Int. J. Oral Maxillofac. Surg. 2019; 48: 1398–1404
https://doi.org/10.1016/j.ijom.2019.06.007, available online at https://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Clinical Paper
Reconstructive Surgery

The value of reconstructive surgery in the management of refractory jaw osteoradionecrosis: a single-center 10-year experience

J. Bettoni[1,2], M. Olivetto[1,2], J. Duisit[3], A. Caula[1], S. Testelin[1,2], S. Dakpé[1,2], B. Lengele[3], B. Devauchelle[1,2]
[1]Department of Maxillo-Facial Surgery, University Hospital of Amiens, Avenue Laennec, 80000 Amiens, France; [2]EA CHIMERE, Picardie Jules Verne University, Avenue Laennec, 80000 Amiens, France; [3]Department of Plastic and Reconstructive Surgery, Université Catholique de Louvain-Clinique Universitaire, St-Luc Avenue Hippocrate, 1200 Bruxelles, Belgium

J. Bettoni, M. Olivetto, J. Duisit, A. Caula, S. Testelin, S. Dakpé, B. Lengele, B. Devauchelle: The value of reconstructive surgery in the management of refractory jaw osteoradionecrosis: a single-center 10-year experience. Int. J. Oral Maxillofac. Surg. 2019; 48: 1398–1404.

Abstract. Mandibular osteoradionecrosis (mORN) is a severe complication of head and neck irradiation. International consensus on the management of mORN is currently lacking. The present study sought to evaluate the effectiveness and benefits of early reconstructive surgery (resection of the diseased bone and immediate reconstruction with a free flap) in treatment-refractory mORN. A single-center retrospective study was carried out of operations performed in a French university medical center between 2003 and 2013 inclusive. For each patient, the surgical modalities and postoperative outcomes were recorded. A total of 55 operations (19 marginal resections and 36 segmental resections) were performed, and the overall success rate was 92.3%. Relative to marginal resections, segmental resections were associated with longer operating times (440 ± 62 min vs. 531 ± 72 min, respectively; $P < 0.05$ in Student's *t*-test), a longer length of hospital stay (16.5 ± 6.5 days vs. 25.6 ± 11.3 days, respectively; $P < 0.05$), and a higher complication rate (26.3% vs. 63.9%, respectively; $P < 0.05$ in Fisher's test). Given the unpredictable progression of treatment-refractory mORN and the risk–benefit ratio observed here, the value of early reconstructive surgery with curative intent should be reassessed.

Key words: Osteoradionecrosis; mandibular; management; surgery; free flap.

Accepted for publication 3 June 2019
Available online 18 June 2019

Mandibular osteoradionecrosis (mORN) is a serious, severe complication of irradiation therapy for head and neck cancer. The main clinical signs and symptoms are chronic pain and oral bone exposure. Worsening of the lesion may result from the triad of local infection, a cutaneous fistula, and a pathological fracture. Although the incidence rate of mORN has fallen within the last 40 years from 38% in 1968 to less than 10%[1] (thanks to better prophylaxis, including the identification of risk factors[2–4], the control of traumatic factors[5], and the development of prophylactic dentistry and topical fluoride treatment[6], and technical progress in the field of radiotherapy[7]), the pathophysiology and therapeutic management of mORN are still subject to debate.

In 2008, D'Hauthuille et al.[8] suggested that transferring vascularized tissue into an irradiated environment would ameliorate the damaging features of mORN (hypoxia, hypocellularization, and hypovascularization[6]), and introduced the notion of 'revascularization surgery' for ORN. This consisted of resection of the osteoradionecrotic damage and then immediate reconstruction using free flap microanastomosis. In 1987, Beauvilain de Montreuil et al.[9] defended the early implementation of radical surgery, with microanastomosis reconstruction for ORN lesions. However, Rice et al.'s meta-analysis in 2015[10] found that that, due to the high complication rate of reconstructive surgery[11] in irradiated areas, the procedure should be restricted to Notani grade III advanced or fracture lesions (e.g., osteolytic lesions below the inferior dental canal, pathological fractures, or skin fistulae[12]).

The objectives of the present study were to (i) report our experience of the surgical management of otherwise treatment-refractory mORN, and (ii) evaluate the effectiveness, advantages, and disadvantages of early revascularization surgery prior to fracture injuries.

Materials and Methods

We performed a retrospective, single-center study of patients attending the Maxillofacial Surgery Department at Amiens University Medical Center (Amiens, France). All patients having undergone revascularization surgery and free flap reconstruction for refractory mORN between January 2003 and December 2013 were included.

