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Pediatric Malignant Mandibular Tumors: Personal Experience and Literature Options Discussion

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Keywords
Pediatric mandibular reconstruction · Mandibular tumor · Mandibular defects · Rib grafts · Osteochondral grafts

Abstract
Introduction: Mandibular defects reconstruction could result challenging in childhood, due to facial and mandibular growth patterns. For these reasons, the choice of the most suitable reconstructive option in pediatric patients, affected by mandibular malignancies, still objects of debate. ***Objective:*** The aim of our study was to compare our reconstructive schedules to the existing literature in order to give a personal contribute to the present panorama. ***Methods:*** We performed, in October 2019, a retrospective evaluation of pediatric patients treated for biopsy-proven mandibular malignancies at our Institute between January 2013 and December 2016. All of them received multimodal therapy in accordance with standard guidelines and their demographic, clinical, treatment, and outcome parameters were collected and analyzed. ***Results:*** We observed a shorter duration of surgery, a faster tracheostomy tube and feeding-tube removal, and a minor hospitalization in patients who received grafts transfer compared to those who underwent microsurgical mandibular reconstruction. After a 36-month period of follow-up, osteochondral grafts showed a pattern of growth similar to the mandibular epiphysis (condilylion-gonion linear and vertical ratio ranging to 0.96–1.03 and 1–1.02 at orthopantomogram, respectively). No bone consolidation delays and functional impairment were recorded. ***Conclusions:*** Free flaps mandibular reconstruction in children needs to be better assessed and proximal fibular epiphyseal free flap indication might deserve further studies. Osteochondral grafts find indication for lateral defects, 50–55 mm in maximum length and located in the mandibular ramus, without massive teeth or soft tissue defect. Condyle involvement does not represent an absolute contraindication to rib graft use.

Introduction

Head and neck malignant bone tumors are extremely rare in pediatric population and they mainly include sarcomas, Burkitt lymphoma and metastatic tumours. Sarcomas are the most frequent and they comprise approxi-

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mately 1–2% of all the head and neck malignancies in children [1, 2]. In most of the cases, they affect the mandibular bone, and their main symptoms include facial swelling or palpable mass, pain, facial paresis, dental mobility and/or dental loss, and hypesthesia along the dental nerve area [3]. Males are more often affected than females (male-to-female incidence ratio is 1.4:1) and the median age at diagnosis is usually 11 years, with a peak of incidence during the puberty. Histology type distribution encloses osteosarcoma as the most common bony malignant lesion, followed by Ewing sarcoma and chondrosarcoma with a percentage of incidence of 43.6, 28.4, and 14.2%, respectively [1].

Surgery represents the main therapeutic option, but in case of high-grade sarcomas curative attempt provides neoadjuvant chemotherapy and/or adjuvant radiation-chemotherapy in association with ablative surgery [3–5]. In this scenario, the achievement of free resection surgical margins appears to be a significant prognostic factor for survival; thus, wide surgical resection is demanded in order to obtain complete tumor excision and to ensure high chance of recovery to the small patients [6]. According to these primary goals, wide tumor resection demands wide mandibular defects reconstruction, which represents an acknowledged challenge in childhood. In specific, facial and mandibular growth patterns, as well as the preservation of permanent dentition, need to be counted into functional purposes in order to gain balanced dental occlusion restoration [7, 8].

Among the great variety of reconstructive options, the most frequently ones used are rib grafts [9, 10] and fibula and iliac crest flaps among microvascular osteocutaneous free flaps [7, 8, 11]. To limit donor site morbidity does always represent a primary goal in each of the abovementioned tissue transfer choices [7, 8].

Although there is agreement in literature about the need of an immediate defect's reconstruction after surgical removal of malignant bone tumor, the choice of the most suitable reconstructive option in pediatric patients is currently subject of debate because of the rarity of the disease and the anatomic and functional peculiarities in this population. For these reasons, we performed a retrospective evaluation of all pediatric patients treated for bone malignancies in our Institute over the last 8 years, focusing our attention on the applied reconstructive strategy with the purpose to compare our reconstructive schedules to the existing literature in order to give a personal contribute to the present panorama.

