Osteoradionecrosis of the Maxilla: Conservative Management and Reconstructive Considerations

Tom Shokri, MD[1] Weitao Wang, MD[2] Aurora Vincent, MD[2] Jason E. Cohn, DO[3] Sameep Kadakia, MD[4] Yadranko Ducic, MD, FRCS(C), FACS[2]

[1] Department of Otolaryngology, Penn State Health Milton S. Hershey Medical Center, Hershey, Pennsylvania
[2] Otolaryngology and Facial Plastic Surgery Associates, Fort Worth, Texas
[3] Department of Otolaryngology–Head and Neck Surgery, Philadelphia College of Osteopathic Medicine, Philadelphia, Pennsylvania
[4] Department of Plastic and Reconstructive Surgery, Wright State University, Dayton, Ohio

Address for correspondence Tom Shokri, MD, Department of Otolaryngology, Penn State Health Milton S. Hershey Medical Center, 500 University Avenue, Hershey, PA 17033 (e-mail: tom.shokri@gmail.com).

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Abstract

The implementation of radiotherapy in the multimodal treatment of advanced head and neck cancer has greatly improved survival rates. In some patients, however, this benefit comes at the potential expense of the tissue surrounding the primary site of malignancy. Osteoradionecrosis (ORN) of the facial bones, in particular the maxilla, is a debilitating complication of radiation therapy. Exposure to ionizing radiation results in devitalization of underlying bone with necrosis of adjacent soft tissue. Controversy surrounding appropriate early intervention in ORN persists and no consensus for clinical treatment has been established. In the present article, we review the pathophysiology of maxillary ORN and discuss the role of both conservative medical therapy and reconstruction.

Keywords

- maxillary osteoradionecrosis
- maxillary osteonecrosis
- management of osteoradionecrosis
- free flap reconstruction

Osteoradionecrosis (ORN) can be both a potentially debilitating and disfiguring sequela of radiation therapy (RT) in the treatment of malignancies within the head and neck. Exposure to ionizing radiation results in devitalization of the facial skeleton and necrosis of the overlying soft tissue envelope.[1,2] Incidence of ORN varies within the primary literature, with reported rates of up to 15%, the majority of which occur within the first 3 years following exposure to RT.[2,3] There is no consensus regarding the temporal relation between exposure to RT and subsequent signs of ORN. Clinical reports describe this phenomenon occurring within months to decades following radiotherapy.[1,4]

Anatomically, the head and neck is particularly susceptible to ORN. The mandible appears to be the most commonly affected osseous structure. This is postulated to be secondary to the relatively poor vascularity within this region as well as local factors including thin mucosal soft tissue coverage, added mechanical stress and remodeling within this region due to forces of mastication, and concomitant dental or periodontal disease.

Although it displays higher porosity, facilitating increased vascularity, the maxilla is the second most commonly affected region within the head and neck.[5,6] Several risk factors are believed to potentiate the development of ORN including radiation dose ($>$ 60 Gy), irradiated bone volume, radiation modality, utilization of concomitant chemotherapy, tumor burden, dental extraction, prior infection, poor oral hygiene, malnutrition, and alcohol or tobacco abuse. Comorbidities such as hypertension, diabetes, and connective tissue disorders appear to increase risk of ORN as well, though their exact mechanism is unknown.[3,4,7,8]

ORN may present with a wide range of clinical symptoms, depending on the primary site of involvement. Patients may experience localized pain, dysesthesia, bone exposure, sinocutaneous or orocutaneous fistula, trismus, and pathological fractures.[9] Clinically, the diagnosis of ORN is characterized

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by the exposure of previously irradiated bone with an inability to heal within at least 3 months. Notably, this must be independent of recurrent malignancy.[10,11] Although diagnosis is clinically based, radiographic imaging may further elucidate underlying pathology in equivocal cases or facilitate early identification when a patient's symptomology remains nonspecific. In cases in which there is high suspicion for ORN, imaging either in the form of computed tomography, magnetic resonance, or scintigraphy may further delineate the extent of disease. Histology is often nonspecific but may show endarteritis, hypovascularity, hyalinization, thrombosis, and generalized fibrotic change.[9,11,12]

