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Radical resection of mandibular ameloblastoma and functional reconstruction with fibula free flap: literature review and cases

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INTRODUCTION: *Ameloblastoma is a borderline bone tumor that origins from the residual epithelium of the teeth germs, the epithelium of the enamel organ or the epithelium of odontogenic cysts. Ameloblastoma management is challenging owing to the necessity of tumor radical excision and the functional and aesthetic reconstruction of the surgical defect. The fibula-free flap (FFF) provides a high-quality and predictable mandibular reconstruction due to the high-caliber vascular pedicle, the bone length that can reconstruct large defects, the possibility for implants-based prosthetic reconstruction, and the possibility of harvesting a composite flap that can replace the mucosa, hence protecting the underlying bone reconstruction.*
CASE REPORTS: *We report adult female and elder male patients, who were addressed to our hospital for mandible swelling and histopathological results of ameloblastoma. The lesions were treated by segmental mandibulectomy and FFF reconstructions. Osteosynthesis plates and screws were enough for the female patient's reconstruction of the lateral mandible defect and a load-bearing plate was necessary for the male patient's reconstruction of the surgical defect that included the anterior part of the mandible. The facial artery was used in both cases, and the surgeries lasted approximately 8 hours. No recurrence was observed at the follow-up and the aesthetic function was well re-established.*
CONCLUSION: *Radical treatment of ameloblastoma is mandatory. The aesthetic function could be properly maintained by FFF. Also, the FFF reconstruction is a reliable method for head and neck large bone and soft tissue defects, microvascular anastomosis on facial artery offering a good blood supply of the flap.*

KEY WORDS: Ameloblastoma, Fibula-free flap, Maxillofacial reconstruction, Radical treatment

Introduction

Epidemiology

Ameloblastoma is a borderline bone tumor with locally aggressive behavior and a high propensity for recurrence and sporadic metastases, especially after de-differentiation into carcinoma [1–3]. The prevalence of head and neck ameloblastoma is approximately 1% of the jaws' cysts and tumors and 10% of the dental origin tumors. Even if it is considered a rare tumor of the head and neck region, it is the most common odontogenic tumor. The incidence is 0.92 per million persons-years, with a worldwide peak incidence in the third decade and a slightly increased age in the European and North American populations (fifth and sixth decades). Ameloblastoma affects almost equally males and females (male to female ratio 1.14:1) and men have a maximum incidence in the middle of the third decade. The females are predominantly affected in the European continent and the men in North America [1].

The mandible is prone to develop ameloblastoma tumors (80%) compared with the maxilla, with a posterior predilection site in the regions of the third molar and ascendent ramus (84.7% in European patients) [1].

Histopathological Features

Ameloblastoma origins from the odontogenic epithelium, more exactly from the remnant of tooth-forming structures, such as dental lamina (Serres remnants) or enamel organ, from the lining of dentigerous cysts or basal layer of the oral mucosa [1].

Based on macroscopic tumor architecture, four types of ameloblastoma are described. The multicystic or solid variant is the most frequent worldwide type (67.7%), followed by the unicystic variant (26.6%). Desmoplastic and peripheral ameloblastoma present a much lower incidence of 3.6% and 1.0%, respectively [1]. The local aggressiveness of the ameloblastoma is related to macroscopic features. Multicystic variant infiltrates through the medullary spaces and develop multiple cyst-like lesions and presents the most aggressive local pattern. Unicystic and desmoplastic lesions are less aggressive than the multicystic variant. The unicystic variant of ameloblastoma appears as a cyst-like tu-

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mor on imaging. There are two histopathological subtypes of unicystic lesions, the luminal and the mural type. The desmoplastic variant is characterized by an extensive stromal collagenization that limits the tumor cells to infiltrate the bone compared with the multicystic one that presents islands of ameloblast cells that invade the medullary as a digitiform extension. The peripheral variant presents the lowest aggressive pattern because it develops exclusively in the oral mucosa (extraosseous) [4,5].

Based on microscopic tumor architecture, six histopathological variants can be identified solely or mixed. Follicular (24.8%) and plexiform variants (24.7%) are the most frequent ones. Also, the mixed subtype is relatively common (10.4%). Contrary, acanthomatous (5.7%), granular cell (2.5%) and basal cell (0.4%) variants are rare [1]. The follicular type presents islands of odontogenic epithelium in fibrous connective tissue, peripheral palisading arrangement, and central cells resembling stellate reticulum. The plexiform type usually shows cords of anastomosing odontogenic epithelial cells, basal cells arranged in a peripheral palisading pattern, and reverse polarity rarely. The stroma of the plexiform ameloblastoma is thin and often associated with cyst-like degeneration. The acanthomatous pattern illustrates different levels of keratinization of the stellate reticulum resembling cells and squamous metaplasia [6]. The follicular and plexiform variants are more aggressive and present higher rates of local recurrence compared with the other variants [7].

Diagnosis

Ameloblastoma is clinically observed as a non-tender bone enlargement with intact mucosa, usually seen after an asymptomatic period of intra-bony development. The growth rate of the tumor is approximately 80% increase per year [8]. Accordingly, many patients are diagnosed after 9 years since the tumor has started to grow. The delay in seeing a doctor may be due to non-compliance to regular dental appointments, ignorance of the swelling, fear of surgery, and economic reasons [8].

The diagnostic process requires both radiological examinations and incisional biopsy. Orthopantomogram (OPG) is the first line of radiological examination that raise the suspicion of ameloblastoma, mandatory followed by a Computed Tomography (CT) or Cone-Beam CT (CBCT) to assess the tumor invasion [9].

The ameloblastoma tumor replaces the bone structure while growing and it appears as a radiolucent lesion with well-defined and scalloped borders. The radiological features of images rely on the tumor architecture. Unicystic ameloblastoma is seen as a well-defined, round, unilocular radiolucency, sometimes associated with a corticated peripheral bone. The cortical bone can be ballooned, and the adjacent teeth can be displaced. Multicystic ameloblastoma presents as a multilocular radiolucency with a polycyclic, well-defined contour (honeycomb of soup balloons), sometimes associated with a tooth. Desmoplastic ameloblastoma presents intricate aspects on radiographs. The images of the desmoplastic lesions can appear as a well-defined irregular multilocular radiolucency, a massive radiolucent honeycomb osteolytic lesion, or a mixed radiopaque-radiolucent lesion with an ill-defined border comparable to fibro-osseous lesions. Peripheral ameloblastoma rarely produces a radiological mark on the underlying bone, being clinically seen as a dome-shaped tumor adjacent to a tooth [10].

The radiological diagnosis is sometimes difficult to establish owing to the similar design to other radiolucent lesions, such as large dentigerous cyst, odontogenic keratocyst, myxoma and aneurismal bone cyst [11,12]. The final diagnosis is established by the histopathological examination based on biopsy samples.

Treatment

The ameloblastoma treatment is challenging due to the imperatives of tumor-free surgical margins and functional and aesthetical results of the reconstructed defect [13].

The surgical treatment of ameloblastoma can be divided into conservative (enucleation or curettage) and radical (marginal or segmental resection). The treatment decision is based on the histopathological type, the tumor dimension, the tumor aggressiveness, the risk of recurrence and the patient's age [8].

The conservative approach refers to enucleation associated with adjacent ostectomy or local adjuvant treatment. For example, unicystic tumors of young adults or peripheral ameloblastoma can benefit from enucleation because it reduces the morbidity of the resection site and will not interfere with the quality of life [14–16]. Moreover, to improve the surgical free margins, the conservative treatment associates local cryotherapy, electrocautery, or application of cauterizing agents, such as Carnoy's solution (60% ethanol, 30% chloroform, 10% glacial acetic acid, and 1 gram of ferric chloride) [8]. Enucleation treatment in conjunction with Carnoy's application decreases the risk of recurrence in unicystic ameloblastoma compared with enucleation alone [17].

