19 The Future of Bioengineering for Head and Neck Reconstruction: The Customized Free Flap

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19.1 Current Methods of Maxillofacial Reconstruction

The aim of maxillofacial reconstruction is to restore the esthetic form of the affected region while concurrently imparting satisfactory functional ability. This objective has been the main driving force behind the advancements of surgical techniques and biomaterials, pushing through many boundaries over the years. While many options exist for the reconstructive surgeon, they can generally be classified into one of two categories: graft and flap reconstructions. Graft tissue relies on the existing vascular network from the recipient site for neovascularization, healing, and integration. It can be taken from donors of different species (xenograft), from donors of the same species (allograft), or from a different site of the same host (autograft). On the other hand, flap tissue retains its existing vascular network and may require anastomosis to the recipient vessels (free flap). In general, flap surgery can be further divided into three categories: local, regional, and free flaps. While a vast majority of reconstructive options exist, the final selection must consider the characteristics of an existing or prospective maxillofacial defect, the patient's demographics and overall health, and the surgeon's experience and resources.

Traditionally, maxillofacial defects have been commonly reconstructed with autogenous particulate bone contained within an allogeneic crib. Under the ideal conditions, this technique is effective and provides excellent functional and esthetic results. Autogenous bone, in the form of a non-vascularized graft or vascularized flap, is considered the gold standard among biomaterials for reconstructive purposes. It is the only bone graft endowed with osteogenic, osteoinductive, and osteoconductive properties. Allogeneic bone and bone substitutes have been extensively studied over the years, although no single material is yet capable of matching the regenerative potential of autogenous grafts to date. A composite system of biomaterials can often be utilized to augment bone regeneration. In Chap. 13, we discussed the use of particulated allogeneic bone supplemented with bone morphogenetic protein (rhBMP-2) and bone marrow aspirate concentrate (BMAC) to reconstruct maxillofacial

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defects. Non-vascularized autogenous or allogeneic bone grafts require a healthy soft tissue envelope to prevent oral contamination and subsequent graft failure. When such requirements cannot be fulfilled, the surgeon can elect for staged reconstruction where a vascularized soft tissue flap can first be transferred into the defect prior to bone grafting at a later time.

In 1989, the fibula free flap was first reported in the literature as a novel method for mandible reconstruction [1]. It has since remained a workhorse for clinicians by providing consistent, excellent surgical outcomes. In addition to the fibula, osteocutaneous composite flaps such as the deep circumflex iliac artery bone or scapula flaps provide the advantage of simultaneously reconstructing both hard and soft tissue defects in a single procedure. Wounds requiring significant soft tissue augmentation can be reconstructed with the radial forearm or anterolateral thigh free flaps. The option for free tissue transfer provides an excellent solution to maxillofacial defects with compromised soft tissue health as a result of injury, radiation, or postsurgical scarring.

19.2 Limitations Associated with Current Reconstructive Options

While various reconstructive options exist, it is important to understand the goals and limitations of each technique. Mandibular continuity defects require stabilization of the non-resected segments in order to establish a functional occlusion and provide a good esthetic outcome. This can be achieved by placement of a reconstruction plate between the segments, with or without bone grafting. The placement of a reconstruction plate in the absence of a bone graft may be necessary in recipient sites that have active infection or inadequate soft tissue coverage. However, this method has demonstrated a high failure rate in the postoperative period. Kim et al. reported a failure rate of 52% when anterior mandible defects were reconstructed with plates alone. In this study, lateral mandibular reconstruction yielded a 7.7–12.5% failure rate. Additionally, 17% of cases resulted in dehiscence of soft tissue overlying the plates [2]. Evidently, it is important to augment mandibular reconstruction with bone grafting when possible.

When primary closure can be achieved, the maxillomandibular defect can be reconstructed with autogenous bone alone, autogenous and allogeneic composite systems, or allogeneic bone augmented with mesenchymal cells and growth factors. The non-vascularized graft is extremely vulnerable to intraoral bacterial contamination and mobility during the healing period. The ideal conditions of autogenous bone grafting involve stable graft fixation and adequate vascularized soft tissue coverage, which is often insufficient as a result of traumatic injury or post-oncologic ablation. When exposed to the oral cavity and salivary contamination, the graft can experience failure rates of up to 50% [3]. Additionally, some oncologic patients require adjuvant radiation therapy that results in hypovascularized and hypocellular local tissue. These challenges increase the risk of wound dehiscence and graft failure. To mitigate these issues, the surgeon can elect for staged reconstruction or application of free tissue transfer.