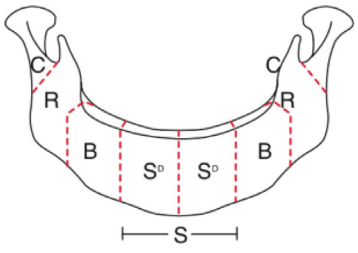
For each patient, we recorded the number of ORN risk factors[2–4], the World Health Organization score, the time between irradiation and diagnosis of the ORN, the time between diagnosis and revascularization surgery, and the provision of local care and iterative milling of bone sequestra during consultations. In the event of bone exposure preventing primary closure without tension, any surgical procedure was contraindicated. Furthermore, each patient's medical records were searched for conservative treatments given before revascularization surgery [e.g., long-term antibiotic therapy, hyperbaric oxygen therapy, pentoxifylline-tocopherol-clodronate (pentoclo) combination therapy, or conservative marginal mandibulectomy with primary mucosal closure].

At the time of surgery, the osteoradionecrotic damage associated with each lesion was characterized (Table 1) in terms of the patient's clinical status (according to Wong's[13] and Epstein's[14] classifications), the mandibular site (according to Urken's classification[15]), and the extent of mandibular bone damage (according to Notani's classification[12]).

Each revascularization procedure included the surgical resection of the diseased bone (marginal or segmental mandibulectomy) until bone bleeding was observed at the resection site. The flap was then chosen by taking into account the need for buccal closure and the recovery of mandibular strength (Fig. 1). The operating time, the type of reconstruction, and the characteristics of the microsurgical anastomoses were recorded. For the free bone flaps, the number of segmental osteotomies and the osteosynthesis material used (miniplate or endoprosthesis) were documented. The diseased bone's resection status was assessed using the radiographic images acquired immediately after surgery [dental panoramic X-rays or a computed tomography (CT) scan] and classified as complete, uncertain or incomplete.

During the follow-up, we distinguished between immediate postoperative complications (<30 days) and delayed complications (>30 days). For each patient, the length of hospital stay (LOS) was recorded. The evaluation of treatment efficacy was based on the radiological

Table 1. Classifications used for the radiological and clinical characterization of mandibular osteoradionecrosis (ORN).

Clinical evaluation	Radiological evaluation
Epstein's[14] score Stage 1: osteoradionecrosis resolved or stabilized; asymptomatic. Stage 2: chronic osteoradionecrosis (>3 months), but not progressive; not very symptomatic or medically controlled. Stage 3a: active and progressive osteoradionecrosis; aggravating symptoms without pathological fracture. Stage 3b: active and progressive osteoradionecrosis, aggravating symptoms with associated pathological fracture.	Urken's[15] classification 
Wong's[13] classification 1. Bone exposure resulting from tumor necrosis where tumor death results in a loss of soft tissue coverage 2. Bone exposure as a consequence of tumor recurrence 3. Bone exposure resultant from oral surgical (surgical lavage operations) or other dental interventions including prosthetic dental treatment 4. Bone exposure de novo without apparent cause aside from radiation exposure	Notani's[12] classification Grade I: ORN confined to alveolar bone Grade II: ORN limited to alveolar bone and/or mandible above the level of inferior alveolar canal Grade III: ORN involving the mandible below the level of inferior alveolar canal and ORN with a skin fistula and/or pathologic fracture