Contrary, the radical approach is recommended in the case of aggressive or extensive tumors, especially if the mandibular canal is affected. Aggressive variants of ameloblastoma can be expanded into cancellous bone 4.5 mm or more beyond the radiological borders of the tumor [8]. Enucleation or curettage treatment in these cases is insufficient to obtain free surgical margins [18]. Hence, the goal to achieve negative margins in such tumors is established by removing 1 to 2 cm of radiologically and clinically healthy-apparent bone from the macroscopic boundaries of the tumors, either by segmental or marginal resection [13]. The usage of intraoperative x-rays helps to confirm the tumor-free resection margins. Multicystic variants or follicular and plexiform forms are examples that need radical resection due to increased rates of recurrence [19,20]. Moreover, in ameloblastic carcinoma, 2 to 3 cm of healthy bone margins

resection is advised [21].

The postoperative defect resulting from radical treatment by mandibular resection induces masticatory dysfunction and aesthetics and social integration issues. Therefore, there is a need for proper bone reconstruction. Large defects that can result after wide excisions are reconstructed by vascular bone flaps or non-vascular bone grafts, depending on the volume of the bone gap. However, the most important aspect is to perform the reconstruction in the same sitting with the resection to improve functional, esthetical, and psychological rehabilitation, as well as to reduce the surgical stress of the patients and the cost of a second surgery. The bone required for reconstruction can be harvested from the iliac crest, scapula, rib, and fibula [22].

The non-vascularized bone graft acts as a scaffold for osteoblast migration and deposition of a new bone on a rigid framework. Hence, the graft will suffer a significant remodeling. The non-vascularized bone graft offers a bulky bone reconstruction for dental implants placement and good contour, and it is associated with shorter hospitalization compared with vascularized bone flaps. Unfortunately, an important volume of the graft will be lost during the healing and remodeling processes. Non-vascularized bone grafts are advisable to be used when the defect is smaller than 5 cm in length and a sufficient remnant soft tissue to cover the graft [8]. However, different authors indicate the success of longer non-vascularized bone (>7 cm) graft in bone reconstruction if the high aseptic technique and rigid graft immobilization are respected. In these cases, Braimah et al. indicate that more than 80% of grafts survived and the patients healed well [22].

Vascularized bone flaps are used in large defects, and where there is not enough soft tissue to cover the bone graft. Owing to the intrinsic vasculature, the bone vascularized flap can reconstruct the entire alveolus and can be transferred to the defect as a composite flap. The healing process is different from the non-vascularized bone graft, keeping vital all the cells of the flap. However, the technique is complex and time-consuming [8].

The fibula-free flap is commonly used in large bone defects owing to the good bone supply, possibility of harvesting a composite flap, good bone perfusion based on medullary and periosteal vascular supply, the long vascular pedicle, and the predictability of the flap survival due to microvascular anastomosis that relies on large caliber peroneal vessels [13]. Disadvantages of fibula flap are represented by the discrepancy between the height of the remaining mandible and the width of the fibula, as well as the difficulty to place dental implants in a bone with reduced vertical dimension [23]. To overcome these shortcomings, the double barrel technique can be used, offering a good height of the alveolar crest, hence a better crown-to-root ratio for implant treatment. Moreover, the folded fibula flap is the first choice in the reconstruction of mandibular defects, especially for the middle part of the mandible defects, providing a good foundation for future implants. In contrast to the single barrel technique, the folded flap provides a better outcome regarding bone height and vertical distance to the occlusal plane [24]. Also, good quality of soft tissue that replaces the mucosa defect will produce a better outcome in mastication, aesthetics, patient confidence, and less inflammation around the implants [25].

Case Series

First Case Report

A 39-year-old female patient, without any associated pathology, presented to the Oral and Maxillofacial Department of Cluj-Napoca County Hospital for left mandibular region swelling. The patient described that the lesion was observed in the lower vestibule 2 months prior to the medical consultation and the patient started to feel a local mild pain while the bone expanded.

At the clinical examination, the patient presented facial asymmetry and a painless and hard tumor that ballooned the mandible cortical bone from tooth 35 to the angle of the mandible (Fig. 1).

Fig. 1: Extraoral clinical view.

A CBCT scan was performed, illustrating a hypodense multilocular lesion with well-defined contour, extended from the apical region of 3.5 to the angle of mandible, measuring 40 x 35 x 37 mm in dimension. The tumor expanded the basilar margin of the mandible, the buccal and lingual plates and displaced the mandibular canal anterolaterally. The roots of teeth 3.6 and 3.7 were resorbed by the tumor, as well as part of the cortical bones (Fig. 2). The blood test results indicated high platelet distribution and low levels of eosinophils.

The patient was prepared for an incisional biopsy. The tumor fragments were sent for histopathological examination. The histopathological examination described islands of medium dimension cylindrical tumor cells with hyper-

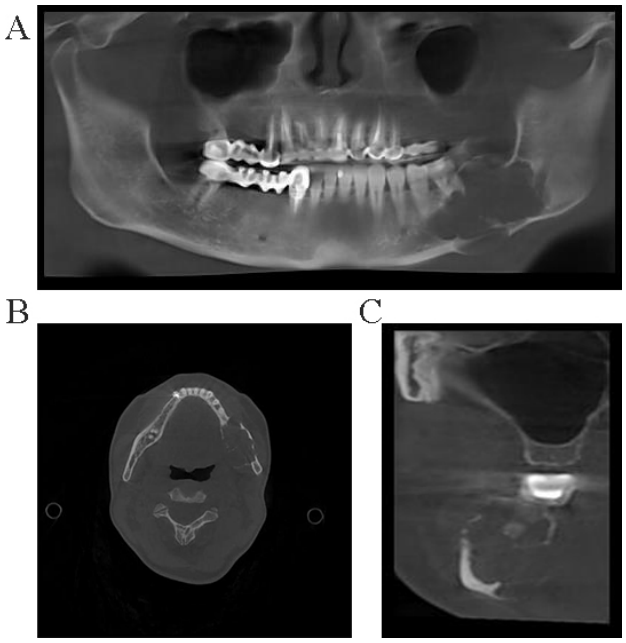

Fig. 2: Preoperative CBCT imaging illustrating large radiolucent bone lesion of left mandible: A) OPG view; B) Axial view; C) Cross-section view.

chromic nucleus and clear cytoplasm associated with cystic and squamous de-differentiation. Palisaded nuclei were observed at the periphery and the cells were surrounded by a fibrous stroma. Immunohistochemical examination illustrated positive CK5/6 marker, low positive CD56 signal and negative stains of Ck7 and CK18. The proliferation index based on ki67 was 1%. Also, necrotic bone was observed adjacent to the tumor. Accordingly, the final diagnosis was follicular ameloblastoma (Fig. 3). Radical treatment was chosen, with composite fibula-free flap reconstruction in the same sitting.

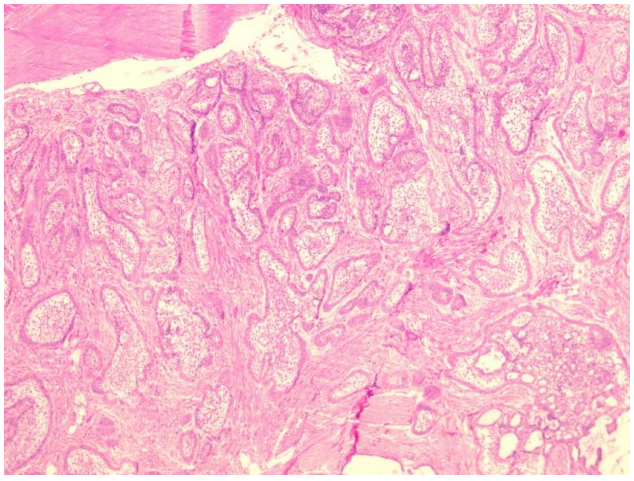

Fig. 3: Histopathological examination of the tumor fragments indicating ameloblastoma.

