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Outcomes of Microvascular Composite Reconstruction for Mandibular Osteoradionecrosis

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Abstract

Background: The aim of this retrospective study is to compare outcomes and reconstruction related complications in patients receiving a composite free flap reconstruction of the mandible for ORN with those reconstructed for other indications.

Patients and Methods: The records of all patients who underwent composite reconstruction of a mandibular defect at Aintree University Hospital, Liverpool were reviewed and analysed. Based on radiotherapy exposure and ORN history, the study cohort was divided into 3 separate case-matched groups.

Results: Local wound healing issues were markedly more common in the ORN setting, as was infection and subsequent osteosynthesis plate(s) removal. Free flap survival was similar among all 3 case-matched groups.

Conclusion: Advanced mandibular ORN may be safely and predictably reconstructed with composite free flaps, and that while the rate of local complications is greater than non-irradiated, and non-ORN case-matched controls, the free flap survival rate compares favorably.

Keywords: osteoradionecrosis; composite free flap; mandible

Introduction

Osteoradionecrosis (ORN) is exposed necrotic bone after radiotherapy in the absence of neoplasia. Affected patients suffer from malnutrition, opiate dependency, infection, disfigurement, and reduced quality of life[1]. The reported incidence of ORN ranges from 2 to 22%, with a steady decrease in more recent published series, which converge on a rate of 6-8% [2, 3, 4, 5, 6]. However, the incidence of head and neck cancer [7, 8] is increasing, as is survival and use of radiotherapy. Therefore, the at-risk population is increasing.

Surgical resection and free flap reconstruction remains the mainstay for advanced ORN (Notani Stage III). However, vessel depletion, tissue fibrosis, and impaired wound healing increase the risk of late wound complications. Historically, reconstruction of irradiated tissues carried a higher risk of complications, including flap failure[9, 10, 11, 12]. Deutsch et al[13] reported that both pre- and post-operative radiotherapy is associated with an increased flap complication rate, and that the timing of radiation therapy did not affect the rate of complications. The effect of radiotherapy on vessels, and therefore microvascular anastomosis remains unclear. Endothelial cell dehiscence, vessel wall fibrosis, and decreased smooth

muscle activity have been demonstrated with scanning electron microscopy of irradiated recipient neck vessels[14]. Others have reported that radiotherapy does not affect the rate of complications associated with free flaps[15].

The aim of this retrospective study is to compare outcomes (free flap survival) and reconstruction related complications in patients receiving a composite free flap reconstruction of the mandible for ORN with those reconstructed for other indications. Additionally, we will explore the effect of post-operative radiotherapy on the outcomes of composite reconstruction in the absence of ORN.

Patients and Methods

The records of all patients who underwent composite reconstruction of a mandibular defect at Aintree University Hospital, Liverpool, between October 1990 and November 2015 were reviewed. In addition to a prospectively updated computerised database[16], case notes including operation notes, histo-pathology reports, and radiographs were used to gather information. The following variables were recorded: patient demographics, indication for resection, length of bone defect, pathological diagnosis and stage, flap donor site, pre- or post-operative radiotherapy (PORT), fixation type and length of admission. Additionally, the mandibular defect was classified according to Brown et al[17].

Among this cohort of 471 patients, the indications for resection were as follows: Squamous Cell carcinoma, n=354 (75%); ORN, n=49 (10%); Ameloblastoma, n=11 (2.3%); Adenoid Cystic Carcinoma, n=8 (1.7%); Mucoepidermoid Carcinoma, n=7 (1.5%); Carcinoma in Ex-PSA, n=4 (0.8%); others (e.g. [osteo-] sarcoma, salivary malignancy, neuroendocrine), n=38 (8%).

For the purposes of comparison, the study cohort was divided into 3 separate case-matched groups, each of 49 patients.

Group 1, Patients who had a resection and reconstruction for ORN; *Group 2*, Patients who had reconstruction following tumour resection and subsequently received PORT; *Group 3*, patients similar to group 2 but who did not receive pre- or post-operative radiotherapy.

The patients in each group were selected as follows: *Group 1* (ORN) as all patients with complete data, *groups 2 and 3* were matched according to age, sex, length and position (class) of defect, donor site, as well as the era (5-year period) during which reconstruction took place. All patients received primary flap reconstruction, i.e. were reconstructed at the time of resection.