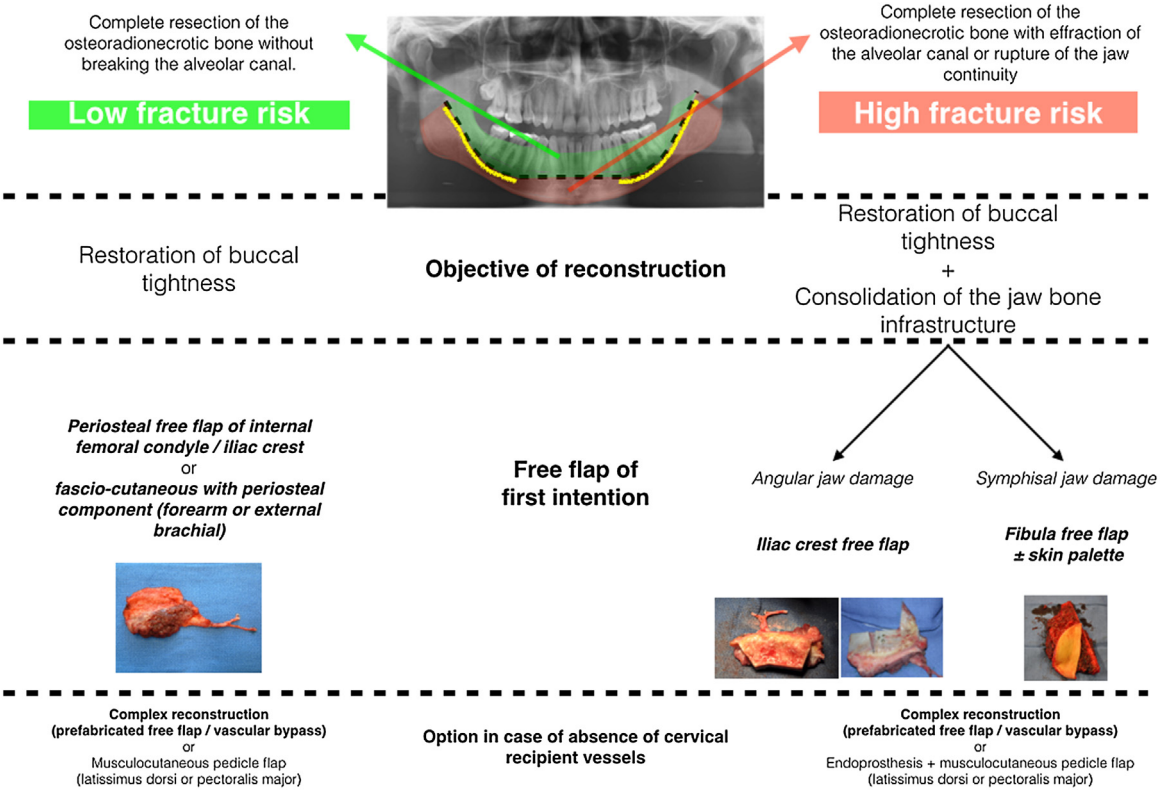


Fig. 1. A decision tree for the choice of the free flap reconstruction, and the characteristics of osteoradionecrotic injuries.

results and clinical observations during long-term follow-up. The ORN's symptomatic status was classified as healed, continued progression, local recurrence after a healing period, and a second area of ORN involving a different mandibular Urken unit. In the event of healing, the type of dental device (a removable prosthesis or a bone implant) was noted.

Results

Characteristics of the study population

A total of 49 patients [mean ± standard deviation (SD) (range) age: 56 ± 7 years (33–72); mean ± SD number of risk factors: 4 ± 1.2] had undergone free flap reconstruction in an indication of mORN. Six patients underwent two treatment sessions each, due to the local recurrence of periodontitis ($n = 1$) or the presence of contralateral osteoradionecrotic lesions ($n = 5$); hence, a total of 55 revascularization procedures were performed during the study period (Table 2). The mean ± SD dose of irradiation delivered to the tumor bed (i.e. to the gross tumor volume) was 63.6 ± 9.3 Gy.

Table 2. Characteristics of the study population.

	Marginal resection ($n = 19$)	Segmental resection ($n = 36$)	Total	*P*
Age (years), mean ± SD	57 ± 8.1	58.2 ± 6.7	57.8 ± 7.2	n.s.
WHO score, mean ± SD	2.16 ± 0.26	2.26 ± 0.43	2.23 ± 0.38	n.s.
Osteoradionecrosis risk factors[2–4]				
Number of risk factors, mean ± SD	3.6 ± 0.8	3.2 ± 1	3.3 ± 1	n.s.
Patient-dependent factors				
Active smoking	4	12	16	
Presence of a triggering factor	13	16	29	
Undernutrition (BMI < 18 kg/m^2)	4	7	11	
Tumor-dependent factors				
Advanced stage of management ($\geq T_3$)	3	12	15	
Bone closeness	15	32	47	
Treatment-dependent factors				
Irradiation dose > 60 Gy	10	18	28	
Chemoradiotherapy)	9	19	28	
Mandibular surgery	3	6	9	
Time between irradiation and diagnosis of ORN (months), mean (range)	40 (2–124)	63 (1–274)	57 (1–274)	$P < 0.05$
Time between diagnosis of ORN and revascularization surgery (months), mean (range)	16.5 (1–146)	17 (1–139)	17 (1–146)	n.s.

BMI, body mass index; n.s., not significant; ORN, osteoradionecrosis; SD, standard deviation.

Characteristics of the lesions

In 48 of the 55 cases (87.5%), the osteoradionecrotic lesion had developed within the gross tumor volume. At the time of revascularization surgery, 29% of the bone lesions ($n = 16$) were located above the alveolar canal (five Notani grade I lesions and 11 Notani grade II lesions, vs. nine Notani grade I lesions and 13 Notani grade II lesions at the time of diagnosis). In five of these 16 cases (31.25%), the pain had been controlled with non-opioid analgesics (Epstein stage II). Thirty-four lesions (61%) featured lysis below the alveolar canal (39 Notani grade III lesions, including 24 pathological fractures, vs. 33 Notani grade III lesions with 15 pathological fractures at the time of diagnosis) (Table 3). Treatment with morphine was ineffective in 97.4% of the cases (Epstein grades IIIa or IIIb).