Despite recent advances in treatment and a greater understanding of the molecular pathophysiology of ORN, prevention remains of utmost importance. No clear consensus regarding an optimal treatment paradigm has been determined to date. Identification and intervention in the form of antibiotics, pharmaceuticals, hyperbaric oxygen, and sequestrectomy have shown greatest efficacy when implemented in early stages of disease.[13] Nevertheless, evidence regarding the true utility of conservative measures in management of ORN remains limited. This may be further confounded by potential bias in the literature introduced by the increased identification of early, less aggressive disease, due to growing application of intensity-modulated radiotherapy (IMRT) and local prophylactic measures.[9–13] However, in the presence of late findings including osseous necrosis, soft-tissue deficit, and cutaneous fistulization radical debridement is necessary. Reconstruction following extirpation of all nonviable tissue is often best achieved with microvascular free tissue transfer.[14–17]

With this in mind, the purpose of this review is to review the pathophysiology, conservative management, and reconstruction of ORN within the maxilla, with a main interest in addressing the challenging reconstructive dilemmas presented within this region and unique to this pathology.

Pathophysiology of Osteoradionecrosis

There are currently two predominant contemporary theories for the pathophysiology of ORN. Marx[9] "3 H's paradigm" postulates that exposure to ionizing radiation and resultant periarteritis, endarteritis, hyperemia, fibrosis, and microthrombosis interfere with tissue homeostasis. This physiologic cascade in turn results in decreased tissue perfusion and reduced oxygen diffusion resulting ultimately in cellular apoptosis.[9,18,19] This theory provides the foundation for the use of hyperbaric therapy in ORN.

The radiation-induced fibroatrophic (RIF) theory suggests that the progression of ORN is secondary to the deregulation of fibroblast activity resulting in tissue atrophy.[19] Since its introduction, the RIF theory has gained broad recognition and has lead to the establishment of antioxidant and antifibrotic therapeutic protocols in the treatment of ORN.[19–21] Overall, the unifying mechanism underlying ORN continues to be unclear. However, both of the above mechanisms likely play a complementary role in the pathophysiologic process (►**Fig. 1**).

Medical Management

Preventive Measures

Given the aforementioned inciting factors in ORN, the primary reductive component may be the prevention of localized tissue trauma, including dental extraction or implantation procedures. Detailed dental examination should be stressed, addressing any areas of carious disease that may later serve as oral septic foci, prior to implementation of RT.[22] Dental extraction is best performed at least 3 to 4 weeks prior to RT.[1,23,24] Adequate oral hygiene and risk reduction including abstinence from alcohol and tobacco are crucial in decreasing the risk of ORN.[23,25] Although a known risk factor for osteonecrosis,[26] there is limited data suggesting steroid use may conversely serve a protective function in ORN.[23,27]

IMRT has demonstrated a lower incidence of ORN when compared with conventional RT. This is postulated to be secondary to its ability to provide more precise radiation dosage to areas of malignancy with concomitant radiation reduction to surrounding tissue.[28] Volume reduction of areas exposed to greater than 50 to 60 Gy may help further decrease the incidence of ORN.[29,30]

Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy (HBOT) is based upon inhalational exposure to 100% O_2 within an environment in which the atmospheric pressure is greater than that at sea level (1 atmosphere absolute). Sessions, or "dives," are performed within a hermetically sealed hyperbaric chamber. Within this hyperbaric environment, oxygen supply is preferentially shunted through selective vasoconstriction of hyperoxic tissues and redistribution of oxygen to hypoxic tissues (the Robin Hood effect).[31] Furthermore, HBOT prompts fibroblast proliferation with a resultant increase in collagen deposition, increases angiogenesis, and prevents infection via both bactericidal and bacteriostatic mechanisms.[11] However, the current body of literature, examining the role of HBOT in treatment of ORN, is limited due to the heterogeneity of study design and variability in employed regimens and resulting outcomes.[32,33]

Interested readers are referred to the Cochrane meta-analysis which further delineates the limited objective data reviewing the role of HBOT in ORN and justifies its use in select patients.[34] Currently, institutional guidelines reference the paucity of data, particularly prospective studies and overall expense of treatment, in avoiding its routine use except in high-risk patients with ORN refractory to medical and procedural intervention.[35]

