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Review Article

Ameloblastoma: A Review and Latest Trends

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ABSTRACT

WHO Classification of Head and Neck Tumours (2017) defines Ameloblastoma as benign intraosseous progressively growing epithelial odontogenic neoplasm characterized by expansion and a tendency for local recurrence if not adequately removed. It reports annual incidence of about 0.5 cases per million populations but it is considered to be the most common odontogenic tumour next to odontoma with a varied global prevalence. Although, there are several researches, reports and reviews on ameloblastoma; our review discusses the recent updates with emphasize on molecular pathobiology of ameloblastoma and also revolves around the controversies on radical vs. conservative management with updates on chemotherapeutic management. This scenario suggested us to clarify the prospects in management of ameloblastoma with the available scientific literature. Our narrative review aims to address recent updates on clinical, surgical management, adjuvant therapies with relevance to clinico-pathological and radiological features and also molecular aspects in relation to management of ameloblastoma.

Keywords: Ameloblastoma; Radiology; Surgical management; Malignant; Tumours; Odontogenic

INTRODUCTION

Adult Odontogenic tumours are distinctly classified based on the histological origin of the tumours and are presented with various radiological and histopathological variants which are either benign or malignant. Ameloblastoma, a benign odontogenic tumour of epithelial origin, presents with different radiological variants and unique histopathological patterns. WHO Classification of Head and Neck Tumours, 2017 defines ameloblastoma as benign intraosseous progressively growing epithelial odontogenic neoplasm characterised by expansion and a tendency for local recurrence if not adequately removed. The peak incidence of diagnosis is usually seen in the fourth and fifth decade of life with an age range of 8-92 years with no sex predilection; the mean age of diagnosis is 30 years. WHO also reports the annual incidence of only 0.5 cases per million populations [1]. Although considered to be rare; ameloblastoma is the most common odontogenic tumour excluding odontoma. There is a varied global prevalence; reported as the most common benign odontogenic tumour in China and Africa [2], reporting a five-fold increased risk of disease among Africans and Americans when compared to Caucasians [3]. Clinically, early stage present with slow, painless growing swelling and sometimes are diagnosed incidentally on radiographic findings. Commonly seen in the ramus or the body of the mandible; and radiologically observed as unilocular, multilobular or multilocular. The benign tumour on histological observation reveals four patterns: solid multicystic, extraosseous/peripheral, desmoplastic and unicystic [4,5]. This clinical narrative review discusses in details the currently available literature on the clinicopathological features, radiological diagnostic evaluation and surgical management of ameloblastoma. Also, it discusses various adjuvant and neoadjuvant therapy available for the management of ameloblastoma. Currently, there are no established treatment algorithms, staging system, and there is a lack of prospective studies or randomised control trials that may help to compare the various treatment outcomes. This narrative review aims to address recent updates on clinical, surgical management, adjuvant therapies with relevance to clinico-pathological and radiological features and also molecular aspects about the management of ameloblastoma.

THE DIAGNOSTIC CLINICAL APPROACH IN AMELOBLASTOMA

The patient usually presents with a painless slow growing expansion

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showing aggressive growth in the later stage. Complications like loosening of teeth, malocclusion, pain, paresthesia; soft tissue invasion, facial deformities, limited mouth opening; masticatory difficulty and even airway obstruction are observed with increasing size of the tumour. Uncontrolled tumour growth may often tend to be fatal [1-5]. Beceli had reported that 35% of the observed cases in their study were incidental findings on radiography [6]. Pain with rapid growth may be associated with a malignant neoplasm. Haemorrhage is uncommon unless in cases following fine needle aspiration, paraesthesia may be seen in cases with perineural invasion. Tooth resorption and displacement have been reported in 25% cases of desmoplastic ameloblastoma [2]. Commonly located in the mandible, followed by the maxilla and later followed by peripheral cases [7]. Extra osseous lesions usually present as a painless, soft, sessile and exophytic type of lesion. Extraosseous types are commonly seen in the soft tissues of the retro molar area and followed by maxillary tuberosity; most tumours are also found in the lingual aspect of the mandible. They present with smooth or papillary/granular surface and are red to dark red. Extraosseous variants sometimes present with tilted adjacent teeth. Very rarely lesions may be seen in the sinonasal tract [1]. Macroscopy of intra-osseous tumours are usually solid to variably cystic, unicystic ameloblastoma present as a monocystic lesion, extra-osseous variant present as a solid mass with occasional cystic spaces [1].