The endpoints of interest were free flap survival, as well as development of reconstruction related complications.

Complications were classified as follows:

1. Flap failure (complete or partial)
2. Non-union
3. Local wound issue requiring re-admission or re-operation (bone exposure/removal, minor infection, and dehiscence)*
4. Plate removal
5. Donor site§

*The classification of local wound complications used here is as in our previous publication on mandible reconstruction[18].

§We measured all donor site complications that were severe enough to require re-admission and/or re-operation.

Results

There were 147 patients (56 female, 91 male) in our study cohort. The mean age was 60.4 years (range, 17 to 86 years). Squamous cell carcinoma or other malignancies accounted for the vast majority of patients in groups 1 and 2, while benign conditions, including trauma, accounted for 22% of patients' in group-3.

Patient, defect, and donor site characteristics are described in *Table 1*. All complications, including partial and complete flap failure, are outlined in *Table 2*.

The distribution of donor sites for the ORN cases is outlined in *figure 2*.

In *group-1*, there were three complete flap failures. The donor sites for these cases were two DCIA flaps and 1 fibula flap. A Latissimus dorsi and two composite radial flaps respectively were used as salvage reconstructions in these cases. The precise cause of flap failure could not be reliably ascertained. Another patient in this group lost the skin paddle component of a fibula flap, and a delto-pectoral flap was used for salvage. One patient suffered partial necrosis of the muscle component of a DCIA flap, which did not necessitate any additional salvage reconstruction.

Local wound healing issues were markedly more common in the ORN setting, occurring in 47% of *group-1*; compared to 28% is *group-2* and only 8% in *group-3*.

In *Group-1*, infection accounted for 78% (n=18), wound dehiscence 13% (n=3), and bone exposure 9% (n=2). In *Group-2*, infection accounted for 36% (n=5), dehiscence 36% (n=5), and bone exposure 28% (n=4); while in *Group-3* infection was 50% (n=2), dehiscence 25% (n=1), and bone exposure 25% (n=1).

Similarly, osteosynthesis plate(s) removal was also more common in ORN. Twenty-two (45%) patients in *group-1* had hardware removed but only 1 patient in *group-3* (no radiotherapy, no ORN) and, again, an intermediate number (14%) in *group-2*. Two patients (4%) in *group-1* suffered a non-union, while this complication did not occur in *group-3*. Within *group-1*, five (10.2%) patients developed further ORN, all on the ipsilateral side. Of these patients, one occurred distal to the free flap in the pre-molar area, while all others occurred proximally (typically the mandibular angle/ascending ramus). A non-union occurred in 3 of 5 patients, all at the site of ORN recurrence. Further ORN in the condyle, which were retained where possible, occurred in only one patient. All ORN recurrences, apart from the condyle, occurred immediately adjacent to the free flap, and represented the resection margin. The patient with ORN recurrence at the condyle had a primary tonsil tumor, unlike all others, which had an oral cavity tumour.

Discussion

Our findings suggest that mandibular ORN may be predictably managed with free flap reconstruction, albeit with an increased complication rate. In this case-matched study, the overall rate of free flap survival in the ORN cohort was similar to patients who underwent free flap reconstruction for other indications. The partial flap failure rate, e.g. skin/muscle necrosis, was also similar among the 3 groups. However, the rate of local complications (47%) and the need for removal of hardware (45%) was significantly higher in the ORN cohort.

Additionally, we found that the late recipient-site complication rate was not influenced by donor site choice but rather that the only significant factor influencing re-admission and late fixation-related complication rate was prior radiotherapy.

Our study is limited by its retrospective nature. While certain data collected was retrieved from our prospectively completed database; some was obtained via operation and case notes, pathology reports, and radiographs, none of which was recorded in a standardised fashion. We were not, for example, able to match according to smoking status, co-morbidities, duration of ORN, and the size of the soft tissue component of the harvested free flap. Similarly, a prospective study looking at reconstruction related complications would have additionally looked at, among other variables, malocclusion, mid-line shift, and marginal mandibular nerve weakness.

ORN cases present with fistulae, infection, fractures, through and through defects but small intra-oral soft tissue volume requirements. Primary cancer resections often have substantial intra-oral soft tissue volume defects and less often require extra-oral skin paddles, and doubtless this disparity is greater in those cases that required adjuvant radiotherapy than in those cases that did not. Soft tissue volume and location is important in determining

complications, but often inadequately measured in surgical records. This is challenging to do quantitatively and is a learning point for future studies.