The surgical resection extended from the anterior border of the mental foramen to the superior level of the lingula. At the time of resection, a second team harvested the fibula from the right leg. The fibula was designed according to the defect before the pedicle was cut. The vascular pedicle was anastomosed to the facial artery and anterior jugular vein (Fig. 4). The fibula bone was fixed into the surgical defect with 4 osteosynthesis plates (2 straight four-holes plates and 2 angled five-holes plates) and 2.0 diameter screws (2.0 Universal Mandible Fracture Module, Stryker, USA), and the skin was sutured intraorally. A temporary tracheostomy was performed. The surgery lasted 8 hours.

The fibula flap healed well, without any sign of postoperative complications. The tracheostomy was closed after 10 days. Histopathological examination of the specimen confirmed the biopsy diagnosis.

A follow-up program was scheduled by CBCT examination, twice annually for the first five years and annually after that, for 20 years. The patient did not present any recurrence at 3-year follow-up (Fig. 5 and Fig. 6).

Second Case Report

A 74-year-old male patient was referred to the Oral and Maxillofacial Department of Cluj-Napoca County Hospital after a routine dental examination performed at a private dental practice. The patient presented left mandibular swelling and local discomfort (Fig. 7). The patient was known with high blood pressure, class I obesity and well-controlled type II diabetes mellitus treated by antihypertensive and oral antidiabetic medications. Blood tests revealed high levels of gamma-glutamyl transferase and blood glucose and low levels of Sodium, Potassium and eosinophils.

The buco-maxillo-facial CT with contrast enhancement illustrated an osteolytic multilocular lesion located in the left mandible, with both cystic and tissular aspects, measuring 45/22/30 mm in dimension. The tumor ballooned and resorbed the mandible cortical bone plates (Fig. 8).

The patient was prepared for an incisional biopsy, and tumor fragments were sent for histopathological examination. The histopathological examination revealed cell proliferation with plexiform architecture, column and cubic cells with hyperchromic nucleus and inverted polarization regarding the basal membrane. Multiple enlarged areas of squamous metaplasia were identified. Accordingly, the established diagnosis by histopathological examination was plexiform and acanthotic ameloblastoma (Fig. 9).

We decide to tread the patient by radical resection of the affected mandible with 2 cm clinical tumor-free margins and to reconstruct the defect by a composite fibula-free flap in the same sitting. Due to the pandemic situation at the time of treatment appointment, the surgical time was postponed for 4 months.

Bone resection and free fibula flap were performed by two different operating teams. The free flap was adjusted according to the preoperative plan at the donor site before the

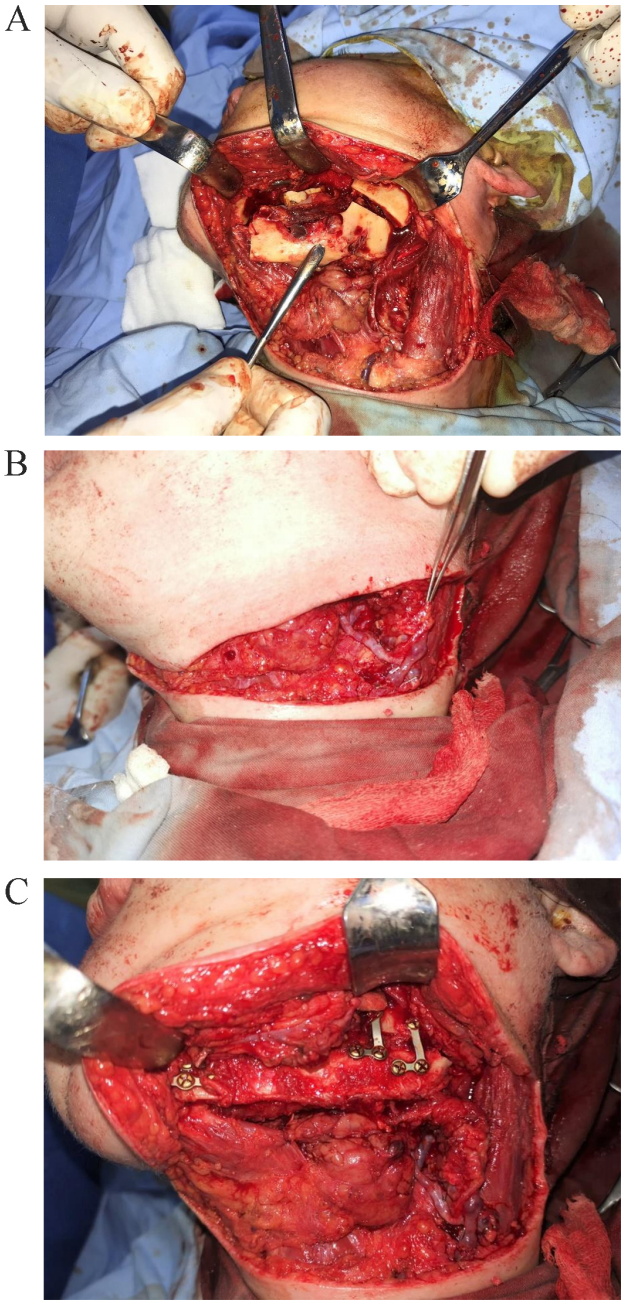

Fig. 4: Intraoperative images: A) Radical mandibular resection with 2 cm of tumor free margins; B) Peroneal vessels anastomosis to the cervical vessels; C) Fibula inserted into the surgical defect and osteosynthesis using multiple plates and screws.

vascular peroneal pedicle was detached. The load-bearing plate was stabilized with 2.3 diameter screws (2.3 Universal Mandible Reconstruction Module, Stryker, USA) at the remnant fragments of the mandible and the peroneal vessels were anastomosed to the facial artery and tiro-lingo-facial branch of the internal jugular vein (Fig. 10). Two suction drains were placed on the neck and the cutaneous island based on musculocutaneous perforators was sutured into the mucosa defect. A temporary tracheostomy was performed to protect the upper airways and to control the oxygenation

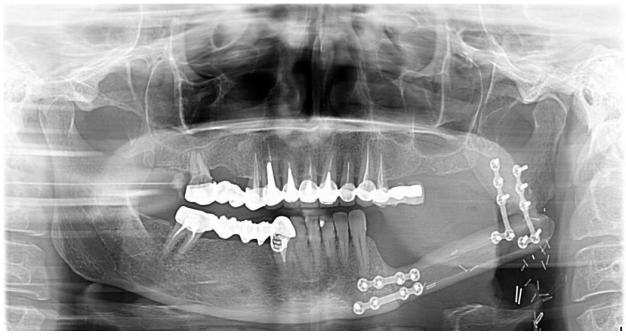

Fig. 5: OPG view at 3 years follow-up indicating no sign of recurrence and good healing of the flap.

of the flap. The surgery lasted 8 hours and 30 minutes.

The patient recovered well after surgery, the vascularized fibula-free flap had proper healing and the patient was discharged 10 days after the surgery, with no signs of local postoperative 17 complications (Fig. 11). However, the partial-thickness skin graft that was fixed at the fibula-donor site had total necrosis and the wound healed after 3 months of debridement Vaseline gauze dressing application (Fig. 12). The final HP examination of the specimen confirmed the initial HP diagnosis and free surgical margins were achieved.

A follow-up program was scheduled by CBCT examination, twice annually for the first five years and then annually for 20 years. The patient was free of recurrence at the first follow-up appointment (Fig. 13).

Discussion

The aforementioned tumors had the specific clinical and radiological features of ameloblastoma, appearing as large, soup balloons designed, radiolucent images with scalloped margins, associating expansion of the cortical mandibular bone. Moreover, both patients had partial resorption of the cortical bony plate. The tumors displaced the mandibular canal, and the roots of the teeth were included into the tumors, similar to the ameloblastoma characteristics described in the literature [10].