Were included in our study, all the patients admitted and operated on for one or more pathologies of the right iliac fossa regardless of the source and who agreed to participate in the study with informed consent.

Were included in our study, all patients admitted and operated for a non-traumatic abdominal surgical emergency and having performed at least one imaging examination with informed consent. During the study period, patients lost to follow-up were excluded. The parameters studied were: hospital frequency, age, sex, profession, origin, marital status, mode of admission, consultation time, reasons for consultation, functional signs, physical signs, history, imaging and biology examinations performed, etiologies, type of treatment, post-operative treatment and length of hospitalization.

RADIOLOGICAL ASPECTS OF DIAGNOSIS AND MANAGEMENT

Pre-operative evaluation for diagnosis includes imaging and biopsy. Ameloblastoma, which commonly is seen within the bone, are commonly detected incidentally on dental X-rays (pantomographs). X-rays usually show a lytic lesion with scalloped margins, resorption of tooth roots, and impacted molars in case of unicystic ameloblastoma. Unilocular appearance is often uncommon. A corticated multilocular appearance presents with a classical soap-bubble or honey-com appearance in pantomography, but the feature is not pathognomonic and is a representation of the septae in the intra-osseous lesion. There is an evident expansion of buccal and lingual plate seen with growth. Very rarely, incipient and root-related ameloblastomas are incidentally discovered. Desmoplastic ameloblastoma may mimic fibro-osseous lesions showing mixed radiolucent and radiopaque Unicystic ameloblastoma presents with a well-defined unilocular radiolucency, usually associated with impacted canine or mandibular molars. It is also seen associated with root resorption; one-third of the cases may show cortical perforation [1,8-10]. Unicystic ameloblastoma associated with an impacted third molar radiographically mimics a dentigerous cyst; often the size of the lesion is larger than the dentigerous cyst (Figure 1). However, plain x-rays do not reveal the extent of bone and soft tissue invasion. Computed Tomography (CT) considered as a beneficial imaging modality shows well defined radiolucent unilocular/multilocular radiolucency; CT is also helpful for determining the extent of cortical expansion and soft tissue extension; CT serves vital to determine the margins of the tumour and for surgical treatment planning. MRI provides more information on the soft tissue extension and marrow extension beyond the lytic bone cavity. Considering the nature of the spread of the tumour in the maxilla, MRI helps to determine the extension to the orbit, paranasal sinuses and skull bases. MRI is found to be found helpful in cases of desmoplastic ameloblastoma often confused with desmoplastic ameloblastoma radiographically. PET-CT is only necessary for cases of malignant ameloblastoma to characterise the tendency to metastasise [2].

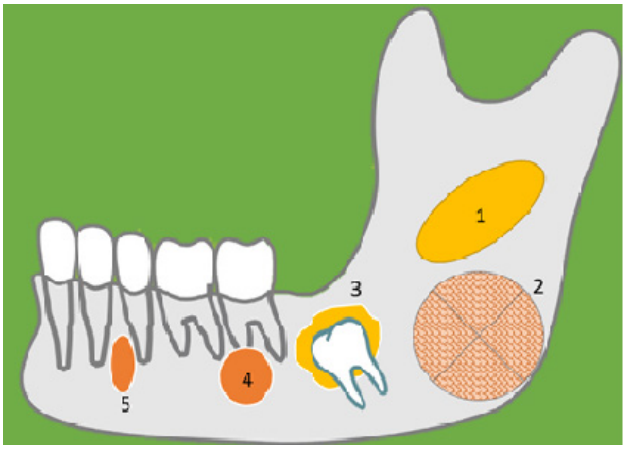

Figure 1: Diagramatic representation of radiographic variants of unicystic amelobastoma. Note: 1) Unicystic ameloblastoma; 2) Multilocular unicystic ameloblastoma; 3) Dentigerous type of amelobastoma (Unicystic type); 4) Periapical type of Ameloblastoma (Unicystic type); 5) Inter-Radicular type of ameloblastoma (Unicystic type).