Less is known regarding the role of HBOT in maxillary ORN as it is underreported due to its more benign clinical course, in contradistinction to mandibular ORN.[24] To date, only two studies have evaluated the utility of HBOT in maxillary ORN. Both are limited by their retrospective nature, heterogeneity of patient population, and small sample size. However, decreased treatment failure was reported with use of HBOT indicating that there may be treatment benefit within the maxilla.[36,37] Presently, several studies are evaluating the role of HBOT in conjunction with multimodal medical and staged treatment protocols for ORN.[38]

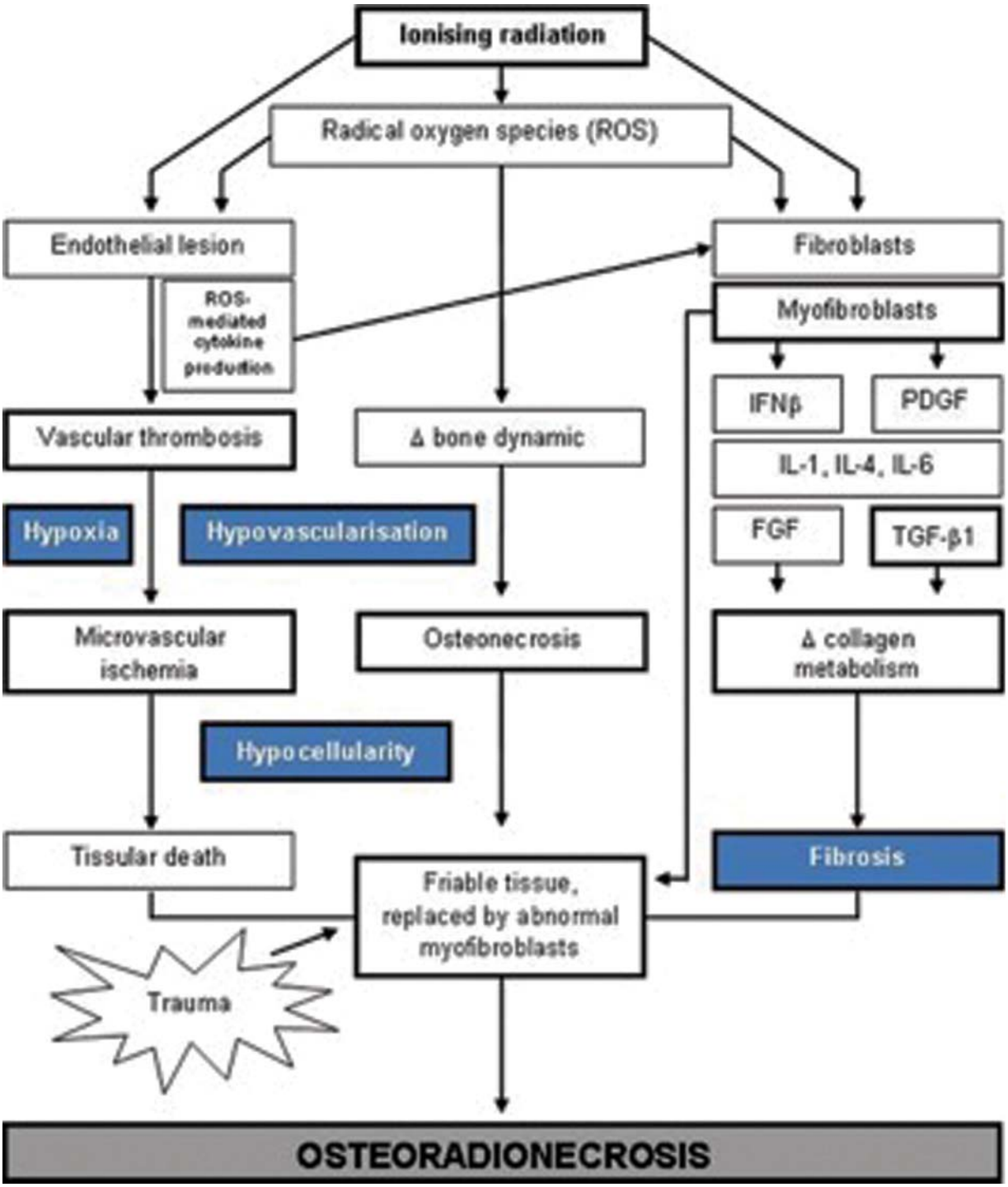

Fig. 1 Pathophysiologic mechanisms in osteoradionecrosis (ORN). (Adapted with permission from Costa et al.[21])