Material and Methods

Between January 2013 and December 2016, 8 children, aged 18 years or younger, were referred to our Institution, Anna Meyer Children Hospital in Florence, to be evaluated for biopsy-proven mandibular bone malignancies. All of them underwent curative treatment in accordance with specific Italian and European clinical trial, according to their stage and pathology, and all of them received a multimodal therapy [12–14].

Only patients who underwent ablative surgery associated or not with neoadjuvant either adjuvant therapies, those who had not previous head and neck treatments, or whose clinical chart records were complete, and patients with at least 36 months of post-treatment clinical follow-up were included in our retrospective observational analysis. The absence of parents' consent agreement to share their own kids' clinical data for research purposes was considered as exclusion criteria. All of the performed procedures were in accordance with the Helsinki Declaration of 1975 as revised in 1983. All of the patients' parents included in the study, signed an informed consent agreement to allow the surgical team, comprising plastic and maxillofacial surgeons, to operate on their children, to collect their parameters, and to use their photos for research purpose.

The information collected included: (1) patients' demographic data; (2) medical history; (3) physical examination, such as primary tumor presentation (site of swelling, its relationship with the surrounding tissue, functional characteristics and changes, presence or absence of cervical lymph nodes), magnetic resonance imaging (MRI) and/or computed axial tomography (CAT) scans; (4) treatment administered, including extension of surgical tumor resection and defect reconstruction, plus neoadjuvant and/or adjuvant systemic therapy; (5) final histopathology report; (6) early and late complications, and (6) clinical functional and oncologic outcomes over the posttreatment follow-up period, focusing on occlusion, facial symmetry restoration, and mandibular deviation issues. In order to give an objective evaluation of the mandibular growth, we analyzed ortophantograms at 12, 24, and 36 months, and we compared the measurement of the healthy and reconstructed side regarding the length of the ramus (condylion-gonion linear and vertical distance), the mandibular body length (gonion-gnathion distance), and the total mandibular length (condylion-gnathion distance) in accordance with previous published reports [8].

Results

We analyzed a total number of 4 patients, 3 males, and 1 female, ranged in age from 7 to 14 years at primary diagnosis, as reported in Table 1. The remaining 4 patients were excluded from our analysis because not meeting the declared inclusion criteria (2 patients were not eligible for surgical resection, 1 patient had uncompleted records, and in the remaining case, the patients did not give their consent to enroll their kid's parameters for research purpose). All the enrolled patients reported in their past medical history a progressive growth mandibular swelling, while mandibular pain and arthralgia were reported

Table 1. Clinical presentation, surgical treatment, complications, and oncological outcomes of the enrolled patients

	Patient 1	Patient 2	Patient 3	Patient 4
Clinical presentation				
Age, years	11	11	7	14
Sex	M	F	M	M
Comorbidity	No	No	Tetralogy of Fallot	No
Side	Right	Left	Right	Right
Size (maximum diameter), mm	45.6	50	56	65
Symptoms	Mandibular swelling	Mandibular swelling	Mandibular swelling	Mandibular swelling, pain, and arthralgia
Angle of mandible involvement	Yes	Yes	Yes	Yes
Condylar involvement	Yes	No	Yes	Yes
Glenoid cavity involvement	No	No	No	No
Tooth involvement	Yes (eighth dental gem)	Yes (eighth dental gem)	Yes (47 and eighth dental gem)	Yes (eighth dental gem)
Nodal involvement	No	No	No	No
Metastatic lesions	No	Yes (rib VIII)	No	No
Histology	EW	EW	OS	OS
Treatment and outcomes				
Protocol of treatment	ISG/AIEOP EW113	ISG/AIEOP EW214	ISG/OS215	ISG/OS215
Neoadjuvant CHT	Yes	Yes	Yes	Yes
Mandibulectomy (sec. Brown)	Ic	I	Ic	Ic
Reconstruction	Osteochondral rib grafts	Osteochondral rib grafts	Fibular free flap	Fibular epiphyseal flap
Duration of surgery, min	300	270	600	600
Tracheotomy, days	6	5	13	11
NGFT, days	7	6	17	14
Early complications	No	No	Yes (flap removal and reconstruction with rib graft)	Yes (arthrotomy)
Margins	Negative	Negative	Negative	Negative
Adjuvant CHT	Yes	Yes	Yes	Yes
Adjuvant RT	No	No	No	No
DFS, months	30	24	27	60
Recurrence	No	No	No	No

NGFT, naso-gastric feeding tube; OS, osteosarcoma; EW, Ewing sarcoma.

by only 1 patient (patient 3). Two out of them were affected by Ewing sarcoma (patients 1 and 2), while the remaining 2 patients presented mandibular osteosarcoma. No patients reported comorbidity, except for the patient 3 who was affected by Fallot's tetralogy.