HISTOLOGICAL VARIANTS OF AMELOBLASTOMA

Imaging studies are often only useful for pre-operative diagnosis but not pathognomonic. Diagnosis is made definite only with histopathological examination following biopsy. FNAC is usually not useful in diagnosis for doubtful cases of ameloblastoma. Hence, biopsy in the form of the curettage may be seen as the primary mode for a definite diagnosis [2]. Among the histologic types of

ameloblastoma, follicular and plexiform patterns are the most common variants, less common variants include acanthomatous and granular cell types. Less common cellular variants are desmoplastic ameloblastoma, basal cell ameloblastoma, keratoameloblastoma, papilliferouskeratoameloblastoma, clear cell ameloblastoma and unicystic ameloblastoma. Few "hybrid forms" having combinations of histologic variants have been reported [11,12]. Histopathology of ameloblastoma has been discussed widely in the currently available literature; hence only highlights of the histopathology will be featured here. The follicular type (Figures 2a and 2b) of ameloblastoma resembles the epithelial component of the enamel organ within the fibrous stoma. The peripheral cells appear cuboidal to columnar with hyperchromatic nuclei. These ameloblast-like cells are arranged in a palisading pattern with reversal of polarity. The central core resembles that of the stellate reticulum with loosely arranged angular cells with a tendency for cystic changes. The Plexiform variants (Figures 3a and 3b) are composed of anastomosing strands of ameloblastomatous epithelium composed of the stellate reticulum. The stroma may undergo cyst like stromal degeneration. Desmoplastic ameloblastoma present with cuboidal to flat peripheral cells with central spindle-shaped cells and densely collagenous stroma. Extreme stromal dysplasia is pathognomonic of desmoplastic ameloblastoma. Luminal type of ameloblastoma shows a simple cyst lined by ameloblastomatous epithelium characterised by peripheral palisading and nuclear polarisation. The overlying epithelium has loosely arranged cells that may resemble stellate reticulum. This type of pattern may be observed focally, and other areas may feature ameloblastomatous features. The intraluminal type is seen with intra-luminal extensions of the lining epithelium with a plexiform pattern. Definite diagnosis of Unicystic ameloblastoma can be made only with careful examination. Unicystic ameloblastoma (Figures 4a and 4b) also is known to behave more aggressively, similar to conventional ameloblastoma. A peripheral variant of ameloblastoma resembles histopathological features that of the intra-osseous ameloblastoma [1,10]. An array of odontogenic tumours should be considered for differential diagnosis of conventional ameloblastoma. Although ameloblastic islands are typical of ameloblastoma, it is not uncommon to see such areas in other odontogenic tumours. Metastasising ameloblastoma shows similar features, but only with evident metastasis, this scene is, however rare and needs to be evaluated carefully for the primary tumour. An ameloblastic carcinoma may also show areas of typical ameloblastoma which should be distinguished carefully to look in the entire histopathology section for features of malignancy including cytological atypia, high N:C ratio increased mitoses with atypical forms and necrosis. Ameloblastic fibroma shares some features of odontogenic epithelial components appearing in strands, cords and islands but is uniquely distinguished from ameloblastoma with the typical primitive and delicate stroma. Adenomatoid Odontogenic Tumour (AOT) is differentiated with its glandular or duct-like nests or cords with focal areas of reversal of polarity like in ameloblastoma. These duct-like spaces may also contain eosinophilic and amyloid-like secretions. Typically, AOT can be differentiated by their clinico-radiological profile. Squamous Odontogenic Tumour can be differentiated with the odontogenic squamous- like epithelium without any peripheral palisading or stellate reticulum. A case of Calcifying Cystic Odontogenic Tumour (CCOT) can also have ameloblastic features and igerous cyst, variants of unicystic ameloblastoma, artypically feature Ghost Cells and anucleate epithelial cells. In cases which feature predominantly cystic architecture, denteas of macrocystic degeneration of conventional ameloblastoma should also be considered. In cases of Desmoplastic ameloblastoma, differential variables like ameloblastic fibroma, squamous odontogenic tumour, odontogenic fibroma and sclerosing odontogenic carcinoma should be considered for evaluation [1,10].