Despite the evident features of ameloblastoma, the final diagnosis requires a biopsy. Each case had an incisional biopsy before ablative and reconstructive surgery. Some research suggested that ameloblastoma produces bioactive factors that can be used as a diagnostic marker or as a molecular target for drug therapy [26]. Calreticulin is a protein produced by ameloblastoma that can be used as an adjunct diagnostic tool. Also, this specific immunohistochemical marker can differentiate ameloblastoma from keratocystic odontogenic tumor [27]. Matrix metalloproteinase (MMP) and Receptor activator of nuclear factor kappa-β ligand (RANKL) are also bioactive factors present in ameloblastoma tumors that provide a favorable environment for tumor growth by increasing bone resorption and tumor extension. The innovative treatment of molecular targeted ther-

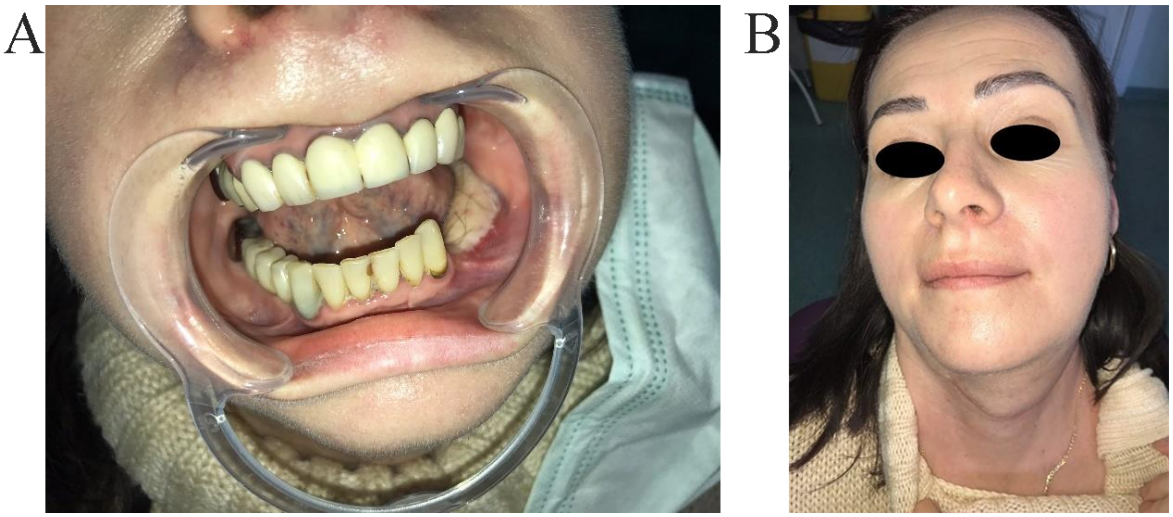

Fig. 6: Postoperative clinical view. A) Intraoral view. B) Extraoral view.

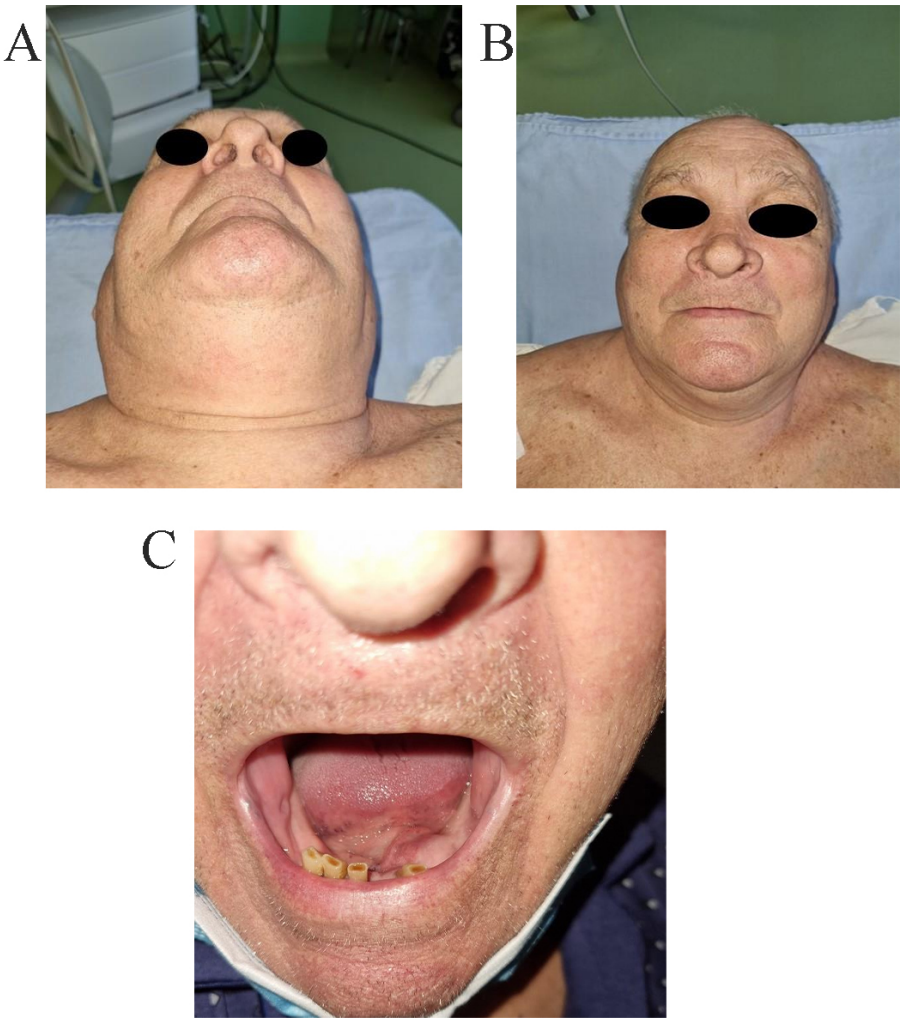

Fig. 7: Preoperative clinical images; A) and B) Extraoral images; C) Intraoral image.

apy with mutant BRAF inhibitors showed important therapeutical results that have the potential of reducing the functional and cosmetic deficiency of the patient after radical surgery [26]. At the time of diagnosis, we were not able to use these markers. However, they may be useful in the diagnosis of ameloblastoma and further in non-surgical treatment. Moreover, large tumors, as presented in our case, can associate early and late complications. Early complications

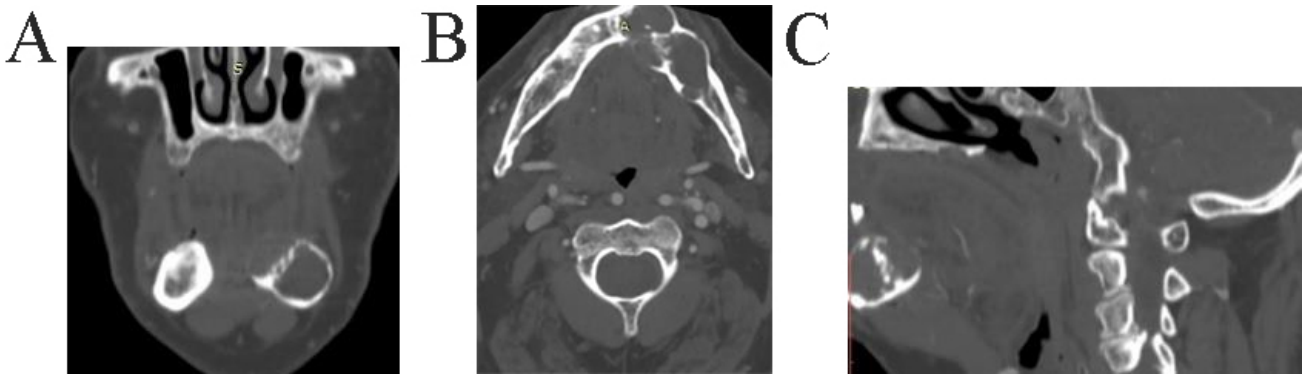

Fig. 8: Preoperative CT imaging illustrating large radiolucent bone lesion of the left mandible: A) Coronal view; B) Axial view; C) Sagittal view.

