deemed low for all comparisons by the Confidence in Network Meta-Analysis (CINeMa) technique because of imprecision and within-study bias. Our NMA revealed segmental resection as the most effective surgical method for decreasing recurrence in patients with multicystic ameloblastoma. Combining different conservative approaches is recommended if the patient cannot afford a radical treatment. However, the findings should be interpreted with caution due to the weak evidence.

Along with epidemiology, this dissertation aimed to formulate novel ameloblastoma therapy strategies. As previously mentioned, radical surgery is still the most effective method of lowering the chance of ameloblastoma recurrence. Targeted therapy is currently receiving a lot of focus for treating various tumor types. A promising way of preventing recurrences is to

combine the radical technique with the administration of targeted medication as adjuvant treatment. Knowing the specific tumor receptors targeted by the drug delivery system is one of the necessities for targeted therapy for tumors or cancers. Therefore, we carried out surface proteomic analyses in **Chapter 6** to look for potential biomarkers that could act as beneficial extracellular targets for the targeted transport and delivery of therapeutic agents to ameloblastoma cells. The ameloblastoma cell line (AM-1)'s biotinylated surface and flow-through (cytoplasmatic) fractions were isolated and subjected to gel electrophoresis and nano-liquid chromatography-tandem mass spectrometry analysis. Protein-protein interactions diagram, gene ontology, and protein clusters were explored to understand the ameloblastoma tumor biology. Based on the screening of multiple variables, 17 proteins were determined to be high-confidence surface proteins. These results were compared to the public normal tissue dataset to assess protein expression in the healthy oral mucosa. Ultimately, we revealed five potential biomarkers with minimal expression in oral mucosa: PTPRF, PLXNA1, PLNA2, DCBLD2, and EPHB4. Finally, we discovered several surface proteins that may serve as ameloblastoma-targeted therapy receptors. Further research utilizing different methods must be conducted to confirm these promising biomarkers.

AUTHORS' CONTRIBUTIONS

Chapter 2 was published as:

Global incidence and profile of ameloblastoma: a systematic review and meta-analysis

Authors:

Faqi Nurdiansyah Hendra (FNH), Ellen M. Van Cann (EVC), Marco N. Helder (MNH), Muhammad Ruslin (MR), Jan G. de Visscher (JGV), Tymour Forouzanfar (TF), Henrica C.W. de Vet (HV)

Authors' contributions:

FNH: data collection, data analysis and interpretation, and drafting the manuscript. EVC: data acquisition, analysis and interpretation of data, and drafting the manuscript. MNH: conception and design of the study, analysis and interpretation of data, and revising the manuscript critically. MR: acquisition of data, interpretation of data, and drafting the manuscript. JGV & TF: conception and design of the study and revising the manuscript critically. HV: analysis and interpretation of data especially in statistic and drafting the manuscript. All authors confirm that the manuscript has been read and approved to be published.

Chapter 3 was published as:

The Epidemiology, treatment, and complication of ameloblastoma in East-Indonesia: 6 years retrospective study

Authors:

Muhammad Ruslin (MR), Faqi Nurdiansyah Hendra (FNH), Arian Vojdani (AV), David Hardjosantoso (DH), Mohammad Gazali (MG), Andi Tajrin (AT), Jan Wolff (JW), Tymour Forouzanfar (TF)

Authors' contributions:

MR: conception and design of the study, data collection, data analysis and interpretation, and drafting the manuscript. FNH: data acquisition, analysis and interpretation of data, and drafting the manuscript. AV & DH: data collection and drafting the manuscript. MG & AT: conception and design of the study, analysis and interpretation of data, and revising the manuscript critically. JW & TF: conception and design of the study and revising the manuscript critically. All authors have read and agreed to the published version of the manuscript.

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Authors:

Faqi Nurdiansyah Hendra (FNH), Diandra Sabrina Natsir Kalla (DNK), Ellen M. Van Cann (EVC), Henrica C.W. de Vet (HV), Marco N. Helder (MNH), Tymour Forouzanfar (TF)

Authors' contributions:

FNH: data collection, analysis and interpretation of data, quality control of data, and drafting the manuscript. DNK: data acquisition, analysis and interpretation of data, quality control of data, and drafting the manuscript. EVC: data acquisition, analysis and interpretation of data, and drafting the manuscript. HV: analysis and interpretation of data especially in statistic and drafting the manuscript. MNH: conception and design of the study and revising the manuscript critically. TF: conception and design of the study, quality control of data, and revising the manuscript critically. All authors confirm that the manuscript has been read and approved to be published.