Concerning lesions diagnosed before a fracture stage, a radiological lesion aggravation rate of 42% was observed between diagnosis and revascularization surgery (16,1 ± 15,1 months) bringing the number of fractures from 15 to 24 (i.e. an increase rate of 60%).

Table 3. Clinical and radiological characteristics of the mandibular osteoradionecrosis lesions.

	Marginal mandibulectomy ($n = 19$)	Segmental mandibulectomy ($n = 36$)	Total	P
Clinical characteristics				
Epstein's classification[14]				n.s.
I	0	0	0	
II	5	1	6	
III	14	35	49	
Wong's classification[13]				$P < 0.05$
1	2	1	3	
2	0	0	0	
3	13	13	26	
4	4	22	26	
Radiological characteristics				
Urken's classification[15]				n.s.
R	3	6	9	
B	7	6	13	
S	3	0	3	
RB	4	14	18	
BS	2	5	7	
SS	0	3	3	
RBS	0	0	0	
BSS	0	1	1	
RBSS	0	0	0	
BSSB	0	1	1	
Notani's classification[12]				$P < 0.05$
I	14	2	16	
II	5	10	15	
III	0	24	24	

n.s., not significant.

Medical management

In addition to standard hygiene measures and iterative milling of the sequestra, 29 patients (52.7%) received additional conservative treatment (Table 4). However, the latter was not clinically or radiologically effective.

Table 4. Characteristics of the conservative treatments received by patients (in addition to local wound care and iterative milling): long-term antibiotic therapy (>30 days), a 6-month course of pentoxifylline-tocopherol-clodronate combination therapy, a 30-session course of hyperbaric oxygen therapy.

	Marginal resection ($n = 19$)	Segmental resection ($n = 36$)	P
Treatments			n.s.
Long-term antibiotic therapy	3	10	
Pentoclo treatment	10	4	
Hyperbaric oxygen therapy	3	6	
Sequestrectomy + primary coverage	5	13	
Mean number (range) of additional conservative treatments per patient	1.1 (0–5)	0.9 (0–5)	n.s.

n.s., not significant.

Characteristics of the surgical procedures

The mean ± SD (range) operating time was 497 ± 82 min (246–783 min) (Table 5). We performed 36 segmental mandibulectomies and 19 marginal mandibulectomies, including four with preservation of the basilar edge only. Although histological analyses rarely characterized the completeness of pathological bone removal, in all cases they concluded in the resection of specific lesions of mORN with bone spans infiltrated with connective tissue without the presence of osteocytes, osteoclasts or osteoblasts. In no case was a cancerous recurrence found. The resection of the diseased bone (as evaluated from postoperative X-rays) was complete in 49 cases (89,1%), uncertain in four cases (7,25%), and incomplete in two cases (3,65%).

In cases of segmental mandibulectomy, 34 of the free flaps (94.5%) had a bone component: we noted 12 fibula free flaps, 21 iliac crest free flaps, and one serratus

Table 5. Characteristics of the free flaps, as a function of the type of bone resection.

	Marginal resection ($n = 19$)	Segmental resection ($n = 36$)	Total
Free flap			55
Soft tissue free flap			16
Latissimus dorsi free flap	0	2	2
Periosteal free flap	13	0	13
Fasciocutaneous free flap	1	0	1
Bone or composite free flap			39
Iliac crest free flap	1	21	22
Fibula free flap	3	12	15
Scapula free flap	1	0	1
Serratus-rib free flap	0	1	1

muscle and rib free flap. The iliac crest flap was preferred in 18 of the 20 cases (90%) in which the loss of substance involved the mandibular angle. In four cases, segmental osteotomies were performed on the iliac crest free flap, in order to optimize flap shaping during attempts to perform an anatomical reconstruction Concerning the 19 marginal mandibulectomies, five free flaps had a bone component (three fibula free flaps, one iliac crest free flap, and one scapula free flap) and 13 had a periosteal component (four periosteal internal condyle free flaps, one iliac crest periosteum free flap, seven forearm free flaps with radial periosteum, one external brachial free flap with humeral periosteum). In four marginal mandibulectomy procedures, an additional bone free flap (three fibula free flaps and one iliac crest free flap) was required to strengthen the mandibular infrastructure after bone resection below the alveolar canal.

Anastomoses (end-to-end in 90% of cases) were performed with a non-absorbable, non-braided suture 9/0 or 10/0.