Mandibular ramus and its angle represented the site of origin of all of the tumors; and, in patients 3 and 4 even the mandibular condyle and its glenoid cavity resulted to be involved at the pre-operative MRI (Fig. 1). Tumor's maximum diameter ranged between 45.6 and 60.0 mm. The right hand side of the mandible was more often affected in our series (in patient 1, 3, and 4; 75%) (Table 1). All of the patients received neoadjuvant chemotherapy in accordance with the NCCN treatment protocol guidelines and recent literature reports [15]; then, once the lesion was found to be resectable at the restaging MRI and thorax CT scans, surgery was proposed.

We performed type Ic mandibulectomy [16] in all of the patients, apart from the patient 2, whose condyle was

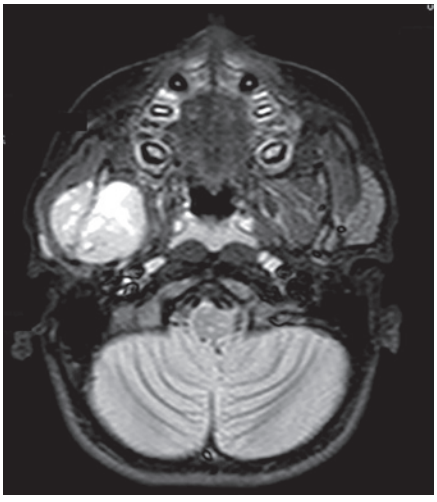

Fig. 1. Preoperative MRI scan (T2 sequence). EW of right mandibular ramus with condylar involvement (patient 1). EW, Ewing sarcoma.

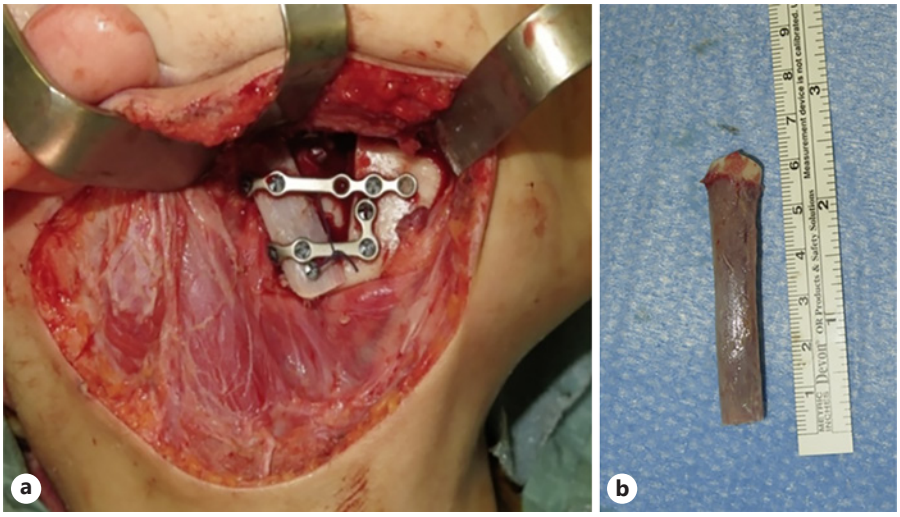

Fig. 2. Mandibular reconstruction with osteochondral rib grafts after type Ic mandibulectomy sec. Brown (patient 1) (**a**); osteochondral rib graft (**b**).