While vascularized free tissue transfer has become the preferred method of reconstruction in complex maxillofacial defects, it too presents with limitations that need to be addressed. Satisfactory surgical results when utilizing microvascular free flaps in part depend on the elected donor site's anatomical shape and size. The surgeon takes what is available and tries to mold it to what is needed. With regard to the esthetic and functional outcomes, the raised flap is often too small or too bulky and may not align to the defect fittingly. Most cases require a revision surgery to debulk, contour, or augment the reconstructed site. The risks of donor site morbidity, prolonged surgical time, and increased hospital stay may render vascularized free tissue transfer unsuitable for select patients. While the anastomosed free flap is more resilient to the damaging effects of radiation or scarring from prior surgery compared to non-vascularized graft, these factors may still play a considerable role in the predictability of a successful reconstruction.

To conform with the reconstructive objective discussed previously, we continue to explore novel methods to restore maxillofacial defects to their inherent form and function. It is logical to believe that in order to maximize such effort, like tissue needs to be replaced with like tissue. Additionally, we aim to increase surgical efficacy, to decrease morbidity associated with the operation, and to optimize healing and flap integration in the postoperative period. These notions led to a new concept of tissue engineering a prevascularized free flap that is customized to the recipient site in shape and size prior to harvesting. By eliminating the anatomical and geometric problems associated with conventional vascularized free flaps, we can provide an optimal reconstructive option and result for the patient.

19.3 Staged Mandibular Reconstruction Using the Space Maintenance, Wound Optimization, and Osseous Reconstruction (SWOR) Technique

19.3.1 Space Maintenance and Wound Optimization

As surgical modalities continue to improve, immediate reconstruction is favored by both patients and the clinicians due to the availability of free tissue transfer. Compared to autogenous or allogeneic grafts, vascularized free tissue transfer is less reliant on the recipient bed's vascular network and soft tissue volume, which may be compromised by radiation, trauma, or scarring from a prior surgery. Despite its versatility and resiliency, immediate reconstruction with a free flap often sacrifices esthetics and function because of the anatomical and geometric differences. In complex maxillofacial defects where the margins are not established (medication- or radiation-induced osteonecrosis), infected wounds (osteomyelitis), or with medically ill patients unable to withstand a prolonged operation, it may be prudent to optimize the defect (by ablation or debridement) and the patient medically prior to the final reconstruction. In these cases, staged reconstruction increases surgical efficiency and can provide the patient with a better and more predictable outcome.

If staged surgery is elected, care must be taken to physiologically optimize the patient and the targeted site prior to the final reconstruction. In the postoperative period, wound contracture and soft tissue prolapse are mechanisms that effectively reduce the volume in the space between the non-resected segments. The associated anatomical structures including nerves and blood vessels are intertwined with granulation tissue during the healing period and eventually become closely approximated with the formed scars. Consequently, accessing the site to be reconstructed will be difficult due to the increased risks of nerve damage and bleeding. Any tissue being excised or dissected during the second surgery must be carefully examined to avoid accidental injuries to vital structures. One solution to this problem is to place an alloplastic material into the defect at the conclusion of the initial surgery. The material will serve to maintain the defect volume and prevent prolapse of the soft tissue during the healing period. This approach essentially gives the wound site and the oral cavity time to heal while being primed for definitive reconstruction.

