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Comparative osteoradionecrosis rates in bony reconstructions for head and neck malignancy

Henry Li[a,*], **Meily Dewi Mulyadi Tan**[a], **Skaria Alexander**[a,b], **Damien Grinsell**[a,b], **Anand Ramakrishnan**[b]

[a] *Department of Plastic and Reconstructive Surgery, St Vincent's Hospital Melbourne. 41 Victoria Parade, Fitzroy, Victoria 3065, Australia*
[b] *Department of Plastic and Recontstructive Surgery, Royal Melbourne Hospital. 300 Grattan Street, Parkville, Victoria 3050, Australia*

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Summary *Background:* Bony free flaps are used to reconstruct head and neck cancer defects. The most commonly used flaps are the free fibula flap and the deep circumflex iliac artery (DCIA) flap. Radiotherapy may be given post-operatively to prevent cancer recurrence. This radiotherapy can, however, destroy the bone; a complication termed osteoradionecrosis (ORN). Although there have been studies comparing free fibula and DCIA flaps in terms of success rates and complications, few have assessed the incidence of ORN in both groups.
Methods: A retrospective cohort study was conducted involving patients from Royal Melbourne Hospital and St Vincent's Hospital Melbourne who had either a free fibula or DCIA flap for head and neck cancer reconstruction in the past 10 years. Data collected included demographic, operative, and postoperative data. Analysis was performed using Statistical Package for Social Sciences and Microsoft Excel, utilising t-tests, chi-square tests and logistic regression analyses.
Results: A total of 154 patients were identified. Of these patients, 127 had free fibula flaps and 27 had free DCIA flaps. Twelve patients had ORN post-op, 10 had free fibula flaps, and 2 had free DCIA flaps. No statistically significant difference was found between the ORN rates in free fibula flaps and free DCIA flaps.
Conclusion: Rates of ORN incidence should not be a major consideration in preoperative planning of free flaps for mandibular reconstruction as both fibula and DCIA free flaps are comparable.

* Correspondence to: 384 Dandenong Road, Caulfield North Victoria 3161, Australia.
E-mail address: henrychestnut1993@gmail.com (H. Li).

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Introduction

Approximately 5000 people in Australia are diagnosed with head and neck cancer per year.[1] This comprises roughly 3.7% of all new cancer diagnoses per year. Worldwide, it is the sixth most common group of cancers.[2] The major risk factors for head and neck cancer are smoking and alcohol consumption.[3] More recently, human papillomavirus and Epstein-Barr virus have been shown to play a more important role in the pathogenesis of head and neck cancers.[4, 5] Minor risk factors include age (> 40), sex, genetics (South China/South East Asia), poor oral hygiene, sun exposure, low immune system and poor nutrition.[6]

The management of head and neck cancer has improved significantly over the past few decades, with overall 5 year survival rates reaching 69%.[1] The goals of treatment of head and neck malignancies include removing or eradicating the primary tumour, preserving or restoring function and form, minimising complications, preventing recurrence and improving or maintaining quality of life. To achieve these goals, management may involve surgery, radiotherapy, chemotherapy or a combination of modalities.

When the resection of the tumour involves the mandible or maxilla, reconstruction using vascularised bony free flaps is considered by many micro surgeons to be the gold standard as it allows dental rehabilitation and gives a better facial contour than soft tissue alone[7]. Within bony free flaps, the free fibula flap and the deep circumflex iliac artery (DCIA) flap are commonly used. Following bony reconstruction, post-operative radiotherapy is often used to prevent cancer recurrence; however, it can cause the unwanted complication of osteoradionecrosis (ORN). This complication can cause significant morbidity and has been variously reported to have an incidence of between 2% and 22% of patients who undergo post-operative radiotherapy.[8] It is classically defined as exposed irradiated bone that fails to heal after 3 months in the absence of residual or recurrent tumour and tumour necrosis[9] (Figures 1 and 2). More recently, however, it has been recognised that radiographic techniques, such as orthopantomogram (OPG) and computerised tomography (CT), can demonstrate ORN without any bone exposed through the oral mucosa or cervicofacial skin.[10] Advanced ORN may even eventuate in the need for radical resection and further free flap reconstruction.[11]

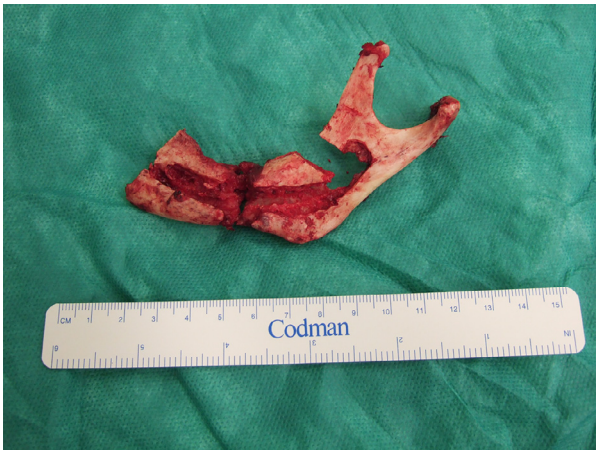

Figure 1 Clinical photo of ORN in a native mandible.

Figure 2 An orthopantomogram demonstrating ORN in a free fibula flap following mandibulectomy.