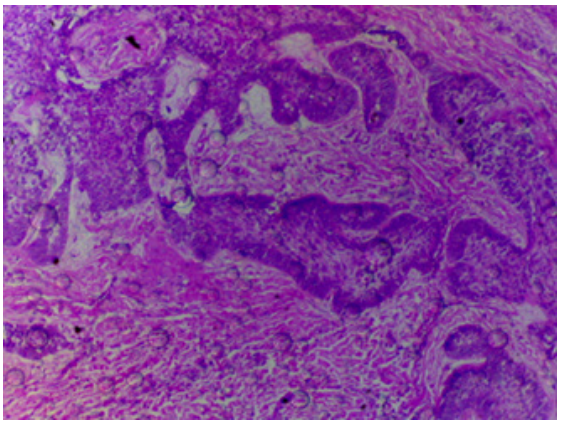

Figure 2a: 10X Magnification shows ameloblastic islands with peripheral columnar cells with reversal of polarity and hyperchromatic nuclei. Central loose stellate reticulum like-cells are seen and dense connective tissue is also seen. Suggestive of follicular variant of Amelobastoma.

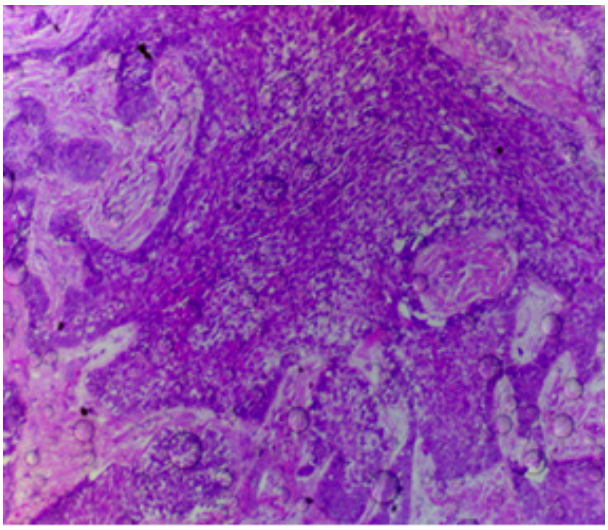

Figure 2b: 10X magnifications shows a large ameloblastic island with cuboidal to columnar peripheral ameloblast like cells, central core shows stellate reticulum like cells are seen. Suggestive of follicular variant of ameloblastoma.

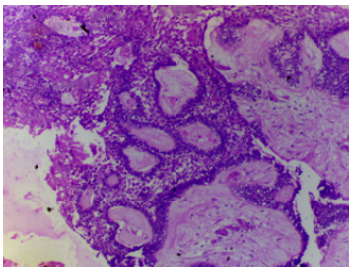

Figure 3a: 10Xs Magnification shows an area of thick anastomosing strands of ameloblastomatous epithelium composed of stellate reticulum. Moderately dense connective tissue stroma is observed. Suggestive of plexiform variant of ameloblastoma.

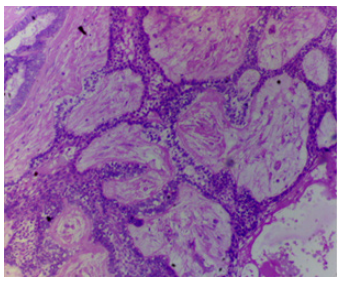

Figure 3b: 10Xs Magnification shows an area of thin anastomosing strands of ameloblastomatous epithelium composed of stellate reticulum. Stoma is loose to moderately dense in nature. Suggestive of plexiform variant of ameloblastoma.

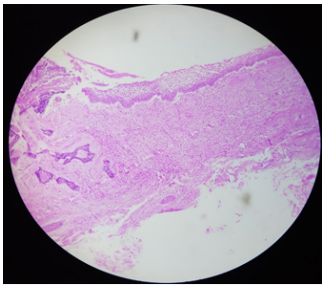

Figure 4a: Low power shows a cystic lining epithelium and tumour islands in the stroma. Hyperchromatic basal cell layer and loosely arranged suprabasal layers are also appreciated.