By taking advantage of computer-aided modeling and current tissue engineering technology, we have introduced the concept of "Space Maintenance, Wound Optimization, and Osseous Reconstruction." (SWOR) (Fig. 19.1) that can further advance maxillofacial reconstruction. In the first stage of this approach, a porous polymethyl methacrylate (PMMA) space maintainer can be fabricated ex vivo to conform to the configuration of the defect. The porous property allows inward tissue migration and interdigitation with fibrous tissue, effectively improving the mechanical attachment between the space maintainer and overlying soft tissue. This relationship enhances the soft tissue's resiliency to the shearing forces of mastication and lowers the rate of wound dehiscence. In a rabbit mandibular defect model, we have demonstrated a lower rate of wound dehiscence when a porous space

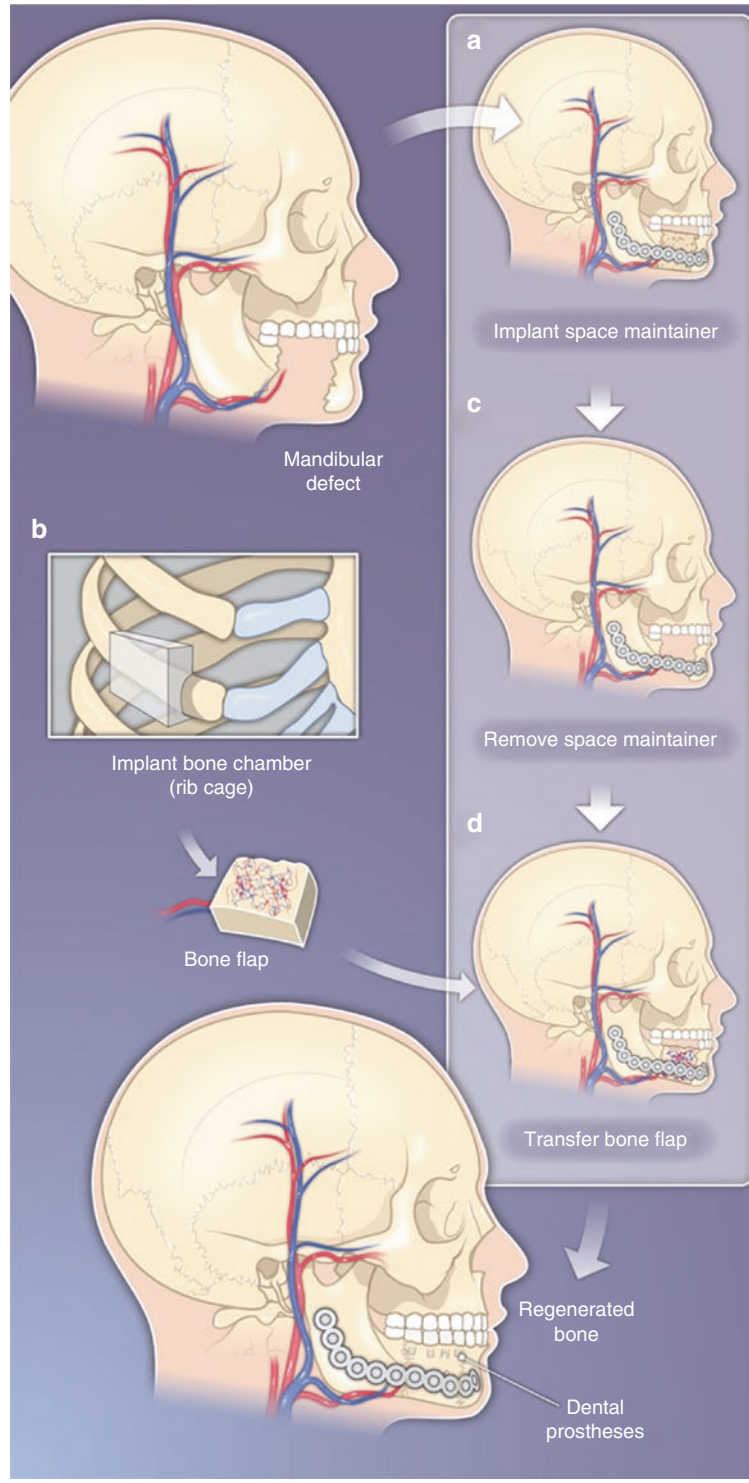

Fig. 19.1 Stage I (A and B) involves placement of an alloplastic implant to prevent volumetric shrinkage of the defect space and optimize the wound site for repair (A). Simultaneously, a chamber filled with bone graft is implanted in a distal site (such as a rib) in approximation to periosteum, in order to form an autologous bone flap (B). Stage II (C and D) involves removal of the alloplastic space maintainer (C) and harvest of the autologous bone flap for vascularized free tissue transfer (D). Microsurgical anastomosis is performed between the pedicle and the recipient vessels to enable continued viability of the transferred bone

maintainer was used compared to a smooth-surfaced, nonporous space maintainer [4, 5].