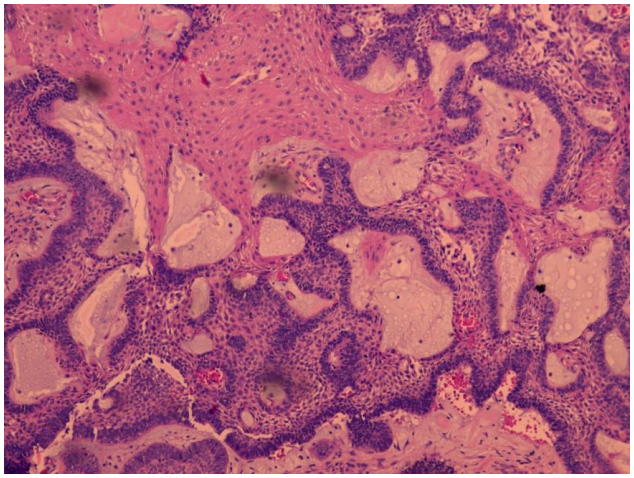

Fig. 9: Histopathological examination of the tumor fragments suggests ameloblastoma.

include hypoproteinemia associated with the protein diffusion through the cyst wall, secondary generalized edema, and secondary anemia due to chronic bleeding from tumor ulceration. Later, trismus and the intraoral bulk of a large tumor will interfere with food intake and speech, and the patients may present upper airway obstruction. These health problems significantly improve after treatment [8]. In our cases, the patients presented mild complications seen in blood test results that showed changes in levels of platelet, gamma-glutamyl transferase, blood glucose, levels of Sodium, Potassium, and eosinophils. Also, our patients complained about mild pain on the tumor site, probably due to the compression of the tumor on the inferior alveolar nerve.

Both of our case cases presented the most aggressive variant of ameloblastoma, multicystic ones with follicular and plexiform histopathological differentiation. These tumor variants penetrate the cortical plates of the bone and invade the overlaying periosteum, that causes tumor expansion beyond the radiological and clinical margins and into the soft tissues [28]. Hence, due to the high risk of recurrence, radical treatment was chosen, and a wide excision was planned preoperatively.

The recurrence rate of ameloblastoma after large bone resection, such as in our cases is approximately 13% in the literature, compared with conservative treatment that has a relapse of approximately 60% [17]. Suboptimal treatment may be due to incorrect diagnosis or technical challenges. Moreover, older age and malignant transformation present poor outcomes [8,28]. Some reports indicate an adjuvant therapy by using I^{125} brachytherapy, with high doses of radiation 110 Gy, that may reduce the risk of recurrence in case of suboptimal treatment or aggressive variants [28,29]. However, in our free surgical margins cases no further treatment was necessary. Ameloblastoma relapse mostly in the first five years after treatment (69.6%) with special consideration for the mandible site [30]. Regarding the conservative treatment, recurrent ameloblastoma can develop earlier, Singh et al. reported 9 relapsed cases in three years of follow-up after ameloblastoma enucleation, in patients with a mean age of 35 years old [31]. However, the time of relapse can be much longer in some cases, up to 20 years, with radical resection being a significant factor for a low recurrence rate of ameloblastoma [31,32]. For example, Beecher et al. indicated an interesting case of recurrent ameloblastoma at 23 years after radical resection and fibula-free flap reconstruction [34]. The three-dimensional examination is best suited for follow-up, due to the capacity of identifying tumor relapse from early stages. Our patients' follow-up program was set up twice annually in the first five years and annually after that, by CBCT examination, due to the high risk of recurrence related to the aggressive histopathological type.

We used fibula-free composite flap for the reconstruction of the defects in both patients. Advancements in surgical techniques made possible the improvement of the vascularized fibula bone graft and its usage in the reconstruction of jaw defects. This flap is optimal for bone and soft-tissue defect reconstructions due to the high quantity of available bone and the composite reconstruction possibility. Also, a vascularized fibula flap is a predictable flap due to large and constant vessels that support the bone and the adjacent soft tis-

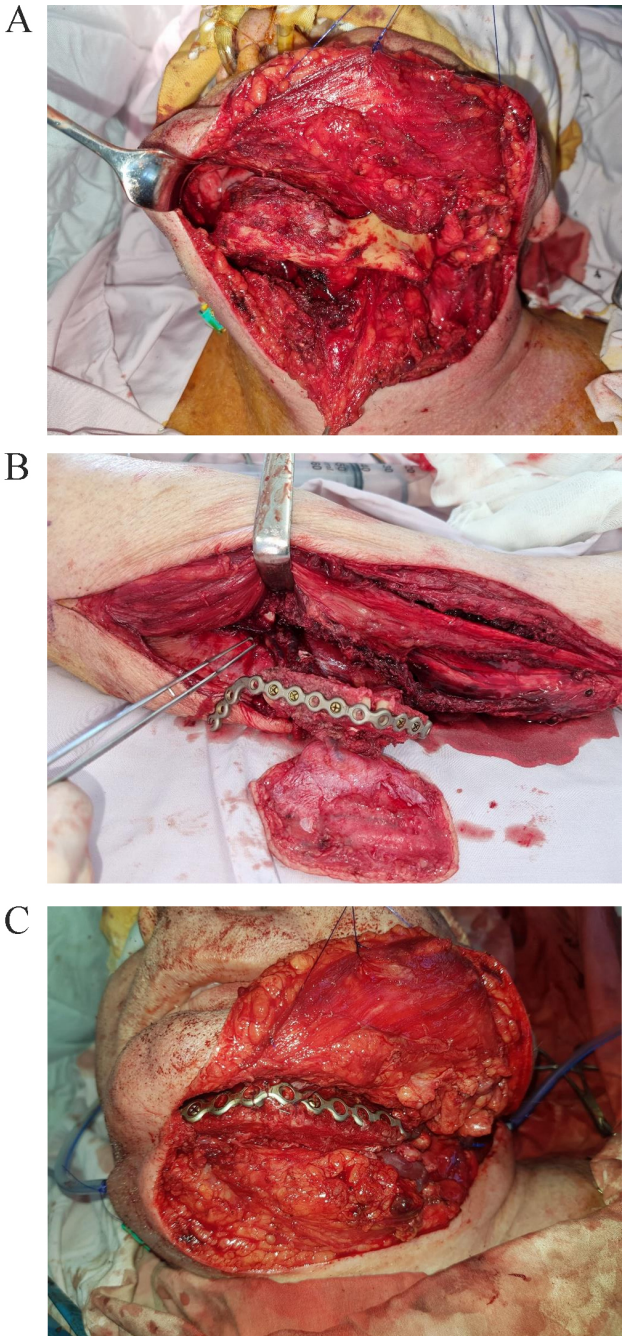

Fig. 10: Intraoperative images: A) Large bone tumor with buccal plate erosion; B) Fibula-free composite flap harvesting and conformation using a load-bearing plate (the instrument indicates the peroneal vascular pedicle); C) Fibula inserted into the surgical defect and fixed with screws.

sue. For example, Adeel et al. used free vascularized fibula in 11 of the 15 cases of mandibular ameloblastoma and lost none of them [13]. The fibula-free flap can be used even in recurrent ameloblastoma that was previously radically treated and reconstructed with a vascularized bone flap [31,34]. We used the one-barrel technique due to the discrepancy between the high of a double-barrel fibula and the height of the remnant mandible in the reported patients. Also, in our cases, we need to reconstruct the lateral mandible, not the anterior part where the double barrel technique is best suited [24,35]. Moreover, we used a load-bearing plate in one case and multiple osteosynthesis plates in the other case. This choice was based on the region of the defect and the anatomical design of the fibula. However, both techniques had good healing of the flap. Similarly, Srivastava et al. used multiple plates for fibula-free flap osteosynthesis, that were removed before implant placement [36].