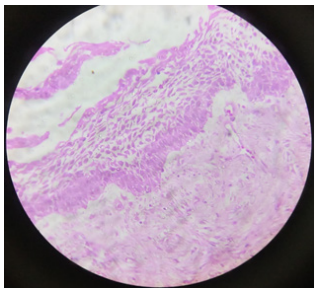

Figure 4b: On higher magnification, the cystic epithelial lining shows typical features of ameloblastoma in an area showing columnar basal cells in palisading arrangement with vacuolated cytoplasm, hyperchromatic nuclei polarized away from basement membrane. The suprabasal layer cells are loosely arranged and non-cohesive resembling the stellate reticulum like cells. Subepithelial separation also seen. Capsule appears to be fibrous.

MOLECULAR BIOLOGY IN AMELOBLASTOMA

The cell of origin for ameloblastoma is known to be from the dental lamina, and it is indicated by the expression of early dental epithelial markers such as PITX2, MSX2, DLX2, RUNX1 and ISL1. Recently there is some clarity regarding the molecular aberrations that may be the underlying cause for ameloblastoma. The vast majority of tumours are seen to contain somatic mutations impacting the Mitogen-Activated Protein Kinase pathway (MAPK) signalling pathway (FGFR2, RAS, BRAF) that controls cell proliferation. MAPK type of mutations was seen in 90% of the cases of ameloblastomas. BRAF mutations were reported to be the most common type of mutation in the mandible and reportedly shows better prognosis. In contrast, the SMO type of mutation was observed in 55% of the maxillary cases (Table 1). SMO mutations are Non-MAPK type of mutation that tends to co-occur with MAPK pathway mutations. Other Non-MAPK mutations include SMARCB1, CTNNB1 and PIK3CA. Ameloblastoma and basal cell carcinomas are known to share mutations in SHH pathway. There are immunohistochemistry studies which show p53 and MDM2 expression, but only a minority of them shows an active p53 mutation [1,2]. Notch signalling pathways and other molecular markers such as syndecan-1 (CD 138) and CD10 have also been reported to be expressed in ameloblastoma [13].

Table 1: Prevalence of mutations in maxillary and mandibular ameloblastoma.

Location	Type of mutations			
	MAPK pathway			NON-MAPK pathway
	BRAF	RAS family	FGFR2	SMO
Maxilla	20%	40%	15%	55%
Mandible	72%	5%	5%	5%

Note: WHO Classification of Head and Neck Tumours WHO Classification of Tumours, 4th Edition, Volume 9 IARC Press; 2017

CURRENT TRENDS IN THE MANAGEMENT OF AMELOBLASTOMA

Conservative vs. radical

Diagnostic workup with a clinical evaluation with different imaging techniques and pre- operative histopathology (if available) are critical to surgical planning and successful management of ameloblastoma irrespective of histological subtype. The nature subtype guides for conventional management of tumour. Treatment of solid multicystic lesions is more; however, more aggressive. Peripheral ameloblastoma can be excised with 1 cm soft tissue margin, and a cuff of uninvolved alveolar bone may also be removed to have a clear deep margin. A pre-operative representative lesion may be difficult to obtain for pre-operative classification of ameloblastoma. Surgery is the standard treatment for ameloblastoma; the option for the type of surgery has, however, been controversial and has two surgical options