Taking this concept one step further, we can utilize patient-specific 3D models to prefabricate the porous PMMA space maintainer in the surgical planning stage. Having a space maintainer already approximated to the defect's size and shape, less time is spent intraoperatively for mixing, molding, and trimming. This strategy of prefabricating patient-specific space maintainers was demonstrated in a case series of patients with benign mandibular pathologic lesions [6]. A group of five patients with the diagnosis of either ameloblastoma, keratocystic odontogenic tumor, or glandular odontogenic cyst underwent resection of their associated lesions. At the conclusion of the resection, a preformed space maintainer was placed into the defect, secured by a bone plate and positional screws, and finally closed primarily (Figs. 19.2 and 19.3). Three patients successfully retained their space maintainers and subsequently proceeded to bony reconstruction. The other two patients had intraoral exposure of their space maintainers during the healing period requiring surgical removal. Two factors may have contributed to the wound dehiscence and space maintainer failure in these patients: (1) the space maintainer was placed in the anterior midline location, which suffers from greater mechanical stress, and (2) the overlying soft tissue was thin as a result of supraperiosteal dissection in the initial surgery. In these situations, soft tissue augmentation with allogeneic dermal graft (allograft) or xenogeneic collagen graft (Mucograft) should be considered.

Prefabricated space maintainers can be an effective and cost-efficient adjunct in staged maxillofacial reconstruction. It is important to note that for this approach, preoperative assessment is critical in the predictability of a successful reconstruction. The patient must be reliable and understand the need for multiple operations. The overlying soft tissue should be carefully examined with regard to volume (for primary coverage of space maintainer) and quality (adequate thickness to prevent wound dehiscence). Intraoperatively, the surgeon should strive for conservative preservation of defect dimensions, especially in the vertical (height) plane. The inserted space maintainer should be in contact with the non-resected bone, fixated with a rigid bone plate and adequate number of bone screws, and must not have rough or sharp edges. In select cases at high risk of infection, antibiotics potentially could be added to the space maintainers for controlled local release to improve outcome [7].

19.3.2 In Vivo Bioreactor Strategy for Customized Autologous Flap Generation

While the advancement of space maintainer technology aims to optimize the defect site in the initial surgery, efforts have also been made to explore and expand a variety of reconstructive

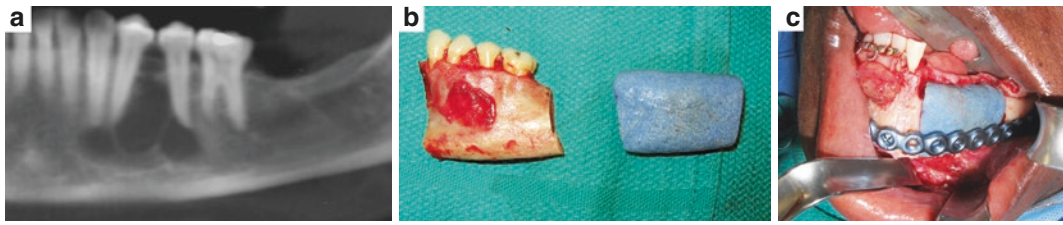

Fig. 19.2 (**a**) Panoramic radiograph of a patient with a left mandibular ameloblastoma. (**b**) Customized porous PMMA spacer (right) approximating the geometry of the resection specimen (left). (**c**) Implantation of porous PMMA spacer into mandibular resection defect