Medicative Treatment Modalities

Antioxidant and antifibrotic pharmaceutical agents have become increasingly implemented in the treatment of ORN as the RIF theory has garnered increased support. These drugs include tocopherol (TCP), pentoxifylline (PTX), and clodronate (CLO).[19] PTX is a methylxanthine derivative that is classified as a hemorrheologic agent, reducing blood viscosity through modulation of erythrocyte deformability and vasodilation thereby mitigating the risk for microthrombus formation. PTX has demonstrated inhibitory function of fibroblast proliferation, extracellular matrix production, and has anti-inflammatory properties.[18,20,39] TCPs have vitamin E activity and are therefore liposoluble antioxidants. Due to this capacity as a free radical scavenger, TCPs function to mitigate the risk of cell membrane damage through prevention of lipid peroxidation.[19] CLO, a first generation bisphosphonate, decreases osteoclastic activity thereby inhibiting bone resorption while activating osteoblasts and increasing osteosynthesis.[40] The above medications have not shown efficacy in treatment of ORN when used in isolation and their individual use is

therefore not supported. Regimens employing a combination of these agents have, however, shown synergism in the treatment of ORN.[40,41] Treatment of advanced refractory ORN, following surgery and with combination therapy of PTX/TCP and CLO (PENTOCLO) has shown complete resolution within a 6- to 9-month interval. Notably, sequestrectomy was performed in the majority of these patients further accentuating the need for multimodal therapy in potentiating the healing process.[20,40,42] Although the preliminary evidence is promising, the long-term utility and side effects of PENTOCLO have yet to be determined in a randomized clinical trial.

Surgical Intervention

Despite the controversy surrounding treatment protocols in ORN, the majority of proposed treatment protocols is multimodal and accentuate the implementation of conservative measures in early-stage disease including antibiotics, debridement, or sequestrectomy. Surgical resection and reconstruction are used in the setting of severe progressive disease or in conservative treatment failure. Treatment regimens aim to avoid major debilitating surgical resections, which remain a last resort.[1,24–27]

Microvascular Free Tissue Reconstruction

In the setting of advanced disease (i.e., pathologic fractures, bone exposure, or fistula formation), surgical resection is pivotal in disease control. The extent of resection is contingent on the establishment of viable tissue margins. Understandably, there is, therefore, a paucity of definitive objective clinical criteria in establishing adequate excision, likely contributing to the relatively high rates, approaching 25%, of recurrence.[43] Recurrent disease has been documented in cases with histopathologically confirmed resection margins suggesting that other contributing factors, aside from residual necrotic bone, may precipitate recurrence.[44] Due to the more indolent course of maxillary ORN, and poor surgical candidacy in afflicted patients, there remains a paucity of literature regarding clinically driven surgical decision making in maxillary ORN.[36,37] Consequently, the majority of treatment protocols are derived from literature specific to mandibular pathology. Following radical debridement and establishment of viable surrounding tissue, reconstruction is performed employing vascularized free tissue.

Reconstructive options are defect driven and therefore dependent on volume, tissue composition, and the degree of dead space. Defects with minimal osseous deficits may be reconstructed with myocutaneous flaps, such as radial forearm or anterolateral thigh. A segment of the cutaneous island can be de-epithelized to obliterate any potential dead space. Large osseous defects, particularly involving the periorbita, require composite flap reconstruction.