However, we have closely matched all ORN patients to similar (non-ORN) cases based on age, class of defect, donor site, length of defect, and the era in which the reconstruction was performed. It is however likely that there has been an under-reporting of complications, particularly minor or late. Nevertheless, the data on flap failure, we believe, is accurate. In addition, we do not comment on the total received dose of radiotherapy, or the extent of fields, as this information was not available to us for all included cases. However, this is likely more relevant to the risk of ORN development as opposed to free flap survival.

The risk of ORN is higher in the posterior mandible and if > 60 Gy has been received[2, 19, 20]. In *Group-1 (ORN),* Class I defects predominate reflecting the commonest site of incidence of ORN. Previous studies have shown an increased frequency of ORN in oral cavity tumours, relative to other sites[21].

Class I defects involve the lateral mandible, excluding the canine and condyle.

Notwithstanding the importance of radiation dose, it is possible that anatomical variation, including muscle insertions and blood supply influence the propensity for ORN at this site. For example, the anterior mandible may benefit from insertion of both the mentalis and genio-hyoid muscles. Similarly, the ramus may benefit from insertion of the medial pterygoid and masseter muscles.

Our data (*Figure. 1*) shows an increase in composite flap reconstruction for ORN, nearly doubling every 5 years. Anecdotally this trend has continued since 2015. Although we cannot extrapolate on the rates of ORN itself, as our study does not account for those patients managed with quadruple therapy (pentoxifylline, tocopherol and clodronate; or variations on

this prescription), or those awaiting surgery, it is clear that the number of cases requiring definitive ablative and reconstructive surgery is increasing.

The other notable trend has been for an increased reliance on the fibula donor site for ORN cases (*figure. 2*). While not presented here; since 2015, we have successfully implemented the tip of scapula in highly selected cases, particularly where peroneal vessels are unsuitable and contralateral neck vascular access is mandated[22].

Lee et al[23], in a systematic review of free flap reconstruction for the management of ORN reported a flap failure rate of 9.8% (range, 9-16%). Our rate of 6% compares favorably to this. In addition, it compares favorably to our control groups (groups 2, and 3) with flap failure rates of 8% and 10% respectively. These results support our hypothesis that composite free flap reconstruction in ORN cases is non-inferior to non-ORN and non-irradiated controls. While our study was not adequately powered to draw statistical significance, there appeared to be no correlation between donor site and rate of failure.

The healing of irradiated tissue is compromised, and this may manifest as infection, local wound breakdown, fistula formation, and/or hardware exposure. In the aforementioned systematic review[23], an overall local wound healing complication rate of 42% was reported. In our study, the incidence of local wound issues in *group-1* was similar, at 47%. These results suggest that post-operative radiotherapy does not affect free flap viability, but rather may increase the rate of local wound and hardware complications. Pohlenz et al[24], in a review of 202 microvascular reconstructions, found that pre-operative radiation therapy was one of the main factors associated with increased risk of recipient site complications. Singh et

al[25] also found a statistically significant association between prior radiotherapy and recipient site complications. However, it must be considered that ORN itself is a risk factor for wound complications (as opposed to free flap survival). In our study, the rate of local wound complications for ORN is 47% versus 28% for those who had radiotherapy but no ORN. Similarly, Suh et al[26], in 2004 found a significantly increased rate of local complications in ORN cases, when compared to non-ORN but irradiated patients.

In our practice, resection margins are based both on clinical findings at operation and pre-operative radiographic evidence for osteonecrosis. Despite aggressive resection of obviously non-viable bone, 10% (n=5) of our patients developed further ORN, of which only one occurred at the condyle. Suh et al[27] reported a 25% recurrence rate in a review of 40 patients who had segmental resection and reconstruction for the management of ORN. Interestingly, 70% (n=7) of their recurrences developed at the condyle or subcondyle. The majority of their patients had oropharynx site primary tumours and it is therefore conceivable that the difference in both the rate and location of recurrence may be related to the area irradiated as well as the dose delivered. They further postulate that the recurrence of ORN following an apparently adequate resection may be related to a poor understanding of the pathophysiology of ORN, and that the presence or absence of bleeding may be insufficient to guide the extent of resection. Changes in bone homeostasis and metabolism may account for an ongoing disease process and therefore recurrence. This is in keeping with the fact that ORN can occur many years after radiotherapy, and that a reduced capacity to heal may be permanent[28]. It should also be noted that surgical trauma in the form of muscle stripping and placement of fixation screws, may render retained bone more susceptible to development of further ORN. Koka et al[29] reported a recurrence rate of 14.5% within 1 to 41 months following mandibulectomy.