Effectiveness and complication rate of revascularization surgery

The mean ± SD LOS was 21.5 ± 10.5 days (Table 6). Immediately postoperative follow-ups (<30 days) were marked by an overall complication rate of 34%, including 18% of major complications. The major complications were total flap necrosis ($n = 7$), and postoperative deaths ($n = 3$) in a context of massive pulmonary embolism ($n = 1$) or a cardiac rhythm disorder ($n = 2$). The emergency treatment of total flap necrosis constituted flap removal and immediate free flap reconstruction ($n = 4$ (57%); one fibula free flap, one latissimus dorsi free flap, one forearm free flap, and one forearm free flap with radial periosteum) or reconstruction [$n = 3$ (43%), using an endoprosthesis and a latissimus dorsi pedicle flap].

Most of the minor complications corresponded to minimal trimming with a local flap ($n = 1$), local care allowing directed healing ($n = 4$), and lavage with a stent graft change ($n = 1$).

The long-term follow-up (mean ± SD duration: 4 ± 2.5 years) was marked by poor tolerance of the osteosynthesis material in 20% of the patients having undergone reconstruction of the bone infrastructure ($n = 8$) (five microplates and three reconstruction plates); this complication was characterized by a cutaneous fistula opposite the lesion site, due to dissociation of the osteosynthesis material. In all patients, surgical closure of the fistula and removal of the osteosynthesis material led to complete healing within the following month.

Progression of the ORN was observed in only four cases due to incomplete ($n = 2$) or uncertain ($n = 2$) resection of the diseased bone. Thus, revascularization surgery for mORN was effective in 48 of the 52 cases (92.3%). During the follow-up, one reactivation of the ORN phenomenon was observed, after a healing period of several months, in relation to a skin fistula with osteosynthesis materiel uncoupling.

All patients were allowed to use removable dentures for rehabilitation after the mouth wounds had healed. Only six patients received an implant.

Effectiveness and outcomes of revascularization surgery in case of segmental or marginal mandibulectomy (Table 5)

Although segmental and marginal mandibulectomies had similar success rates (88.9% vs. 94.7%, respectively; $P > 0.05$ in Fisher's test), segmental resections were associated with a longer mean operating time (531 ± 72 min vs 440 ± 62 min for marginal resections; $P < 0.05$ in Student's *t*-test), a longer mean LOS (25.6 ± 11.3 days vs. 16.5 ± 6.5 days; $P < 0.05$ in Student's *t*-test) and a higher complication rate (63.9% vs 26.3.%; $P < 0.05$ in Fisher's test) (Table 5). Indeed, there was only one major complication (flap necrosis) in the marginal mandibulectomy group, vs. nine (three deaths and six cases of flap necrosis) in the segmental mandibulectomy group. There were no postoperative deaths in the marginal mandibulectomy group. In the segmental mandibulectomy group, reconstruction of the bone infrastructure was linked to undernutrition and frailty (World Health Organization score: 3) ($n = 2$), and a second revascularization operation within 5 years ($n = 1$). All the chronic complications were related to an inflammatory response to an osteosynthesis plate or to a vascular clip healing immediately after local surgery and removal of the material.

Table 6. Surgical procedures, postoperative follow-up, and the effectiveness of revascularization surgery, as a function of the type of bone resection.

	Marginal resection ($n = 19$)	Segmental resection ($n = 36$)	*P*
Free flap			$P < 0.05$
Soft tissue free flap	14	2	
Bone or composite free flap	5	34	
Operating time (min)	440 ± 62	531 ± 72	$P < 0.05$
Length of hospital stay (days)	16.5 ± 6.5	25.6 ± 11.5	$P < 0.05$
Number of cases with a complication	5 (26.3%)	23 (63.9%)	$P < 0.05$
Minor complications	3	6	
• Partial necrosis	3	2	
• Haematoma	0	2	
• Infection	0	2	
Severe complications	1	9	
• Death	0	3	
• Total necrosis	1	6	
Chronic complications	1	8	
• Poor tolerance of osteosynthesis or a vascular clip	1	7	
• Haematoma	0	1	
Effectiveness	94.7%	88.9%	n.s.

n.s., not significant.

Discussion

Our observation of an overall effectiveness rate of 92.3% for mORN that was refractory to conservative management confirmed the value of revascularization surgery as the reference treatment not only for advanced or fracture lesions but also for early-stage treatment in this context. With a complication rate of 51% ($n = 28$) in our series, including 16.4% ($n = 9$) of serious complications, the indication for revascularization surgery is never simple. Thus, technical constraints and the high incidence of complications or necrosis[10,16–21] have prompted some surgeons to adopt a wait-and-see attitude, in which revascularization surgery is only performed for cases of advanced mandibular lesions (pathological fractures or pre-fracture lesions)[22,23]. Our early management of treatment-refractory ORN was justified by (i) the progressive nature of osteoradionecrotic lesions, and (ii) the risk

of underlying neoplastic lesions that can sometimes be confused with osteoradionecrotic damage[8]. With a view to offering early surgical management for fast-progressing lesions, some researchers[8,12] have attempted to identify severity factors for ORN damage. However, the similarity between severity factors and risk factors can be confusing.