Goals specific to maxillary reconstruction include: separation of the oral and nasal cavities, restoration of palatal competency, reestablishment of orbital contour, obliteration of the orbital cavity in cases of exenteration, obliteration of the maxillary defect, and restoration of functional dentition and facial contour.[45] No uniform reconstructive approach has been described that achieves all the above goals. Maxillofacial prostheses may be implemented in obturation of maxillary defects. However, these are limited by need for extensive cleaning and maintenance, inadequate retention, loss of oronasal seal in cases of inadequate residual soft tissue and dentition, and nasal reflux.[46] A multimodal reconstructive effort employing prosthetics, local flaps, and free tissue transfer has been shown to optimize outcomes.[47–49]

The use of soft tissue flaps with concomitant osseous grafts has been well documented in complex midfacial reconstruction. Cordeiro and Santamaria[50] described their use of rectus abdominis free flap with nonvascularized split calvarial or iliac crest bone grafts in composite defects. The bone grafts reconstitute the underlying skeletal framework and are draped with rectus muscle and subcutaneous fat facilitating midface contour.[50] Additional studies have illustrated the utility of nonvascularized bone grafts with myocutaneous latissimus dorsi or anterolateral thigh free flaps.[48,49] It is of paramount importance that bone grafts are enveloped in vascularized muscle or fascia with an adequate skin paddle to reline the oral cavity and provide a seal for the nasal wall, palate, and external cheek if needed.

Although nonvascularized bone grafts are extensively described within the literature, many authors contend that composite free flaps containing a vascularized osseous component remain the best option for single-stage maxillary and midface reconstruction when a considerable bony deficit is encountered. The osseocutaneous radial forearm free flap has been implemented in reconstruction of limited and subtotal maxillectomy defects. A "sandwich" technique in which the cutaneous paddle is draped over the radius, recreating the maxillary arch while relining both nasal and oral cavities, may be utilized.[51] However, the bone stock provided in this reconstructive technique is inadequate to support osseointegrated dental implants and patients therefore require dentures.[49,51]

The osteocutaneous scapular system provides a reconstructive option with two separate bipedicled osseous flaps. The lateral scapular border retains its vascular supply from the circumflex scapular artery and maybe harvested with surrounding muscle and a large skin paddle.[52,53] A second scapular tip osseous flap can also be harvested from the angular artery, either from the serratus anterior branch or directly off of the thoracodorsal artery.[54] The scapular tip offers an ideal osseous conformation for maxillary reconstruction (►**Fig. 2**) and may be harvested with multiple skin paddles and the teres major muscle, facilitating reconstitution of soft tissue and lining of both oral and nasal cavities.[53,54] The osseous stock of this flap also allows for successful dental implantation. Additionally, the midsegment of the scapular body displays a curve similar to that of the orbital floor and may be utilized as a nonvascularized bone graft if additional reconstruction of the floor is required. Limitations to this flap are few, namely that it cannot be harvested in a two-team approach and requires patient positioning that adds difficulty to the initial ablative surgical component.[52–54]