The incidence of ORN[5], at 6%, is low. However, the incidence of head and neck malignancy and use of radiation therapy is increasing. Human papillomavirus (HPV) has a significant role in the increasing incidence in the oropharynx, and with near universal use of radiotherapy in its management of this disease group, younger age and better survival, the 'at-risk' population for ORN is increasing. Radiation induced vascular atrophy has led to concerns about free flap survival in previously irradiated tissue. Our findings suggest that advanced mandibular ORN may be safely and predictably reconstructed with composite free flaps, and that while the rate of local complications is greater than non-irradiated, and non-ORN case-matched controls, the free flap survival rate compares favorably.

Ethics statement/confirmation of patient permission

This is a retrospective review of anonymised data and therefore ethical approval is not applicable.

Conflict of Interest

No conflicts of interest

References

[1] Rogers SN, D'Souza J, Lowe D, Kanatas A. Longitudinal evaluation of health related quality of life following osteoradionecrosis of the mandible. Br J Oral Maxillofac Surg. 2015 Aug 24, 261-2.

[2] Chen J-A et al. Osteoradionecrosis of mandible bone in patients with oral cancer–associated factors and treatment outcomes. Head Neck 2016;38:762–8.

[3] Owosho AA et al. The prevalence and risk factors associated with osteoradionecrosis of the jaw in oral and oropharyngeal cancer patients treated with intensity-modulated radiation therapy (IMRT): The memorial sloan kettering cancer center experience. Oral Oncol 2017;64:44–51.

[4] Tsai CJ et al. Osteoradionecrosis and radiation dose to the mandible in patients with oropharyngeal cancer. Int J Radiat Oncol Biol Phys 2013;85:415–20.

[5] Caparrotti F, Huang SH, Lu L et al. Osteoradionecrosis of the mandible in patients with oropharyngeal carcinoma treated with intensity- modulated radiotherapy. Cancer. 2017 Oct 1;123(19):3691-3700.

[6] Shaw RJ, Butterworth C et al. HOPON (Hyperbaric Oxygen for the Prevention of Osteoradionecrosis): A Randomized Controlled Trial of Hyperbaric Oxygen to Prevent Osteoradionecrosis of the Irradiated Mandible After Dentoalveolar Surgery. Int J Radiat Oncol Biol Phys. 2019 Jul 1;104(3):530-539.

[7] [1] McCarthy CE, Field JK, Rajlawat BP, Field AE, Marcus MW. Trends and regional variation in the incidence of head and neck cancers in England: 2002 to 2011. Int J Oncol 2015; 47:204–10.

[8] Schache AG, Powell NG, Cuschieri KS, Robinson M, Leary S, Mehanna H, et al. HPV-related oropharynx cancer in the United Kingdom: an evolution in the understanding of disease etiology. Cancer Res 2016.

[9] Margolis IB, Smith RL, Davis WC: Reconstruction of defects of the mandible. Surgery 1976; 79(6): 638-643.

[10] Salyer KE, Newsom HT, Holmes R, Hahn G: Mandibular reconstruction. Am J Surg 1977; 134(4): 461-464.

[11] Serafin D, Riefkohl R, Thomas I, Georgiade NG: Vascularized rib-periosteal and osteocutaneous reconstruction of the maxilla and mandible: an assessment. Plast Reconstr Surg 1980; 66(5): 718-727.

[12] Krag C, Holck S, DeRose G, Lyczakowski T, Freeman CR: Healing of microvascular anastomoses. A comparative study using normal and irradiated recipient vessels for experimental free flaps in rabbits. Scand J Plast Reconstr Surg 1982; 16(3): 267-274.

[13] Deutsch M, Kroll SS, Ainsle N, Wang B: Influence of radiation on late complications in patients with free fibular flaps for mandibular reconstruction. Ann Plast Surg 1999; 42(6):662-664.

[14] Guelinckx PJ, Boeckx WD, Fossion E, et al: Scanning electron microscopy of irradiated recipient blood vessels in head and neck free flaps. Plast Reconstr Surg 1984; 74:217.