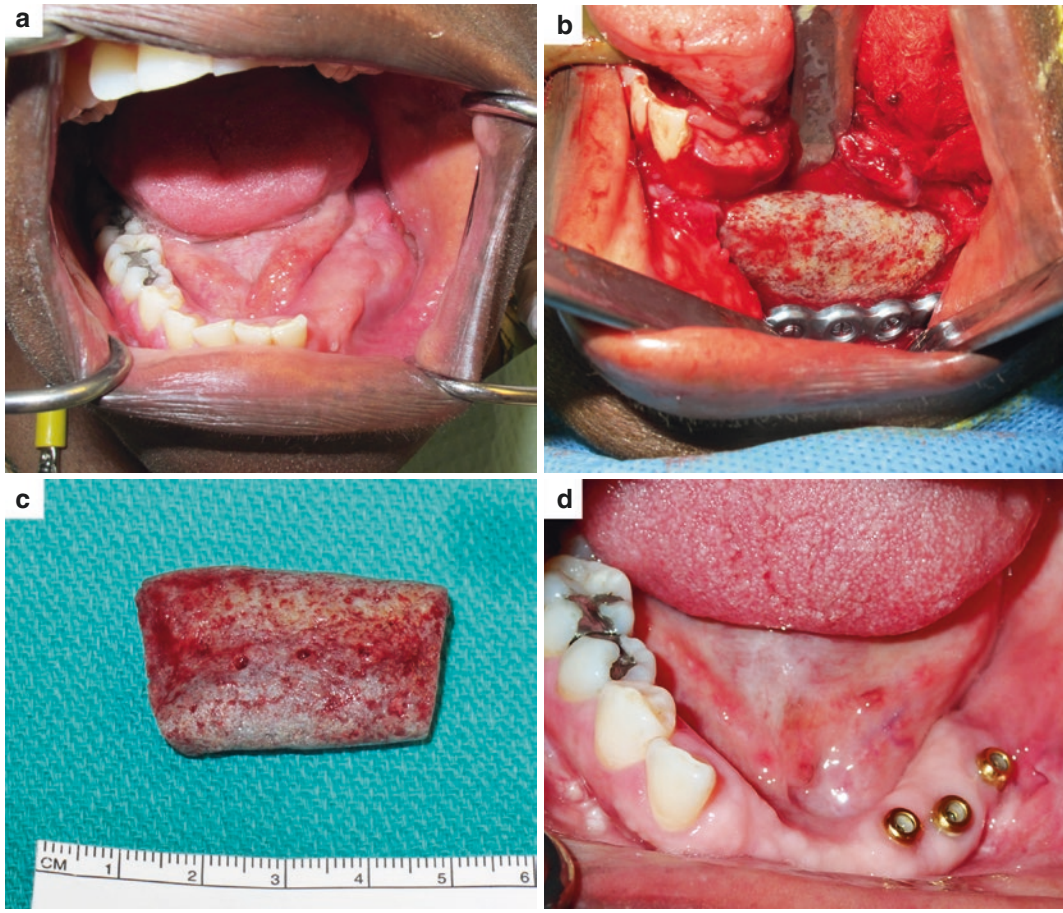

Fig. 19.3 (**a**) Postoperative healing of mandibular resection site with spacer in place at 4 months. (**b**) Exposure of porous PMMA spacer at the time of reconstruction. (**c**) Removal of porous PMMA spacer from mandibular defect showing gross evidence of soft tissue ingrowth. (**d**) Mandibular defect reconstruction 3 years status post bone grafting and dental implant placement

options. Non-vascularized autogenous graft or allogeneic graft that is supplemented with growth factors can produce excellent results when a sufficient healthy soft tissue volume exists. On the other hand, versatile and resilient free flaps give the surgeon a reliable tool for reconstruction of complex craniofacial defects. With regard to free tissue transfer, we previously discussed in this chapter the frequent need for revision surgery in order to improve flap esthetics. By utilizing the concept of tissue engineering, our group (and others) is attempting to explore a novel method to eliminate this geometric limitation between donor and recipient sites. Specifically, we believe that the human body can be harnessed as a bioreactor capable of generating autologous tissue flaps or grafts that are customizable to the target defect site [8].

Traditionally, the bioreactor model is reserved for the generation of cells and tissues in the laboratory or in vitro. The generated tissues are grown and maintained in optimized laboratory conditions, but they typically are found to lack certain key components such as the associated vasculature. This is hypothesized to be due to the inability to replicate the complexities of the in vivo environment [8]. As an alternative, we sought to utilize the human body as a natural bioreactor, encouraging it to generate its own autogenous tissues by providing it with essential growth factors

and resources. A chamber molded to a specific shape and size can be filled with osteoconductive or osteoinductive biomaterial and implanted at a body site that is distant from the defect. Cellular migration and ingrowth of local vasculature subsequently occur that initiate the formation of vascularized autogenous bone with the desired size and shape. The bone formed in this chamber can then be harvested as a graft (without a vascular supply) or flap (with a vascular supply) and transferred to the target defect. If needed, local soft tissue such as the muscle or connective tissue can also be harvested for definitive reconstruction.