– 'conservative' vs. 'radical'. Conservative treatment includes enucleation/curettage of the bony cavity. Conservative treatment has better patient compliance and is usually done as an outpatient procedure. Patient acceptance is also better as it may not require reconstruction. Radical treatment is usually considered for conventional ameloblastoma; current treatment is wide surgical excision, including the area of bone beyond the radiological margins. Clinically it is recommended to have a surgical margin of 1 cm. Radical surgery is recommended for a biologically aggressive subtype of primary and recurrent ameloblastoma. Conservative surgery reportedly exhibits recurrence of about 60%-80% of the cases. The histological subtype may not determine prognosis. More than 50% of the cases may recur within five years of initial treatment. Also, this nature of recurrence of tumour recommends for long term follow up of the cases. A pre-operative evaluation may be helpful in cases of Unicystic ameloblastoma where it mimics a dental cyst in radiographs and this similarity results in the initial treatment of curettage. Further management is determined by the extent and the pattern of the growth/proliferation of the cyst to the cyst upon removal of the entire lesion. Mural involvement of the tumour may suggest further additional surgery or extended careful follow-up. Recurrence is usually treated as conventional ameloblastoma with aggressive treatment. Unicystic ameloblastoma requires long term follow up as they might re-occur ten years after initial treatment. To limit the chances of recurrence adjuvant treatment like cryotherapy, tissue fixatives like Carnoy's solution and cautery has also been evaluated, and reports decreased recurrence rates. Non-surgical approaches include different forms of radiation therapy reported to be successful with ameloblastomas, especially in patients who are not stable for surgical therapy. These radiation therapies include helical tomotherapy, photon beam therapy, image-guided radiation therapy and intensity-modulated radiation therapy. These additional treatment options are often combined with surgery and/or chemotherapy. The risk of usage of radiotherapy should be dealt with the chances of malignant transformation. Studies on molecular signalling pathways and genetic mutations in the pathogenesis of ameloblastoma led to the development of targeted therapies for the management of ameloblastoma. Therapies targeting MAPK and Non-MAPK (SMO) pathways show variable outcomes in the management of ameloblastoma [12-15].

DISCUSSION

Ameloblastomas are unique, benign, locally invasive, slow growing and aggressive [12] tumour of the oral cavity with a significantly high rate of recurrence, which may cause potential deformity and debilitation if left unattended. Recurrence of such aggressive tumour is influenced by number factors such as the age of the patient, location of the tumour, anatomic site, and histological variants, adequate primary surgical procedures. There exists a significant difference regarding the thoughts and opinions relating to the surgical management of this benign tumour based upon various case series, retrospective studies, and histological evidence. Standard treatment protocol for resection of this unique tumour remains controversial due to its high recurrence [12]. Globally treatment differs from patient to patient except for the principle of resection, which remains the same. In accordance to data collected from various literatures, two therapeutic strategies exist, a simple non-radical surgical procedure like enucleation and curettage, combined with liquid nitrogen spray cryosurgery to radical resection surgical procedures with or without marginal integrity [16]. According to Nakamura, rate of recurrence is 7.1% after radical surgery, 33.3% after conservative treatment, and recommended extensive resection as the best treatment option Nakamura concluded that treatments including marsupialisation and enucleation followed by bone curettage were deemed to be useful and reduced the need for resective jaw surgery [17]. Sampson and Pogrel showed that nearly 31% of tumours recurred after conservative surgery and were thought to be unacceptable recurrence rate [18]. Sammartino. offered a new treatment protocol to support surgeons to build up a "rational" protocol based on their ten-year experience from their establishment. Based on various authors, small Ameloblastomas are managed through extensive resection which incorporates a minimum of 1 cm of healthy bone around the tumour margin. Large lesions with no bony perforations include a conservative approach. Sammartino further concluded that recurrence was less when detected earlier and treated accordingly [19]. It emphasised that when detected earlier and surrounded by uninvolved bone, it may be possible to treat with radical resection. Shatkin and Hoffmeister looked at information from 1918 onwards and concluded that under-treatment of Ameloblastomas might bring unresectable recurrences. Hong claimed recurrences of 4.5% individuals dealt with segmental resection or maxillectomy, 11.6% resection with a bony edge, 29.3% conventional treatment (enucleation, curettage and marsupialisation). In this long term follow up study by Hong, it was concluded that resection with a safety margin is the best treatment option for most cases of ameloblastomas and suggested that conservative treatment may be suggested for patients in their first decade [20]. According to Chidzonga, management of ameloblastoma in the paediatric population is treated with radical resection with 0.5 cm to 1 cm into the healthy bone. Arotiba also considers a radical approach to treatment instead of conservative management. Considering the behaviour of unicystic ameloblastoma authors suggested conservative management but later adopted for the principle of radical management in response to the aggressive nature of the tumour [21]. Haq suggested the use of conservative treatment in certain mandibular solid/multicystic cases with enucleation and application of Carnoy's solution. This study suggested the potential benefits of conservational surgery and also eliminating the need for reconstruction; further reported only low recurrence [14]. This option, however, may be controversial and will require prospective long term studies to validate the use of the procedure in conventional cases. Clary suggested that radical surgery is the current standard of care for ameloblastoma, and it includes en-bloc resection with 1-2 cm bone margins and followed with immediate bone reconstruction to improve speech and