[15] Choi W, Schwartz DL, Farwell DG, et al: Radiation therapy does not impact local complication rates after free flap reconstruction for head and neck cancer. Arch Otolaryngol Head Neck Surg 2004; 130:1308.

[16] Rogers SN, Bierne JC, Pate1 M, Vaughan ED, Brown JS. A clinician friendly computerised head and neck oncology audit. Ann R Coll Surg Eng 1996; 87(l Suppl):14–18.

[17] Brown JS, Barry C, Ho M, Shaw R. A new classification for mandibular defects after oncological resection. Lancet Oncol 2016;17: e23–30.

[18] Shaw RJ, Kanatas AN, Lowe D, Brown JS, Rogers SN, Vaughan ED. Comparison of miniplates and reconstruction plates in mandibular reconstruction. Head Neck. 2004 May; 26(5):456-63.

[19] Lee IJ, Koom WS, Lee CG, et al. Risk factors and dose-effect relationship for mandibular osteoradionecrosis in oral and oropharyngeal cancer patients. Int J Radiat Oncol Biol Phys 2009;75:1084-1091.

[20] Murray CG, Herson J, Daly TE, Zimmerman S. Radiation necrosis of the mandible: A 10 year study. Part I. Factors influencing the onset of necrosis. Int J Radiat Oncol Biol Phys 1980;6:543-548.

[21] 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 Jul 30;11:101.

[22] [1] Ho MW, Brown JS, Shaw RJ. Refining the indications for scapula tip in mandibular reconstruction. Int J Oral Maxillofac Surg. 2017 Jun;46(6):712-715.

[23] Lee M, Chin RY, Eslick GD, Sritharan N, Paramaesvaran S. Outcomes of microvascular free flap reconstruction for mandibular osteoradionecrosis: A systematic review. J Craniomaxillofac Surg. 2015 Dec; 43(10):2026-33.

[24] Pohlenz P, Blessmann M, Heiland M, et al. Postoperative complications in 202 cases of microvascular head and neck reconstruction. J Craniomaxillofac Surg 2007;35:311–5.

[25] Singh B, Cordeiro PG, Santamaria E, et al. Factors associated with complications in microvascular reconstruction of head and neck defects. Plast Reconstr Surg 1999;103:403–11.

[26] Suh JD, Sercarz JA, Abemayor E, et al. Analysis of outcome and complications in 400 cases of microvascular head and neck reconstruction. Arch Otolaryngol Head Neck Surg 2004;130: 962– 6.

[27] 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 Apr;142(4):586-91.

[28] Epstein J, Meij E, McKenzie M, et al: Postradiation osteonecrosis of the mandible: A long-term follow-up study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 83:657, 1997

[29] Koka VN, Deo R, Lusinchi A, et al: Osteoradionecrosis of the mandible: Study of 104 cases treated by hemimandibulectomy. J Laryngol Otol 104:305, 1990

Figures for ORN manuscript

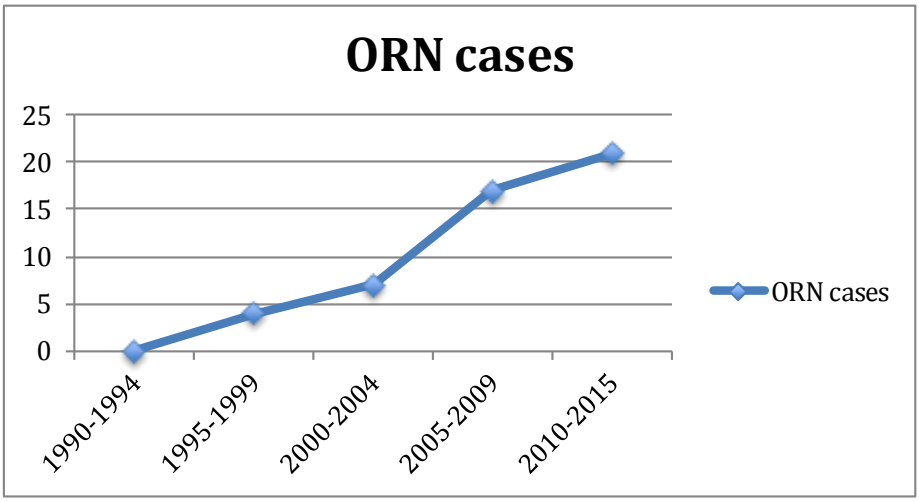

Figure 1. Number of ORN cases per 5-year period.