Early research of this concept was done in sheep models using PMMA chambers implanted in apposition to the cambium layer of the periosteum of the ribs [9, 10]. In this study, the rectangular-shaped chambers were filled with morcellized bone graft and/or porous poly(lactic-*co*-glycolic acid) (PLGA) polymer wafers prior to implantation. After 6–13 weeks, the chambers were surgically removed and analyzed. Histologically, the bone extracted from the chamber was well-vascularized and approximated the geometry of the PMMA chamber, demonstrating that the generated tissue can be harvested as a non-vascularized graft or flap with the associated intercostal vessels [9]. This large animal study was the first of many that aimed to prove the practicality of the in vivo bioreactor strategy.

Subsequent studies aimed to characterize factors associated with in vivo bioreactor efficacy, including types of scaffold materials, optimal implantation duration, and stability of tissues within the chambers over time. In one animal study, PLGA wafers were implanted with or without morcellized bone graft. The result was that bone formation only occurred in areas containing the bone graft, emphasizing the importance of providing an osteoinductive signal to facilitate new bone generation [10]. In a follow-up study, the PMMA chambers filled with morcellized bone graft were either autoclaved to denature the growth factors or left as is prior to implantation in the sheep model [11]. Bone level was significant only in chambers with the native morcellized bone graft, again demonstrating the effects of osteogenic cues and osteoconductive scaffold to support bone formation. Optimal duration of implantation was found to be at 9 weeks in order to generate quality bone. At 12 and 24 weeks, significant decrease in bone volume was observed [11, 12].

While initial animal studies yielded excellent results when the chambers were implanted in orthotopic site, other sites in the human body are continually being explored as bioreactor candidates. A study led by Brey et al. in 2007 compared the level of bone formation when the chambers are implanted in an orthotopic site with appositional contact to the periosteum versus those implanted in contact with the fascia of the latissimus dorsi [13]. While both groups demonstrated vascularized tissue formation, significant bone formation was observed in the chambers in contact with the periosteum. Brey and his group concluded that the orthotopic site is more suitable for engineering bone tissue than ectopic sites. Other studies in small [14, 15] and large [16] animal models have demonstrated that ectopic sites can be utilized effectively in engineering vascularized bony tissue by incorporating exogenous osteogenic growth factor in the chamber.

Based on the current evidence, the in vivo bioreactor approach has demonstrated to be capable of generating vascularized autologous tissue configured to the desired geometrical shape and size. Nevertheless, the success of this technique lies in the viability of the engineered tissue after the transfer of the flap to the recipient site. This was only recently explored and evaluated in a sheep model. The chambers were initially filled with morcellized bone graft, a synthetic ceramic-based bone graft material, or a combination of both materials. They were then implanted in the ribs of the sheep and placed in contact with the periosteum. After 9 weeks, the vascularized bone flaps were harvested and transferred to a mandibular defect [17]. The tissue remained viable for 12 weeks in all three sheep that received the transfers. In this study, the successful use of ceramic-based bone graft also suggested the potential role of synthetic material in the in vivo bioreactor strategy, eliminating the requirement of autologous bone and thus decreasing associated donor site morbidity.

Current (unpublished) preclinical work by our group has advanced the SWOR treatment concept further by utilizing 3D printing technology to generate high-fidelity patient-specific vascularized flaps. Sheep with a challenging superior marginal mandibular defect received a porous space maintainer at the defect site immediately following the marginal mandibulectomy. A separate surgical team simultaneously implanted 3D printed bioreactors filled with either synthetic (Mastergraft® Granules) or autologous (morcellized rib) scaffold material into orthotopic rib resection sites. After a 9-week healing period, the mandibular space maintainers were removed, and the tissues generated from the 3D printed in vivo bioreactors were transferred as both vascularized bone flaps and free bone grafts to the sheep mandibular defect (Fig. 19.4). Twelve weeks after reconstruction, the mandibles were harvested for evaluation. Utilizing both surgical and radiological outcomes, there were no statistically significant differences in radiological markers of bone architecture between tissues generated in bioreactors filled with either autologous or synthetic materials. Furthermore, this customized in vivo bioreactor strategy was successful in facilitating reconstruction of the challenging large tissue defect in 83% of animals, illustrating the potential of this "personalized medicine" type of approach to the reconstruction of patients with complex maxillofacial defects.