Table 2. Functional outcomes of all of the 4 enrolled patients

Patient	Mandibular measurement after first surgery				Final outcomes			
	condilylion-gonion ratio	condilylion-gonion vertical ratio	gonion-gnathion ratio	condylion-gnathion ratio	facial symmetry	occlusion	subjective assessment	functional limitation
1	0.96	1.00	0.99	0.96	Optimal	Maintained	Optimal	None
2	1.03	1.02	1.00	1.03	Optimal	Maintained	Optimal	None
4	1.30	1.25	0.79	1.03	Good	Maintained	Good	None

spared by the disease. We always performed simultaneous reconstruction as following: fibula-free flap in patient 3, fibular epiphyseal-free flap in patient 4, and osteochondral rib graft in the remaining 2 patients (patients 1 and 2) (Fig. 2). No patients required soft tissue repair.

Temporary tracheostomy and naso-gastric feeding tube (NGFT) placement were always used to prevent airway compromise, to promote oral wounds' fast healing, and to guarantee an optimal postoperative nutrition. Tracheostomy tube removal and oral intake starting were recorded between 13 and 17 days postoperatively, and median hospital stay was of 14 days. In specific, patients 1 and 2, who both underwent osteochondral rib graft reconstruction, had a shorter surgical operative time (median 315 min), a more rapid tracheostomy tube and NGFT removal (about 6–7 days after surgery) and a maximum hospital stay of 11 days in comparison to patients 3 and 4, who had free flap microsurgery procedure (Table 1).

Regarding early complication, no partial or total flap necrosis occurred in our series; however, 1 patient (patient 3) required flap removal and salvage reconstruction with osteochondral rib graft because of local infection and wound dehiscence with bone exposure which occurred within the first postoperative month. The following secondary recovery was uneventful.

Final histology reports showed tumor-free resection margins and a complete histological response after neoadjuvant therapy in 100% of the cases. In addition, patients 3 and 4 had a total remission of disease (Grade 4: 100% of necrosis) in accordance with Huvos system [17]. All of the patients underwent adjuvant chemotherapy according to the clinical protocol, whereas no one required postoperative radiotherapy [12–14]. Data regarding patients' protocol of treatment and follow-up are summarized in Table 1.

Global follow-up time ranged from 36 to 84 months, and none of the patients had tumor recurrence. Functional and esthetic outcomes were analyzed at 12, 24, and 36 months postoperatively (Fig. 3). In specific, orthopantomogram and magnetic resonance imaging were performed at 3 months after surgery to assess post-