The immediate reconstruction of segmental mandibular resection is essential, restoring the continuity of the bone that offers support for the lower third of the face and the muscle attachments, even in large bony defects. The fibula flap is indicated as the workhorse for mandibular reconstruction in a systematic over 25 years of Brown et al. [37]. The very good periosteal blood supply of the fibula permits a well bone contouring and dental rehabilitation by implants. However, the bone volume and the skin flap of the fibula-free flap are more generous and can be used in larger defects, including more than one mandibular part [25]. Also, due to the vascularized bone, the union between the graft and the remnant bone fragments of the mandible appears very soon (4 to 6 weeks) and the resorption and remodeling process is less important compared with non-vascularized bone graft [38]. Kalwagadda et al. reported less rate of complications in fibula-free flap (3.5%) compared with the 28% complication rate in free grafts and 18% in reconstruction plates used for mandibular resection management [39].

Moreover, the surgery can be performed by two different teams, a resection team and a harvesting team, hence reducing the time of general anesthesia [35]. The time required by the surgery to be performed, in the case of free fibula reconstruction, was 9 hours and a half and in the case of the non-vascularized bone graft or plating was 3 hours and three-quarters in Adeel el al. paper [13]. In our reports, the surgery lasted shorter, approximately 8 hours.

The fibula-free flap is the golden standard reconstruction for large mandibular resection after tumor excisions in our hospital. We have used free-fibula flap in 24 cases in the last 8 years, 4 benign tumors and 20 malign tumors or osteoradionecrosis, with patients' age ranging from 16 to 74 years old (unpublished data). Also, until now, we did not lose any fibula-free flap reconstruction, but we had local complications, such as plate-associated osteitis (4 cases) or oral wound dehiscence (2 cases). All patients were conservatively treated by debridement (5 cases), except one cancer patient treated before by radiotherapy that associated plate exposure and required removal of the load-bearing plate (1 case). Also, we had skin graft necrosis on the fibula-donor site (2 cases) that required debridement and healing by secondary intention.

The facial artery is a good recipient vessel for the vascularized flaps of maxillofacial reconstruction. The vascularized fibula pedicle is well suited for anastomosis with this vessel [40,41]. Also, the anastomosis of the fibula can be per-

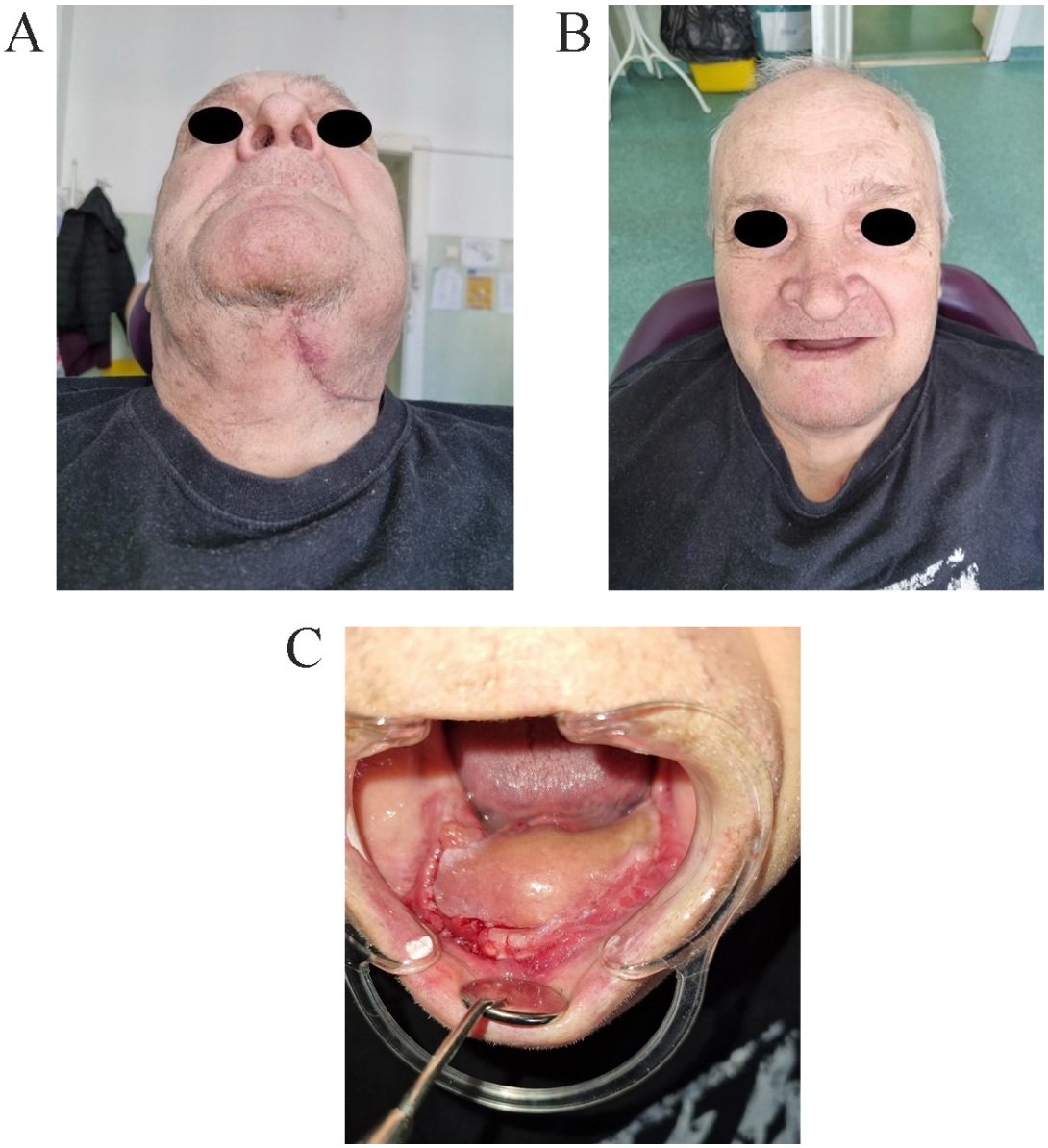

Fig. 11: Postoperative clinical images; A) and B) Extraoral images; C) Intraoral image.

formed in a retrograde way if the fibula matches the defect in the opposite direction [42]. We performed arterial anastomosis to the facial artery and venous anastomosis to the tiro-lingo-facial venous trunk and the anterior jugular vein in an anterograde fashion. For the anastomosis procedure we used 4.5X magnification loupes (ZEISS EyeMag Pro S, Carl Zeiss Meditec, Germany).

An important particularity of our second case was the delay of the treatment by 4 months due to the pandemic situation. Patients with benign tumors and reconstructive surgeries were not a primary target of treatment during the COVID-19 epidemic period [43].

Conclusion

We conclude that radical resection of large ameloblastoma, especially of those who present aggressive histopathological variants, is the best treatment choice to reduce the risk of recurrence. The fibula-free composite flap is a reliable method for the reconstruction of large mandibular defects resulting from the radical excision of ameloblastoma tumors. Patients need to respect the follow-up program for a long period of time after surgery.

Summary

L'ameloblastoma è un tumore osseo borderline che origina dall'epitelio residuo dei germi dei denti, dall'epitelio dell'organo dello smalto o dall'epitelio delle cisti odontogene. Il comportamento aggressivo dell'ameloblastoma, soprattutto delle varianti multicistiche o delle forme follicolari e plessiformi, rende la gestione impegnativa per la necessità dell'escissione radicale del tumore e della ricostruzione funzionale ed estetica del difetto chirurgico.