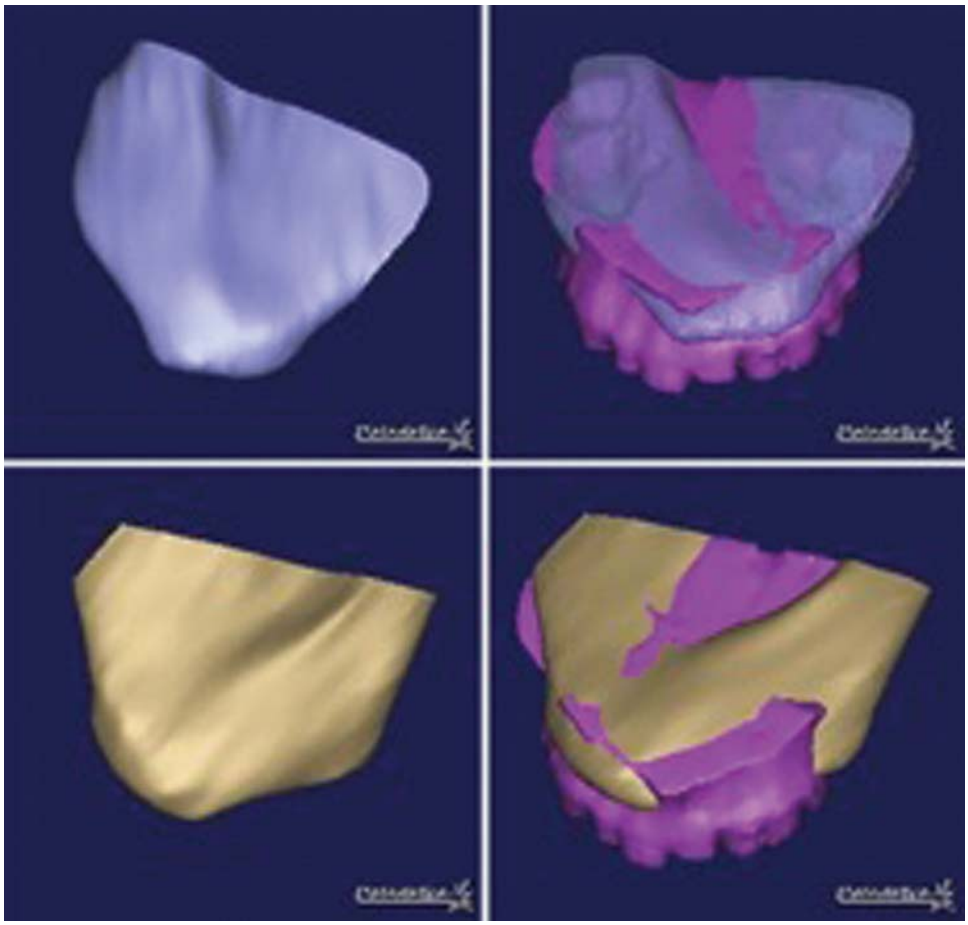

Fig. 2 Computed tomography (CT) conformance studies showing similar contour of scapular tip with that of native palatal shape. Upper row: conformance of patient's left scapular tip. Lower row: conformance with right scapular tip. Mean reported conformance distance 2.04 mm indicating near perfect reconstructive contour. (Reproduced with permission from Shrime et al.[53])

The myoosseous iliac crest free flap addresses many of the limitations, with respect to bone stock, of the previously mentioned flaps. It may be harvested with a significant volume of attached internal oblique muscle. Its orientation can be modified to reconstruct palatal, maxillary alveolar, or zygomaticomaxillary buttress defects (►**Fig. 3**). The associated muscular component may be implemented in palatal reconstruction or obliteration of the orbital cavity.[55] Although it provides significant bone stock for osseous reconstruction, limitations of this flap include its large bulk, limited muscle and cutaneous paddle mobility, and prohibitively short pedicle (4–5 cm).

The fibula free flap has long remained a workhorse in maxillofacial osseous reconstruction. This is particularly true within the midface where it provides more than adequate osseous volume required for palatal and midface structural support (►**Fig. 4**). Several studies have documented its osseous integrity, ease of flap harvest, large caliber pedicle, capacity for pedicle lengthening, and pliable skin paddle.[56–59] The available bone stock facilitates osseointegrated dental implantation allowing dental appliance retention and rehabilitation.[56,57] Although the fibular flap is an ideal candidate in reconstruction of the inferior maxilla, composite osseous defects involving the orbit and zygomaticomaxillary complex pose a reconstructive dilemma potentially requiring additional free tissue transfer or nonvascularized bone grafts.

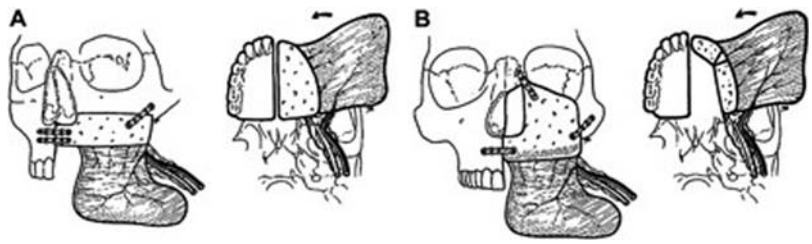

Fig. 3 (**A**) Reconstruction of inferior maxillectomy defect using iliac crest free flap oriented horizontally. (**B**) Reconstruction of "middle-height" maxillectomy defect implementing vertical orientation of iliac crest. Internal oblique rotated medially to close palatal defect. (Reproduced with permission from Brown.[60])