The placement of healthy, vascularized tissue within a diseased, irradiated environment appears to have a true biological dimension, with the provision of neoangiogenic stimuli and cell induction[24]. We hypothesized that free flap reconstruction both revascularizes and recellularizes adjacent tissues compromised by hypoxia, hypocellularity and hypovascularity – pathognomonic features of osteoradionecrotic lesions[6]. It is noteworthy that after the complete resection of diseased bone, the preserved perilesional bone does not present with ORN – despite having received the same dose of irradiation as the diseased area. With all cases of disease progression in the present study concerning incomplete or uncertain resections, complete excision of the pathological bone appears to be a key success factor for revascularization surgery. Under these conditions, perioperative surgical navigation might be promising, i.e. with imaging-guided resection of the damaged bone to avoid underestimating the amount of bone to be removed. However, the termination of the osteoradionecrotic process cannot be explained by excision. The use of in vivo haemodynamic magnetic resonance imaging sequences for monitoring or quantifying vascular flow (e.g., arterial spin labelling[25] or phase contrast[26]) might establish whether or not bone is revascularized by free flap reconstruction.

In fact, the current treatment paradigm[10] recommends reserving revascularization surgery for advanced or fracture lesions. The publication of studies questioning the effectiveness of medical treatment has made this attitude even more controversial. Annane et al.'s[27] placebo-controlled, randomized study found that hyperbaric oxygen therapy was ineffective in treating mORN. Madrid et al.[28] and, more recently, Martos-Fernandes et al.[29] questioned the efficacy of long-term antibiotic therapy and the pentoclo protocol, and concluded that placebo-controlled randomized studies were important for accurately evaluating the efficacy of medical treatments. Despite its high effectiveness rate (86–100%)[11], revascularization surgery appears to be handicapped by its high complication and necrosis rates. In 1996, Kroll et al.[30] showed that the most complex reconstructive procedures are associated with higher complication and failure rates are. Thus, it is unfair to blame revascularization surgery for a high complication rate if the technique is reserved only for complex reconstructions of advanced or fracture lesions. In the present study, 42% of the non-fracture lesions progressed between diagnosis and surgery, and 15 of the 55 lesions (27.3%) were diagnosed at the fracture stage. Thus, we wish to insist on the need for early diagnosis of osteoradionecrotic lesions and concerted treatment strategies refractory lesions – thus enabling marginal resections, less complex reconstructions, and thus a significant reduction in the complication rate and the post-surgery LOS. Our study results challenge the current paradigm, and suggest that the role of revascularization surgery in the therapeutic algorithm for ORN injury should be reappraised in order to break the vicious circle (late surgery – segmental resection – bone reconstruction – high complication rate) and initiate a virtuous circle (early surgery – marginal resection – low complication rate).

With regard to the choice of the reconstruction procedure (soft tissue flap vs. bone flap), we consider that it is important to determine whether the osteolysis is above or below the sub-alveolar canal; the objective of reconstruction must be to restore function by restoring or maintaining bone integrity and the strength of the mandibular infrastructure. Given that 15% of the long-term complications in the present study were related to poor tolerance of osteosynthesis material (in line with the values from 7% to 57.5% reported in large series[10,11,16–21]), we suggest that reducing or optimizing osteosynthesis is essential. From this perspective, revascularization surgery using a soft tissue free flap and surgery that spares the basilar edge would be valuable treatment options. A significant increase in the frictional surface between the flap and the native bone (as with a 'tongue in groove' type of assembly) would be more solid and might require the use of less inert osteosynthetic material.

However, given that 60% of the osteoradionecrotic lesions showed subcanal damage on diagnosis, our study also revealed a significant diagnostic delay. Thus, changing the current paradigm will require greater awareness of the issues faced by irradiated patients among physicians and other healthcare professionals. It is also important to inform irradiated patients about prophylactic measures[6] and the possible first symptoms of ORN, with a view to promoting earlier consultation and treatment initiation; treatment delays will lead to more complex reconstructions and thus a greater risk of complications.

In conclusion, revascularization surgery is the only therapy that has proven its efficiency in the treatment of advanced or refractory mORN. Its technical difficulties and high complication rate remain significant limitations. However, our present results suggest that the indications of revascularization surgery should be extended to treatment-refractory lesions that can be accessed by marginal mandibulectomy (with lower complication and failure rates than segmental bone resection), in order to provide a single-step, functional, curative approach to the management of mORN.