swallowing function. The review also recommends a bone margin of about 1-1.5 cm for unicystic and 1.5 cm to 2 cm for solid/multicystic histological subtypes; 2-3 cm bone margins for cases of ameloblastic carcinoma. Tumours originating from maxilla are not advised for elective neck dissection. The recommendations were made from numerous studies but not based on randomised control trials based on standardised treatment protocols which should be kept under consideration [2]. Largely, data available on the management of ameloblastoma show the greatest recurrence related to simple enucleation and low recurrence associated with radicular resection. However, factors like the age of the patient, social acceptance, cosmetics should also be considered in choosing the appropriate treatment option. In either case, only long term follow up of patients will lead to better monitoring of the patients. Frozen section of soft tissue overlying cortical perforation and bone marrow are strongly recommended apart from using imaging modalities that help in ensuring adequate surgical margin. Silva suggest that intraoperative specimen CT serves as a better tool to assess margin; however other higher level comparative studies were required to establish a gold standard rule on the use of CT for intra-operative margin assessment [22]. Milman indicate in their study that a radical surgical approach like segmental resection, maxillectomy or mandibulectomy serve as a strong predictor of recurrence-free survival among patients with ameloblastoma [23]. Peacock comparing intraoperative radiographs and frozen sections suggested that resection of ameloblastoma with planned margins of a minimum of 1 cm margin is enough to prevent any recurrence of ameloblastoma. The study concluded that a radiographic margin of at least 5 mm provided a minimal histopathological margin of 5 mm in 83.3% of the time [24]. Radiation therapies in ameloblastoma are a concern due to the risk of malignant transformation and remain controversial. There not many human or animal studies that give substantial data to validate the use of radiotherapy for ameloblastoma. Chemotherapy may, however, help to improve the clinical symptoms in non-surgical patients [2]. Chemotherapy is, however, recommended in ameloblastic carcinoma and recurrent following multiple post-surgical recurrences. Drug combinations that may be used along with surgery and/or radiotherapy include combinations like vinblastine+cisplastin+bleomycin; Adriam ycin+cisplatin+cyclophosphamide; doxorubicin+cisplatin and gemcitabine+Carboplatin. However, standardized multi-centric randomized controlled clinical trials are necessary to validate the use of radiotherapy and chemotherapy as an additional treatment option for ameloblastoma [13]. The genetic landscape of mutations has opened venues for the development of new non-invasive treatment options for management of ameloblastoma; development of drugs targeting mutated BRAF and MEK to dysregulate the growth, proliferation and differentiation of ameloblastic cells are being evaluated. BRAF gene inhibitors include Vemurafenib, MEK gene inhibitors like trametinib, drugs like ponatrinib and regoratinib inhibit mutated FGFR2 genes. However, the signalling pathways develop other resistance mechanisms activating MAPK pathways associated with vemurafenib treatment. This suggests the use of MEK inhibitors in treating ameloblastoma [25]. Large clinical trials are required to demonstrate the efficacy of the therapy to be applied in a clinical setup.

CONCLUSION

The decision to choose conservative vs. radical management relies on the surgeon with a pre- operative evaluation with available clinical data, radiographical and histopathological data. Ameloblastoma's nature of delayed recurrence further emphasises the absolute necessity for long-time or lifelong monitoring of the patients. Irrespective of the surgical procedures a long term monitoring and patient coordination is mandatory for prevention of recurrence soon. Recent advancement in molecular medicine points out the effectiveness of targeted therapy in ameloblastoma. However, on a long term basis for complete cures of large ameloblastoma adjuvant or neo-adjuvant therapies need to be considered if feasible. Combination therapy may help in further reducing the recurrence rate and a better lifestyle for the patients. We recommend multi-centric prospective controlled clinical trials to further establish the appropriate use of an effective treatment plan in the management of ameloblastoma.

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