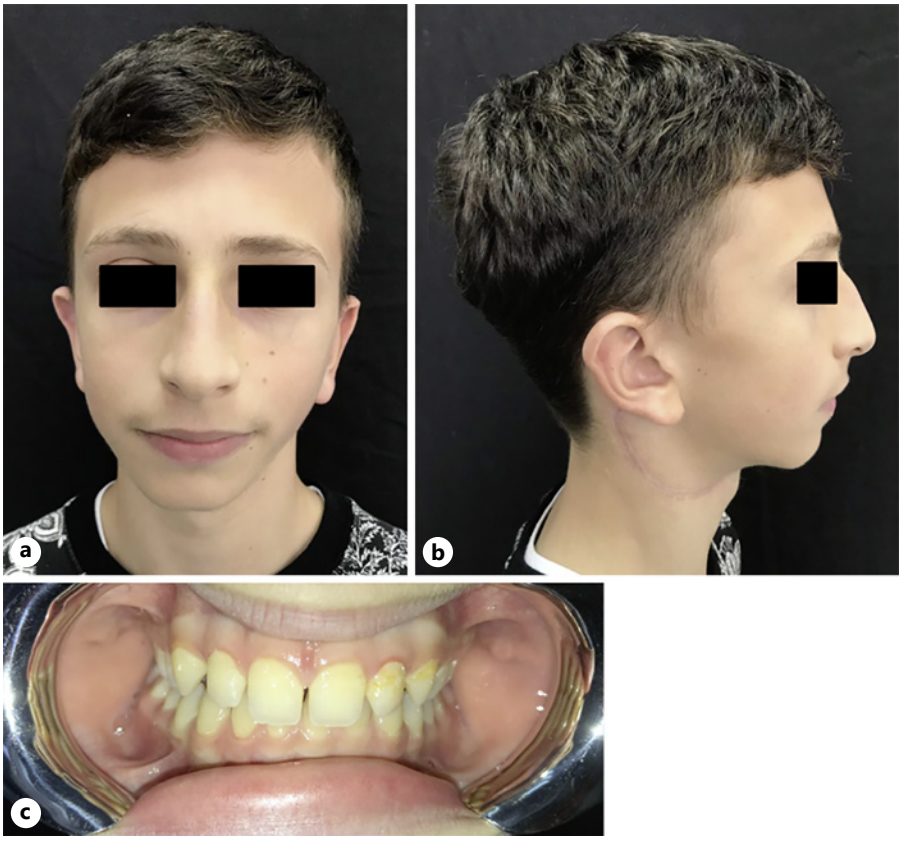

Fig. 3. Clinical evaluation at 30 months after mandibulectomy and osteochondral rib grafts reconstruction (patient 1). Frontal view (**a**); lateral view (**b**); and mandibular occlusion (**c**).

surgical mandible consolidation. We choose 2.0-mm titanium miniplates and monocortical screws as the osteosynthesis system in all patients and no delayed healing, lack of stability, or pseudarthrosis was detected; on the other hand, patient 3 developed mandibular osteomyelitis and partial plates exposure as early complication, which required a salvage procedure as reported previously.

Regarding bone reconstruction outcomes, Table 2 summarizes the measurements of each patient orthopantomograms. Patients 1 and 2 showed a good agreement between the reconstructed and the healthy hemi-mandible with regard to the length of the reconstructed ramus and the position of the angle (Fig. 4). On the other hand, we observed in patient 4 a disproportionate growth of the fibular epiphyseal free flap resulting in an evident facial asymmetry with an excessive length of the reconstructed mandibular branch (condylion-gonion ratio = 1.30 and condylion-gonion vertical ratio = 1.25 at the 12-month postoperative time orthopantomogram) and a mandibular deviation toward the healthy side (Fig. 5). In order to correct the resulting malocclusion, we performed an arthrotomy and right condylectomy to re-establish the mandibular symmetry (Fig. 6). No other late complications were recorded in both donor and receiving sites in the remaining cases, and we did not observe any major impairment in chewing, speech, phonation, and breath at least in 3 years of follow-up.

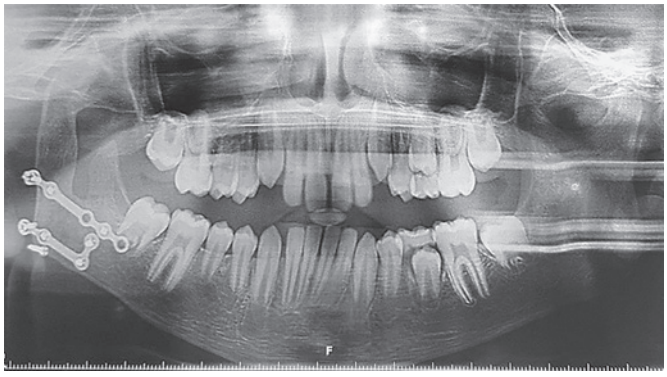

Fig. 4. Orthopantomogram at 30 months after mandibular reconstruction with rib grafts (patient 1).