Funding

This study was not funded

Competing interests

The authors have o conflicting interests to disclose.

Ethical Approval

This study adhered to the principles of the Declaration of Helsinki in terms of medical protocols and ethics.

Patient consent

Not required.

References

1. Nabil S, Samman N. Risk factors for osteoradionecrosis after head and neck radiation: a systematic review. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012;**113**:54–69. http://dx.doi.org/10.1016/j.tripleo.2011.07.042.
2. Goldwaser BR, Chuang SK, Kaban LB. Risk factor assessment for the development of osteoradionecrosis. *J Oral Maxillofac Surg* 2007;**65**:2311–6. http://dx.doi.org/10.1016/j.joms.2007.05.021.
3. Kuhnt T, Stang A, Wienke A, Vordermark D, Schweyen R, Hey J. Potential risk factors for jaw osteoradionecrosis after radiotherapy for head and neck cancer. *Radiat Oncol* 2016;**11** (July (30)):101. http://dx.doi.org/10.1186/s13014-016-0679-6.
4. Glanzmann C, Grätz KW. Radionecrosis of the mandibula: a retrospective analysis of the incidence and risk factors. *Radiother Oncol* 1995;**36**:94–100. (PMID: 7501817).
5. Meyer I. Infection diseases of the jaws. *J Oral Surg* 1970;**28**:17–26. (PMID: 5262227).