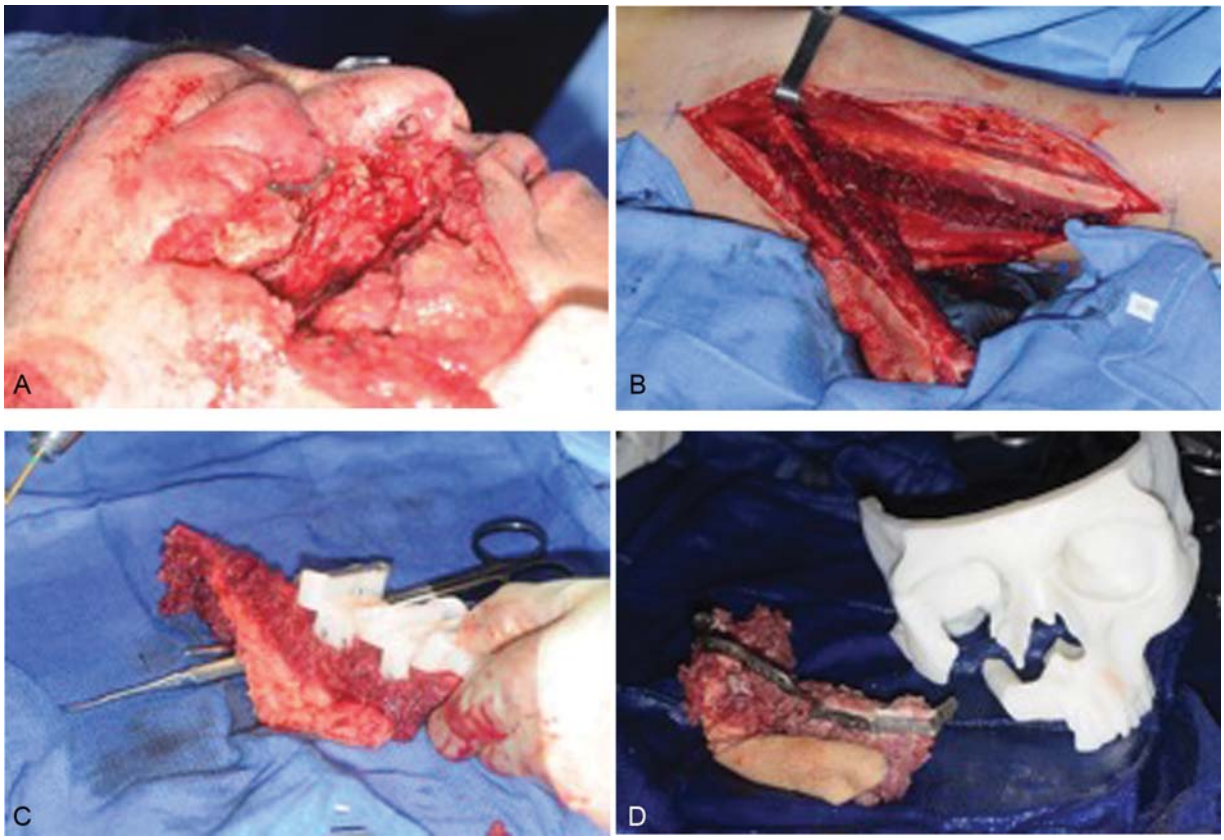

Fig. 4 (**A**) Left subtotal maxillectomy defect following ablation. (**B**) In situ right harvested fibula free flap. (**C**) Harvested fibular flap with cutting guide for segmented osteotomies. (**D**) Patient-specific three-dimensional (3D)-printed facial skeleton with fibula free flap following osteotomies and placement of reconstructive plate.

Conclusion

ORN, particularly when involving the maxilla, can be a potentially devastating complication following radiotherapy in head and neck cancer patients. Given its complex pathophysiology, no gold standard treatment modality or consensus guidelines have been established. A combination of therapeutic modalities should be implemented based upon the severity of the disease. Early-stage disease may be treated with local control, via sequestrectomy, antibiotics, and meticulous oral hygiene. However, early surgical intervention is recommended in the setting of disease progression. Although preliminary data are promising, the role of HBOT and medical therapeutic agents has yet to be delineated with progressive randomized trials, some of which are currently ongoing. Aggressive radical resection followed by free flap reconstruction should be reserved for advanced or refractory disease.

Conflicts of Interest
None.

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