Fig. 12: The fibula donor site with the partial-thickness skin graft necrosis.

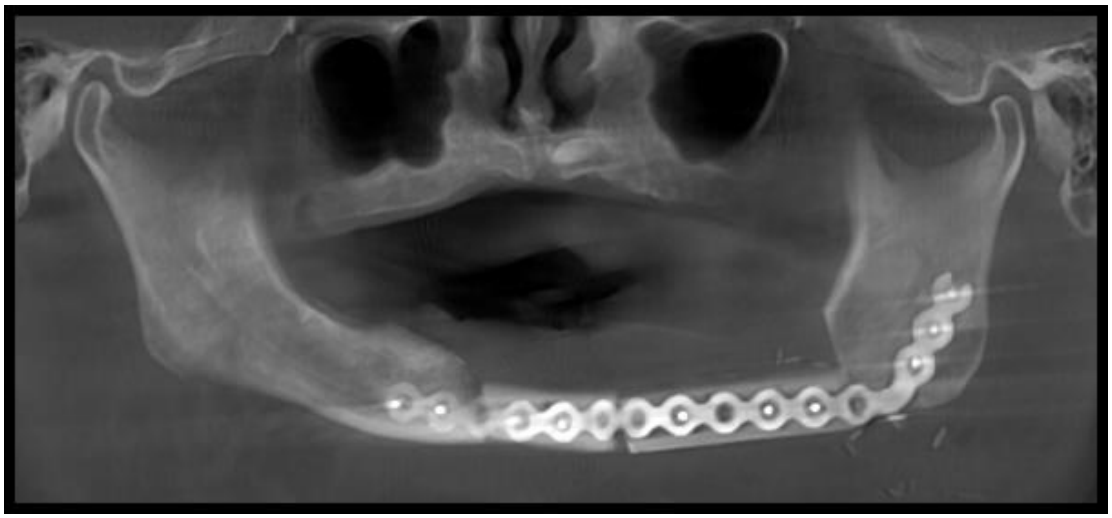

Fig. 13: OPG view at 6 months postoperative with good healing of the fibula-free flap.

Il Lembo libero di fibula (FFF) fornisce una ricostruzione mandibolare predicibile e di alta qualità grazie al peduncolo vascolare di alto calibro, alla lunghezza dell'osso che può ricostruire grandi difetti, alla possibilità di ricostruzione protesica basata su impianti e alla possibilità di prelevare un lembo composito in grado di sostituire la mucosa, proteggendo così la sottostante ricostruzione ossea.

Segnaliamo pazienti adulti femmine e maschi anziani, che sono stati indirizzati al nostro ospedale per tumefazione mandibolare ed esiti istopatologici di ameloblastoma. Le lesioni sono state trattate mediante mandibulectomia segmentale e ricostruzioni FFF. Le placche e le viti di osteosintesi sono state sufficienti per la paziente di sesso femminile per la ricostruzione del difetto mandibolare laterale ed è stata necessaria una placca portante per il paziente di sesso maschile per la ricostruzione del difetto chirurgico che comprendeva la parte anteriore della mandibola. In entrambi i casi è stata utilizzata l'arteria facciale e gli interventi sono durati circa 8 ore. Nessuna recidiva è stata osservata al follow-up e la funzione estetica è stata ben ristabilita.

Concludiamo che il trattamento radicale dell'ameloblastoma è obbligatorio. La funzione estetica potrebbe essere adeguatamente mantenuta da FFF. Inoltre, la ricostruzione FFF è un metodo affidabile per

grandi difetti ossei e dei tessuti molli della testa e del collo, anastomosi microvascolari sull'arteria facciale che offre un buon apporto di sangue del lembo.

References

1. Hendra FN, Van Cann EM, Helder MN, Ruslin M, de Visscher JG, Forouzanfar T, et al.: *Global incidence and profile of ameloblastoma: A systematic review and meta-analysis.* Oral Dis, 2020; 26(1):12-21. Available from: https://pubmed.ncbi.nlm.nih.gov/30614154/

2. Valkadinov I, Conev N, Dzhenkov D, Donev I: *Rare case of ameloblastoma with pulmonary metastases.* Intractable Rare Dis Res, 2017; 6(3):211. Available from: /pmc/articles/PMC5608933/

3. Gunaratne DA, Coleman HG, Lim L, Morgan GJ: *Ameloblastic Carcinoma.* Am J Case Rep, 2015; 16:415-419.

4. Hertog D, Bloemena E, Aartman IHA, van-der-Waal I: *Histopathology of ameloblastoma of the jaws; some critical observations based on a 40 years single institution experience.* Med Oral Patol Oral Cir Bucal, 2012; 17(1):e76. Available from: /pmc/articles/PMC3448205/

5. McLean-Holden AC, Magliocca K: *Pathology Outlines - Ameloblastoma. PathologyOutlines.com website.* Available from: https://www.pathologyoutlines.com/topic/mandiblemaxillaameloblastoma.html

6. Turki IM, Douggaz A: *Up-to date review and case report. A histologic variant of ameloblastoma: the acanthomatous type.* Med Buccale Chir Buccale, 2016; 22:55-57. Available from: www.mbcb-journal.org

7. Milman T, Ying GS, Pan W, LiVolsi V: *Ameloblastoma: 25 Year Experience at a Single Institution.* Head Neck Pathol, 2016; 10(4):513-520. Available from: https://pubmed.ncbi.nlm.nih.gov/27272180/

8. Chae MP, Smoll NR, Hunter-Smith DJ, Rozen WM: *Establishing the Natural History and Growth Rate of Ameloblastoma with Implications for Management: Systematic Review and Meta-Analysis.* PLoS One, 2015; 10(2):e0117241. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0117241

9. Ruquaya M, Singh VP: *Ameloblastoma—A Locally Destructive and Invasive Tumour—Review of Literature.* Int J Otolaryngol Head & Neck Surg, 2014; 3(5):216-222. Available from: http://www.scirp.org/Html/2-2460195_49636.htm

10. Savithri V, Janardhanan M, Suresh R, Kumar R: *Desmoplastic ameloblastoma with osteoplasia: Review of literature with a case report.* J Oral Maxillofac Pathol, 2013; 17(2):298. Available from: /pmc/articles/PMC3830246/

11. Barrett AW, Sneddon KJ, Tighe J V., Gulati A, Newman L, Collyer J, et al.: *Dentigerous Cyst and Ameloblastoma of the Jaws.* Int J Surg Pathol, 2017; 25(2):141-147. Available from: https://pubmed.ncbi.nlm.nih.gov/27621276/

12. Kreppel M, Zöller J: *Ameloblastoma—Clinical, radiological, and therapeutic findings.* Oral Dis, 2018; 24(1–2):63-66. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/odi.12702

13. Adeel M, Rajput MSA, Arain AA, Baloch M, Khan M: *Ameloblastoma: Management and Outcome.* Cureus, 2018; 10(10). Available from: /pmc/articles/PMC6289562/

14. Kalaskar R, Unawane AS, Kalaskar AR, Pandilwar P: *Conservative management of unicystic ameloblastoma in a young child: Report of two cases.* Contemp Clin Dent, 2011; 2(4):359. Available from: /pmc/articles/PMC3276868/

15. Kim J, Nam E, Yoon S: *Conservative management (marsupialization) of unicystic ameloblastoma: literature review and a case report.* Maxillofac Plast Reconstr Surg 2017 391, 2017; 39(1):1-6. Available from: https://jkamprs.springeropen.com/articles/10.1186/s40902-017-0134-0

16. Borrello R, Bettio E, Bacci C, Valente M, Sivolella S, Mazzoleni S, et al.: *A Conservative Approach to a Peripheral Ameloblastoma.* Case Rep Dent, 2016; 2016.