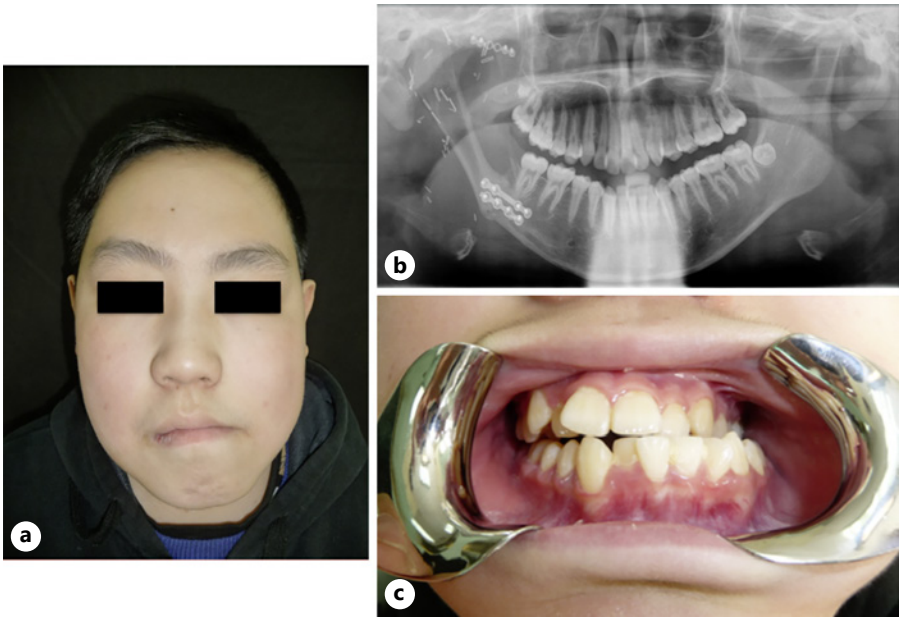

Fig. 5. Patient 4 with a: disproportionate growth of the fibula epiphyseal free flap resulting in an evident facial asymmetry (**a**), with an excessive length of the reconstructed mandibular branch (condylion-gonion ratio = 1.30 and condylion-gonion vertical ratio = 1.25 at the 12-month postoperative time orthopantogram) (**b**) and a mandibular deviation toward the healthy side (**c**).

Discussion

Mandibular defect reconstruction in pediatric patients might represent a challenge for surgeons. Unlike in the adult, the most considerable aspects for reconstructive choice in pediatric population are defect's extension and restoration of a proper occlusal plane by considering mandibular and condylar pattern of growth, while comorbidities and previous head and neck treatments are more rarely noticed [8, 11, 18].

Mandibular growth depends mainly on two mechanisms: epiphyseal proliferation and bone remodeling. The first one is responsible for mandibular growth during the first 18 years of life, and it depends on the integrity of the mandibular epiphysis, which is located just beneath the condyle in the proximal sub condylar ridge; thus, its preservation together with condyle and glenoid cavity saving are strongly recommended. The second mechanism, which takes place in adulthood, is determined by the action of masticatory muscles; for this reason, it is important to save the soft tissues, when feasible [18]. Other important aspects to consider when planning pediatric mandibular malignancies treatment are patient's age and indications to adjuvant radiotherapy; in fact, a recent review reported a better functional outcome incidence in patients aged between 8 and 12 years, who did not undergo postoperative radiation, which showed a negative impact on mandibular growth [11].

Among the great variety of reconstructive options, free flaps represent the most frequent choice for mandibular reconstruction after tumor resection in childhood. Most of the authors do prefer the osseous or osteocutaneous fibula-free flap, while iliac crest-free flap seems to find fewer indications [7, 8, 11]. Bianchi et al. [8] reported a 100% of flap survival success rate with no major neither minor complications at either the donor or recipient sites after free flap reconstruction of mandibular defects. In their case series, only 1 patient underwent a second surgery for significant scar retraction and facial asymmetry at 4 years after the primary treatment, whereas no patients presented functional impairment in swallowing and speech. Even if condylar resection was performed in only 1 patient, the author reported a slight decrease in growth of the reconstructed mandible in all of their cases, despite an optimal facial symmetry, and mid-face and maxilla development were documented at the frontal analysis. Nevertheless, because of the rarity of the disease and the small number of studies published in literature, the fibula graft growth cannot always be predicted, and there are no specific factors that can influence its development. Moreover, complications such as weakness, tibia fractures, and ankle instability may occur at the donor site [19].

In our small experience, we used free flaps for mandibular reconstruction in only 2 patients; and unfortunately, both of them experienced postoperative complications. One (patient 3) had flap failure due to early local