6. Marx RE. A new concept in the treatment of osteoradionecrosis. *J Oral Maxillofac Surg* 1983;**41**:351–7. (PMID: 6574217).
7. Ben-David MA, Diamante M, Radawski JD, Vineberg KA, Stroup C, Murdoch-Kinch C-A, Zwetchkenbaum SR, Eisbruch A. Lack of osteoradionecrosis of the mandible after intensity-modulated radiotherapy for head and neck cancer: likely contributions of the both dental care and improved dose distributions. *Int J Radiat Oncol Biol Phys* 2007;**68**:396–402. http://dx.doi.org/10.1016/j.ijrobp.2006.11.059.
8. D'Hauthuille C, Testelin S, Moure C, Gbaguidi C, Devauchelle B. Ostéoradionécroses mandibulaires. Partie II: efficacité de la chirurgie de revascularisation. *Rev Stomatol Chir Maxillofac* 2008;**109**:296–300. http://dx.doi.org/10.1016/j.stomax.2007.12.009.
9. Beauvillain de Montreuil C, Billet J, Bonnet J, Gordeeff A, Legent F. Limited mandibular osteoradionecrosis. Early conservative surgical management. *Ann Otolaryngol Chir Cervicofac* 1987;**104**:579–85. (PMID: 3445974).
10. Rice N, Polyzois I, Ekanayake K, Omer O, Stassen LFA. The management of osteoradionecrosis of jaws — a review. *Surgeon* 2015:101–9. http://dx.doi.org/10.1016/j.surge.2014.07.003.
11. Lee M, Chin RY, Eslick GD, Sritharan N. Outcomes of microvascular free flap reconstruction for mandibular osteoradionecrosis: a systematic review. *J Craniomaxillofac Surg* 2015;**43**:2026–33. http://dx.doi.org/10.1016/j.jcms.2015.03.006.
12. Notani K, Yamazaki Y, Kitada H, Sakakibara N, Fukuda H, Omori K, Nakamura M. Management of mandibular osteoradionecrosis corresponding to the severity of osteoradionecrosis and the method of radiotherapy. *Head Neck* 2003;**25**:181–6. http://dx.doi.org/10.1002/hed.10171.
13. Wong JK, Wood RE, McLean M. Conservative management of osteoradionecrosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997;**84**:16–21. (PMID: 9247943).
14. Epstein JB, Wong FL, Stevenson-Moore P. Osteoradionecrosis clinical experience and a proposal for classification. *J Oral Maxillofac Surg* 1987;**45**:104–10. (PMID: 3468211).
15. Urken ML, Weinberg H, Vickery C, Buchbinder D, Lawson W, Biller HF. Oromandibular reconstruction using microvascular composite free flaps. Report of 71 cases and new classification scheme for bony, soft-tissue, and neurologic defects. *Arch Otolaryngol Head Neck Surg* 1991;**117**:733–44. (PMID 1863438).
16. Brown JS, Lowe D, Kanatas A, Schache A. Mandibular reconstruction with vascularised bone flaps: a systematic review over 25 years. *Br J Oral Maxillofac Surg* 2017;**55**:113–26. http://dx.doi.org/10.1016/j.bjoms.2016.12.010.
17. Ionnides C, Fossion E, Boeckx W, Hermans B, Jacobs D. Surgical management of the osteoradionecrotic mandible with free vascularised composite flaps. *J Craniomaxillofac Surg* 1994;**22**(6):330–4. (PMID: 7884003).
18. Gal TJ, Yueh BY, Futran ND. Influence of prior hyperbaric oxygen therapy in complications following microvascular reconstruction for advanced osteoradionecrosis. *Arch Otolaryngol Head Neck Surg* 2003;**129**:72–6. (PMID: 12525198).
19. Alam DS, Nuara M, Christian J. Analysis of outcomes of vacularized flap reconstruction in patients with advanced mandibular osteoradionecrosis. *Otolaryngol Head and Neck Surg* 2009;**141**:196–201. http://dx.doi.org/10.1016/j.otohns.2009.03.013.
20. Suh JD, Blackwell KE, Sercarz JA, Cohen M, Liu JH, Tang CG, Abemayor E, Nabili V. Disease relapse after segmental resection and free flap reconstruction for mandibular osteoradionecrosis. *Otolaryngol Head Neck Surg* 2010;**142**(4):586–91. http://dx.doi.org/10.1016/j.otohns.2009.12.008.
21. Baumann DP, Yu P, Hanasono MM, Skoracki RJ. Free flap reconstruction of osteoradionecrosis of the mandibule: a 10-year review and defect classification. *Head Neck* 2011;**33**:800–7. http://dx.doi.org/10.1002/hed.21537.
22. Cannady SB, Dean N, Kroeker A, Albert TA, Rosenthal EL, Wax MK. Free flap reconstruction for osteoradionecrosis of the jaws — outcomes and predictive foctors for success. *Head Neck* 2011;**33**:424–8. http://dx.doi.org/10.1002/hed.21463.
23. Pitak-arnnop P, Sader R, Dhanuthai K, Masaratana P, Bertolus C, Cjaine A, Bertrand JC, Hemprich A. Management of osteoradionecrosis of the jaws: an analysis of evidence. *Eur J Surg Oncol* 2008;**34**:1123–34. http://dx.doi.org/10.1016/j.ejso.2008.03.014.
24. Yancopoulos GD, Davis S, Gale NW, Rudge JS, Wiegand SJ, Holash J. Vascular-specific growth factors and blood vessel formation. *Nature* 2000;**407**:242–8. http://dx.doi.org/10.1038/35025215.
25. Paiva FF, Tannus A, Silva AC. Measurement of cerebral perfusion territories using arterial spin labelling. *NMR Biomed* 2007;**20**:633–42. http://dx.doi.org/10.1002/nbm.1177.
26. Bettoni J, Pagé G, Salsac AV, Constans JM, Testelin S, Devauchelle B, Balédent O, Dakpé S. Quantitative assessment of the flox distribution in the branches of the external carotid by non-injected flow MRI. *Dentomaxillofac Radiol* 2018;**47**:20180153. http://dx.doi.org/10.1259/dmfr.20180153.
27. Annane D, Depondt J, Aubert P, Villart M, Géhanno P, Gajdos P, Chevret S. Hyperbaric oxygen therapy for radionecrosis of the jaw: a randomized, placebo-controlled, double-blind trial from the ORN96 study group. *J Clin Oncol* 2004;**22**(24):4893–900. http://dx.doi.org/10.1200/JCO.2004.09.006.
28. Madrid C, Abarca M, Bouferrache K. Osteoradionecrosis: an update. *Oral Oncology* 2010;**46**:471–4. http://dx.doi.org/10.1016/j.oraloncology.2010.03.017.
29. Martos-Fernandez M, Saez-Barba M, Lapez-Lopez J, Estrugo-Devesa A, Balibrea-Del-Castillo JM, Bescos-Atin C. Pentoxifylline, topopherol, and clodronate for the treatment of mandibular osteoradionecrosis: a systematic review. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2018;**125**(5):431–9. http://dx.doi.org/10.1016/j.oooo.2018.02.004.
30. Kroll SS, Schusterman MA, Reece GP, Miller MJ, Evans GR, Robb GL, Baldwin BJ. Choice of flap and incidence of free flap success. *Plast Reconstr Surg* 1996;**98**(3):459–63. (PMID: 8700982).

Address:
Jérémie Bettoni
Department of Maxillo-Facial Surgery
University Hospital of Amiens
Avenue Laennec
80000 Amiens
France
Tel.: +33 3 22 08 90 50;
Fax: +33 3 22 66 79 94
E-mails: jeremiebettoni@gmail.com, jeremie.bettoni@chu-amiens.fr