17. Pogrel MA, Montes DM: *Is there a role for enucleation in the management of ameloblastoma?* Int J Oral Maxillofac Surg, 2009; 38(8):807-812. Available from: https://pubmed.ncbi.nlm.nih.gov/19297131/

18. McClary AC, West RB, McClary AC, Pollack JR, Fischbein NJ, Holsinger CF, et al.: *Ameloblastoma: a clinical review and trends in management.* Eur Arch Oto-Rhino-Laryngology 2015 2737, 2015; 273(7):1649-1661. Available from: https://link.springer.com/article/10.1007/s00405-015-3631-8

19. Muñoz-Gutiérrez T, Luna-Ortiz K: *Radical surgery in plexiform ameloblastoma and reconstruction with free fibula.* Rev Mex Cirugía Bucal y Maxilofac, 2017; 13(1):16-19. Available from: www.medigraphic.org.mx

20. Menezes JD da S de, Yaedú RYF, Valente AC, Oliveira M, Taveira LA de A, Bullen IRFR: *Recurrence of multicystic ameloblastoma: case report.* Rev da Fac Odontol - UPF, 2016; 20(3):355-360.

21. Neagu D, Escuder-de la Torre O, Vázquez-Mahía I, Carral-Roura N, Rubín-Roger G, Penedo- Vázquez ángel, et al.: *Surgical management of ameloblastoma. Review of literature.* J Clin Exp Dent, 2019; 11(1):e70-e75. Available from: https://pubmed.ncbi.nlm.nih.gov/30697397/

22. Braimah RO, Ibikunle AA, Abubakar U, Taiwo AO, Oboirien M, Adejobi FA, et al.: *Mandibular reconstruction with autogenous non-vascularised bone graft.* Afr Health Sci, 2019; 19(3):2768-2777.

23. Antúnez-Conde R, Salmerón JI, Díez-Montiel A, Agea M, Gascón D, Sada Á, et al.: *Mandibular Reconstruction With Fibula Flap and Dental Implants Through Virtual Surgical Planning and Three Different Techniques: Double-Barrel Flap, Implant Dynamic Navigation and CAD/CAM Mesh With Iliac Crest Graft.* Front Oncol, 2021; 11:4036.

24. Borghesi A, Nardi C, Giannitto C, Tironi A, Maroldi R, Di Bartolomeo F, et al.: *Odontogenic keratocyst: imaging features of a benign lesion with an aggressive behaviour.* Insights Imaging, 2018; 9(5):883. Available from: /pmc/articles/PMC6206371/

25. Gao N, Fu K, Cai J, Chen H, He W: *The role of folded fibular flap in patients' reconstruction of mandibular defects: a retrospective clinical study.* Sci Reports, 2021; 11(1):1-9. Available from: https://www.nature.com/articles/s41598-021-03331-7

26. Fuchigami T, Ono Y, Kishida S, Nakamura N: *Molecular biological findings of ameloblastoma.* Jpn Dent Sci Rev, 2021; 57:27-32. Available from: https://doi.org/10.1016/j.jdsr.2020.12.003

27. Anandani C, Metgud R, Singh K: *Calretinin as a diagnostic adjunct for ameloblastoma.* Patholog Res Int, 2014; 308240.

28. Aramanadka C, Kamath AT, Kudva A: *Recurrent Ameloblastoma: A Surgical Challenge.* Case Rep Dent, 2018; 8271205.

29. Liu JY, Man QW, Ma YQ, Liu B: *I125 brachytherapy guided by individual three-dimensional printed plates for recurrent ameloblastoma of the skull base.* Br J Oral Maxillofac Surg, 2017; 55(7):e38-e40. Available from: http://www.bjoms.com/article/S0266435617302097/fulltext

30. Yilmaz O, Sagnak-Yilmaz Z, Balaban E, Candirli C, Yilmaz O, Sagnak-Yilmaz Z, et al.: *Management of Recurrence of Ameloblastoma and Odontogenic Keratocyst: A Cross-Sectional Study.* Odovtos Int J Dent Sci, 2020; 22(3):174-186. Available from: http://www.scielo.sa.cr/scielo.php?script=sci_arttext&pid=S2215-34112020000300174&lng=en&nrm=iso&tlng=en

31. Singh CA, Devaraja K, Kumar R: *Recurrent Ameloblastoma: Long Term Outcomes with Free Fibular Bone Graft.* Indian J Otolaryngol Head Neck Surg, 2020; 74:1773-1779. Available from https://doi.org/10.1007/s12070-020-01790-4

32. Au SW, Li KY, Choi WS, Su YX: *Risk factors for recurrence of ameloblastoma: a long-term follow-up retrospective study.* Int J Oral Maxillofac Surg, 2019; 48(10):1300-1306. Available from: http://www.ijoms.com/article/S0901502719311051/fulltext

33. Ram R: *Ameloblastoma relapse after 16 years of resection in symphysis of mandible sparing the bone graft.* Natl J Maxillofac Surg, 2010; 1(2):190. Available from: /pmc/articles/PMC3304200/

34. Beecher S M, Lennon P, O'shaughnessy M, et al.: *Recurrent Ameloblastoma Involving Fibula Neo- mandible: Management with Digital Planning and Reconstruction Using a Contralateral Free Fibula Flap.* Cureus, 2020; 12(4): e7880. DOI 10.7759/cureus.7880

35. Lade AY, Saluja H, Sachdeva S, Shah S: *Reconstruction of large ameloblastoma crossing midline with free fibula flap- A case report.* IP International Journal of Maxillofacial Imaging, 2022; 8(1):16-19. Available from: https://doi.org/10.18231/j.ijmi.2022.005

36. Srivastava G, Padhiary SK, Nayak TK, Mishra N: *Rehabilitation using implants in free fibula flap of a patient with ameloblastoma: Case report with 4-year follow-up.* Natl J Maxillofac Surg, 2022; 13:S194-S198.

37. Brown JS, Lowe D, Kanatas A, Schache A: *Mandibular reconstruction with vascularized bone flaps: a systematic review over 25 years.* Br J Oral Maxillo Fac Surg, 2016; 55(2):113-126.

38. Chai KS, Omar FH, Mat Saad AZ, Wan Sulaiman WA, Halim AS: *A 20-year experience of immediate mandibular reconstruction using free fibula osteocutaneous flaps following ameloblastoma resection: Radical resection, outcomes, and recurrence.* Arch Plast Surg, 2019; 46:426-432. Available from: https://doi.org/10.5999/aps.2018.01487

39. Kalwagadda S, Kumar B, Nair SC, Shah AK, Shroff SS: *Management of Ameloblastoma with Free Tissue Flap in Comparison with Other Reconstructive Options Available.* J. Maxillofac. Oral Surg, 2020; 19(2):283-288. Available from: https://doi.org/10.1007/s12663-019-01203-2

40. Zheng L, Lv X, Shi Y, Zhang J, Zhang J: *Intraoral anastomosis of a vascularized iliac-crest flap in maxillofacial reconstruction.* J Plast Reconstr Aesthetic Surg, 2019; 72(5):744-750. Available from: http://www.jprasurg.com/article/S1748681518304534/fulltext

41. Hoffman GR, Islam S, Eisenberg RL: *Microvascular reconstruction of the mouth, face and jaws. Oromandibular reconstruction – free fibula flap.* Aust Dent J, 2012; 57(3):379-387. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1834-7819.2012.01709.x

42. Nambi GI, Dhiwakar M: *Retrograde vascularisation of fibula free flap in composite oro- mandibular reconstruction.* Indian J Plast Surg, 2013; 46(1):134. Available from: /pmc/articles/PMC3745101/

43. Kwon TG: *Maxillofacial surgery beyond the perfect storm of COVID-19.* Maxillofac Plast Reconstr Surg, 2021; 43(1):1-2. Available from: https://jkamprs.springeropen.com/articles/10.1186/s40902-021-00293-8