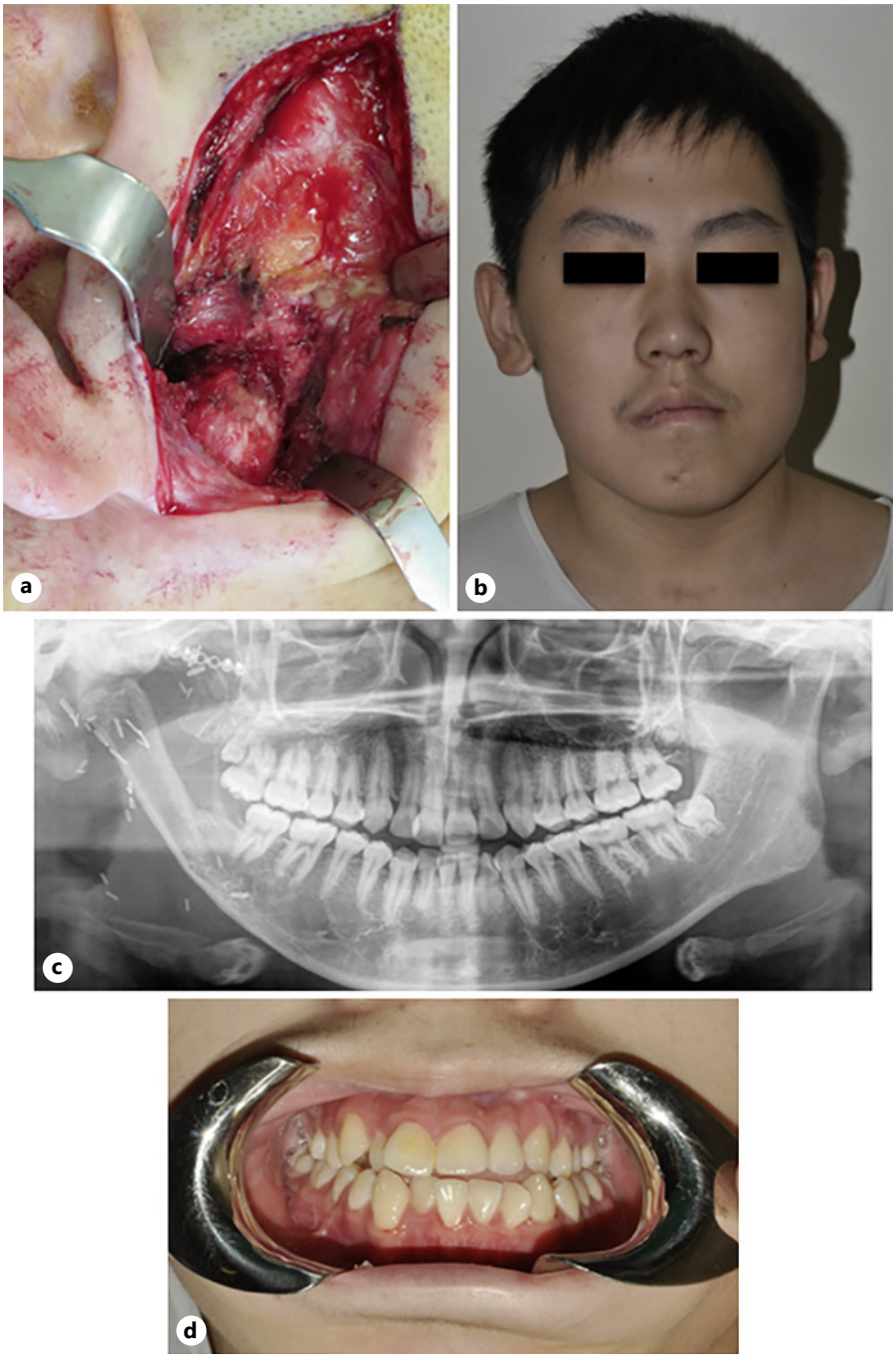

Fig. 6. Two years postoperative primary treatment patient 4 underwent arthrotomy and right condylectomy to re-establish his mandibular symmetry Treatment and outcomes (**a**); and his 5-year follow-up final esthetic results (**b**) with the orthopantogram exam (**c**) and final dental occlusion (**d**).

infection, while patient 4 needed further surgical procedures to restore facial symmetry and dental occlusion (Table 1).

In our opinion, the occurrence of postoperative osteomyelitis in patient 3 was mainly linked to his comorbidities rather than merely surgical issue. In our patients, we performed the mandibular osteosynthesis by using 2.0-mm titanium miniplates. Despite the lack of recent literature regarding mandibular fixation in pediatric patients following surgical mandibulectomy with bone grafts reconstruction, the use of titanium miniplates is considered effective and safe; in fact, it guarantees mandibular restoration and functional outcomes comparable with other techniques, such as biodegradable plate, and does not in-

volve an increased risk of post-surgical infective complications, even if osteosynthesis tools might had increased and maintained the local infection when present [20–22].