Chapter 5 was published as:

A network meta-analysis assessing the effectiveness of various radical and conservative surgical approaches regarding recurrence in treating solid/multicystic ameloblastomas

Authors:

Faqi Nurdiansyah Hendra (FNH), Marco N. Helder (MNH), Muhammad Ruslin (MR), Ellen M. Van Cann (EVC), Tymour Forouzanfar (TF)

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Chapter 6 was prepared as:

Proteomic analysis of ameloblastoma to identify potential surface receptors for targeted therapy

Authors:

Faqi Nurdiansyah Hendra (FNH), Richard Goeij de Haas (RGH), Sander R. Piersma (SRP), Tymour Forouzanfar (TF), Connie R. Jimenez (CRJ), Marco N. Helder (MNH)

Authors' contributions:

FNH: performing the experiments, analysis and interpretation of experimental data, and drafting the manuscript. RGH: performing the in-gel digestion, analysis of data, and drafting the manuscript. SRP: performing the mass spectrometry and protein identification and quantification. TF: conception and design of the study and revising the manuscript critically. CRJ & MNH: conception and design of the study, interpretation and quality control of data, and revising the manuscript critically. All authors have read and agreed to the prepared version of the manuscript.

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LIST OF PUBLICATIONS & AWARDS

List of publications

Hendra FN, Helder MN, Ruslin M, Van Cann EM, Forouzanfar T. **A network meta-analysis assessing the effectiveness of various radical and conservative surgical approaches regarding recurrence in treating solid/multicystic ameloblastomas**. Scientific Reports. 2023 May 25;13(1):8445.

Natsir Kalla DS, Alkaabi SA, **Hendra FN**, Nasrun NE, Ruslin M, Forouzanfar T, Helder MN. **Stem Cell-Based Tissue Engineering for Cleft Defects: Systematic Review and Meta-Analysis**. The Cleft Palate Craniofacial Journal. 2023 May 18:10556656231175278.

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Ruslin M, **Hendra FN**, Vojdani A, Hardjosantoso D, Gazali M, Tajrin A, Wolff J, Forouzanfar T. **The Epidemiology, treatment, and complication of ameloblastoma in East-Indonesia: 6 years retrospective study**. Medicina oral, patologia oral y cirugia bucal. 2018 Jan;23(1):e54.

Awards

High-Quality Scientific Articles and Productive Writers Award 2020 by Indonesian Ministry of Research and Technology (KEMRISTEK-BRIN) for “Global incidence and profile of ameloblastoma: A systematic review and meta-analysis” article (first author).

The 2020 Crispian Scully Best Review Article Award Winner in *Oral Diseases* Journal for “Global incidence and profile of ameloblastoma: A systematic review and meta-analysis” article.

CURRICULUM VITAE

Faqi Nurdiansyah Hendra was born on 12 January 1989 in Ujung Pandang, now known as Makassar, one of the cities in East Indonesia. In 2006, Faqi started studying Medicine at the Faculty of Medicine, Hasanuddin University in Makassar, Indonesia and earned his Bachelor of Medicine degree in 2009. Then, he continued his medical doctoral education with the same faculty. He passed his medical competency exam and earned his medical doctor's degree with cum laude predicate in 2011. After graduating, he interned as a general practitioner at Kassi-Kassi Community Health Center and Daya Hospital in Makassar until 2012. At the end of 2012, he was accepted as a permanent lecturer at the Faculty of Medicine, Hasanuddin University, and he continues to work as a general practitioner at one of the health clinics in Makassar. In April 2016, he got a Ph.D. scholarship from the Indonesia Endowment Fund for Education (LPDP), Ministry of Finance, the Republic of Indonesia. Faqi started his Ph.D. program in September 2016 at the Oral & Maxillofacial Surgery/Oral Pathology department at VU University Medical Center, Amsterdam. During his Ph.D. program, he obtained several awards for his publications from the Indonesian Ministry of Research and Technology and the *Oral Diseases* Journal in 2020. In addition, he has been a speaker at several workshops and seminars related to systematic review and meta-analysis in Makassar, Indonesia.