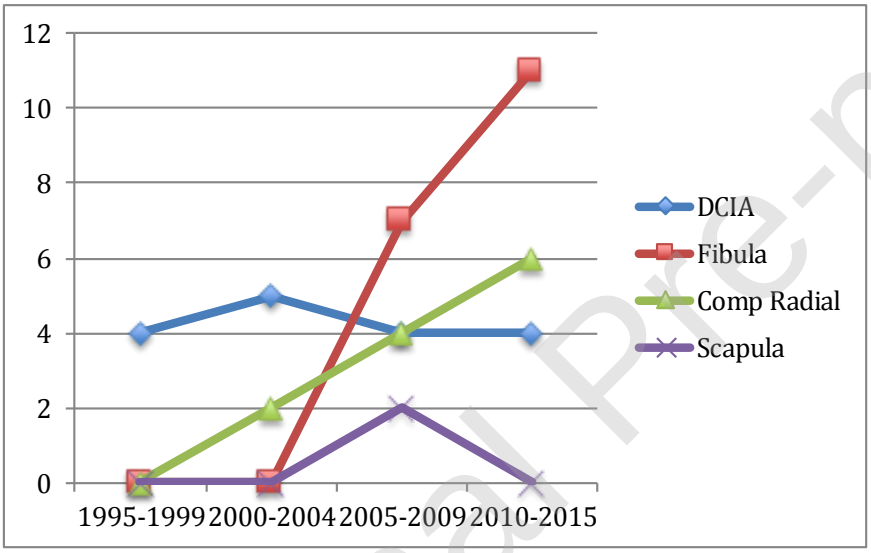

Figure 2. Donor sites for ORN reconstructions

Tables for ORN Manuscript

	Group 1 (ORN)	Group 2 (Rad, No ORN)	Group 3 (No Rad, No ORN)
Number of patients	49 (12 F, 37M)	49 (27F, 22M)	49 (17F, 32M)
Age (years)	Mean 58.1 (range, 44-74)	Mean 63.9 (range, 43 - 84)	Mean 59.3 (range, 17-86)
Classification			
• ***Class I***	37 (76%)	29 (60%)	31 (63%)
• ***Class II***	7 (14%)	13 (26%)	11 (23%)
• ***Class III***	3 (6%)	6 (12%)	7 (14%)
• ***Class IV***	2 (4%)	1 (2%)	0
Donor Site			
• ***DCIA***	17 (35%)	16 (33%)	18 (37%)
• ***Fibula***	18 (37%)	19 (39%)	18 (37%)
• ***Radial***	12 (24%)	12 (24%)	11 (22%)

• ***Scapula***	2 (4%)	2 (4%)	2 (4%)
Length of defect (mm)	Mean 75.7 (range, 27-125)	Mean 79.9 (range, 40-130)	Mean 72.4 (range, 43-120)
Length of stay (days)	Mean 22 (range, 6-156)	Mean 25.6 (range, 11-148)	Mean 19.3 (range, 7-60)
Number of cases per 5-year period			
• ***1995-1999***	4	4	4
• ***2000-2004***	7	7	7
• ***2005-2009***	17	17	17
• ***2010-2015***	21	21	21
Osteotomy in osseous component of Free flap (%)	32 (66%)	28 (57%)	28 (58%)
Method of fixation (%)			
• ***Reconstruction plate***	49	71	54
• ***Mini-plate***	44	29	46
• ***Both***	7	0	0

Table 1. Groups according to ORN/Radiotherapy status

Complication	Group 1, (ORN) Number (%)	Group 2, (RT, no ORN) Number (%)	Group 3, (no RT) Number (%)
Flap failure (complete)	3 (6)	4 (8)	5 (10)
Flap failure (partial)	1 (2)	2 (4)	1 (2)
Non-union	2 (4)	1 (2)	0
Reconstructed site complications*	23 (47)	14 (28)	4 (8)
Donor site: minor	4 (8)	2(4)	1 (2)
Osteosynthesis plate removal	22 (45)	7 (14)	1 (2)

Table 2. Complications. *Bone exposure/removal, minor infection, and soft-tissue dehiscence.