Even patient 4, who underwent proximal fibular epiphyseal-free flap, was not speared by late complications. This flap, based on the anterior tibial artery, was first introduced in clinical practice at the end of the 90s for the upper limb reconstruction in children because of its promising advantage to preserve the bone growth potential [23]. Despite interesting results in this field, we noticed an excessive epiphyseal proliferation of the flap during mandibular growth.

In our experience, even if free flaps could represent a good option for mandibular reconstruction in pediatric patients, they determine an increase of surgical time (600 min in free flaps compared with 300 min in rib graft use), a delayed tracheostomy tube and NGFT removal and consequently a longer hospitalization. However, despite brilliant results published in the literature, grafts might show promising outcomes, especially, when mandibular defect does not determine an important soft tissue and teeth involvement. Accordingly, Eckardt et al. [9] described their experience in lateral mandibular defects reconstruction through osteochondral rib grafts in 4 patients. No complications were recorded and all of patients were discharged in about 10 days; however, during follow-up, a slight vertical growth excess and transversal growth inhibition of the reconstructed mandible were observed at orthopantomogram.

We performed osteochondral grafts for lateral mandibular defects reconstruction as first option in 2 patients, and as salvage procedure after free flap transfer failure in another case. All of the grafts showed good consolidation and we did not record any postoperative complications both at the donor site and at the receiving site. Regarding functional outcomes and the objective and subjective esthetic results, we observed a complete preservation of the facial profile and symmetry without any kind of functional impairment, even in case of condylar reconstruction. As reported in Table 2, osteochondral grafts showed a pattern of growth similar to the mandibular epiphysis with a condylion-gonion linear and vertical ratio ranging between 0.96 and 1.03 and 1–1.02, respectively.

Conclusion

Based on recent literature analysis, with the addendum of our small personal experience, we could affirm that mandibular reconstruction with iliac or rib bone grafts is less invasive but certainly of lower quality in comparison to free flap transfer and for this reason in some cases graft should be considered, since the beginning, as a temporary reconstructive modality. According to our experience, osteochondral grafts represent a good option for lateral mandibular defects reconstruction in pediatric patients because they ensure shorter surgical operating-time and faster hospital recovery compared with microsurgical procedures; in addition, functional outcomes, and mandibular growth pattern do not appear negatively affected. It is worthy of consideration that once the growth of the mandible is over the patient will be able to obtain the definitive reconstruction, including improved function and esthetic outcomes, preferably with microvascular flaps.

Even if our case series is limited in number and longer follow-up are advisable in pediatric population, based on our clinical experience, osteochondral grafting finds indication when mandibular defects do not determine an important teeth or soft tissue impairment and when defect's dimension is <50–55 mm in maximum length and located in the mandibular ramus with or without condylar involvement. However, it should be considered that the rib grafts are not suitable for prosthetic dental rehabilitation and the use of free bone flaps should be preferred in case of a wide defect with massive inferior alveolar crest involvement.

Here, we highlighted the possible late complication that might occur in case of proximal fibular epiphyseal free flap transfer, but since the lack of reports of its indication in head and neck reconstruction, we do not feel to discourage its use in this field, and we prompt further case series studies to better assess its indication in children mandibular reconstruction. Last, neoadjuvant and adjuvant chemotherapy does not appear to compromise the esthetic and functional outcome, while further studies are needed to determine the impact of postoperative radiotherapy on rib grafts reconstruction.

Statement of Ethics

The article is exempt from Ethical Committee approval because it is a retrospective small case series study. All of the performed procedures were in accordance with the Helsinki Declaration of 1975 as revised in 1983. All of the patients' parents included in the study signed an informed consent agreement to allow the surgical team, comprising plastic and maxillofacial surgeons, to operate and collect their children's parameters.

Conflict of Interest Statement

The authors have no conflicts of interest, financial, or otherwise.

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Author Contributions

This manuscript was approved by all authors, and all of them have participated in the writing and correcting of this work. Each author has participated actively in designing and writing this article: Giuditta Mannelli and Giuseppe Spinelli are the main creator and reviewer of the work; Lara Valentina Comini and Giuditta Mannelli wrote the article and revised all of the literature; Angela Tamburini and Marco Innocenti assisted in conception of the study and gave final approval for this version of the manuscript.

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