The in vivo bioreactor strategy was first applied to humans in 2006 through a case of mandibular augmentation [18]. In this case, the iliac crest was elected to be the bioreactor site. A PMMA chamber that was filled with autograft bone was implanted in contact with the periosteum of the iliac crest. After 8 weeks, the generated tissue was extracted and transferred along with the periosteum to the donor mandibular site. Follow-up at 16 months showed adequate mandibular height for the insertion and maintenance of osseointegrated dental implants. While the patient eventually died from hepatocellular carcinoma, this case demonstrated successful application of the in vivo bioreactor strategy in mandibular augmentation. Other case reports have also been published that demonstrated craniofacial reconstruction using the in vivo bioreactor strategy with a variety of scaffold materials implanted in both orthotopic and ectopic sites. In these studies, the duration of implantation ranged from 7 weeks to over 6 months. Additionally, growth factors or bone marrow aspirate was added to augment bone formation in some cases [19–23]. Despite short-term successes in most of these cases, the variability in regard to biomaterial used, duration of implantation, and role of growth factors stress the importance of continued investigation in order to develop a standardized surgical approach [8]. The in vivo bioreactor strategy aims to generate autologous vascularized bone flaps, with or without associated soft tissue, that is shaped to match the geometry of a craniofacial bony defect. At the same time, the space maintainer serves to prime and preserve the geometry and physiology of the defect for future reconstruction [24].

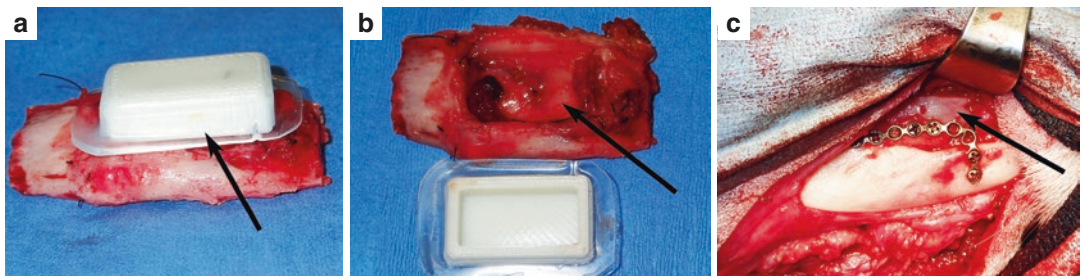

Fig. 19.4 (**a**) 3D printed bioreactor (black arrow) attached to the underlying rib removed at 9 weeks postimplantation. (**b**) After 9 weeks of implantation, the tissue had grown within and conformed to the dimensions of the 3D printed bioreactor (black arrow). (**c**) The tissue (black arrow) was transferred to the mandibular defect site and found to have appropriate volume and geometry for reconstruction

19.4 Conclusion

The reconstruction of composite defects of the head and neck region poses a number of challenges. The ability to replace multiple tissue types in an inhospitable environment is one of them. Additional challenges include the need to develop reconstructive systems that are both functional and esthetically acceptable, considering the prominence of the face and the dynamic roles played by its components. To this end, a variety of tissue engineering and virtual surgical planning tools are being developed to facilitate functional and esthetic reconstruction targeted to the patient-specific geometry of the defect, with a particular focus on the skeletal component (see Chap. 18) [25–29]. Indeed, 3D printing techniques are being applied in the fabrication of custom-shaped scaffolds to support mandibular regeneration in preclinical models [26]. While the proof of concept of translation of 3D printing in the in vivo bioreactor strategy has been established, several aspects of the approach remain to be explored, including the ability to generate and harvest bone of complex geometries. Nevertheless, emerging bioengineering strategies present exceptional potential to advance the options available to the informed surgeon for reconstruction of complex maxillofacial defects.

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