There is a paucity of literature surrounding the rates of ORN between the different bony free flaps used to reconstruct head and neck defects. While comparisons have been made between the free fibula flap and free DCIA flap in terms of success rate and advantages[7], currently there are no data to suggest either flap over the other with respect to rates of ORN, and this forms the basis for our study.

Methods

A retrospective cohort study was conducted to investigate the rates of ORN in bony free flaps in line with the STROBE guidelines. Patients were recruited from The Royal Melbourne Hospital and St Vincent's Hospital Melbourne, two major tertiary centres within a metropolitan area. Patients of The Royal Melbourne Hospital were identified through a query of the BioGRID system, and patients of St Vincent's Hospital were identified through a manual search through previous audits. Selection criteria included consecutive patients who either had free fibula or free DCIA flap reconstructions for head and neck cancers within the past 10 years from July 2007 to August 2017. Patients were followed-up closely by the plastic and reconstructive surgery departments of their respective hospitals. The diagnosis of ORN was based on a combination of history, clinical examination and radiographic techniques including OPG and CT. ORN secondary to bisphosphonate use was not included in this study. Patients were excluded if they had either flap for management of pre-existing ORN.

Demographic data collected included age at time of operation, sex, comorbidities, smoking status, alcohol use, preoperative diagnosis, staging and preoperative radiotherapy. Operative data collected included date of operation, type of free flap (fibula or DCIA) and the success of the flap. Post-operative data included post-operative radiotherapy, date of first radiotherapy, total Gray administered, ORN, re-operation, type of secondary procedure, speech assessment, dental implantation, donor site complications, death and date of death. All data were collected from electronic medical records and paper medical records in a manner that protected patient's records confidentiality. Institutional ethics approval was granted prior to collection and submission of data.

Statistical analysis was performed using Microsoft® Office Excel (Microsoft Excel for Windows, Version 1803, 2016, Microsoft Corporation, Redmond, WA, USA) and Statistical

Table 1 Patient's characteristics for free fibula and free DCIA groups. Data are in mean (SD) or number (%).

Variable	Fibula flap ($n = 127$)	DCIA flap ($n = 27$)	p-value
Age	63.4 (11.1)	57.8 (14.3)	0.03
Sex			0.94
Male	81 (64%)	17 (63%)	
Female	46 (36%)	10 (37%)	
Smoking history			0.40
Current or past	77 (61%)	14 (52%)	
Never	50 (39%)	13 (48%)	
Heavy ETOH use	67 (53%)	15 (56%)	0.79
Episode type			0.93
Primary	109 (86%)	23 (85%)	
Recurrence	18 (14%)	4 (15%)	
Histology			0.39
Squamous cell carcinoma	109 (86%)	18 (67%)	
Adenocarcinoma	4 (3%)	2 (7%)	
Melanoma	1 (1%)	2 (7%)	
Other*	13 (10%)	5 (19%)	
Pre-operative radiotherapy	10 (8%)	1 (4%)	0.45
Time to post-op radiotherapy (days)	79.4 (29.3)	71.8 (23.2)	0.31
Dose of post-op radiotherapy (Grays)	59.6 (9.4)	62.4 (7.4)	0.24

* Other histology included mucoepidermoid cyst, sarcoma, adenoid cystic carcinoma, carcinoma not otherwise specified, esthesioneuroblastoma and no residual tumour.

Package for Social Sciences (SPSS for Windows, version 25.0. 2017, SPSS Inc, Chicago, IL, USA). Differences in continuous and categorical data between the two free flap groups were compared using t-test or chi square test where appropriate, with p-values of < 0.05 being accepted as significant. Associations between variables and the outcome of ORN were analysed with binary logistic regression and odds ratios, again with p-values of < 0.05 being significant.

Results

A total of 154 patients were identified across The Royal Melbourne Hospital and St Vincent's Hospital Melbourne. Fifty patients were identified from St Vincent's and 104 from Royal Melbourne.

Overall, the two groups that underwent either free fibula flaps or free DCIA flaps were very similar (Table 1) with regards to sex ($p = 0.93$), primary or recurrent disease ($p = 0.84$), smoking history ($p = 0.40$), heavy alcohol use ($p = 0.79$), pre-operative radiotherapy ($p = 0.62$), histology ($p = 0.39$), time to post-op radiotherapy ($p = 0.46$) and dose of post-op radiotherapy ($p = 0.14$). The only significant difference found between the two groups was age, with the fibula group being older than the DCIA group ($p = 0.025$).

A total of 127 patients had free fibula flaps and 27 had free DCIA flaps. Twelve patients had ORN post-op, 10 had free fibula flaps and 2 had free DCIA flaps.

The incidence of ORN in the free fibula group was 7.9%, whereas the incidence in the free DCIA group was 7.4% (Table 2). The odds ratio for ORN in the DCIA flap compared to the fibula flap was 0.94 (95% confidence interval 0.193-4.537). A chi-square test was performed to compare the two groups, and no statistical significance was found ($p = 0.93$).

Table 2 Incidence of ORN in free fibula and DCIA groups. Data are in number (%).

Variable	Fibula flap ($n = 127$)	DCIA flap ($n = 27$)	p-value
ORN	10 (7.9%)	2 (7.4%)	0.93
No ORN	117 (92.1%)	25 (92.6%)	

Table 3 Factors affecting the development of ORN presented in odds ratios (OR), 95% confidence intervals (95% CI) and p-value.

Variable	OR	95% CI	p-value
Flap type (Fibula or DCIA)	0.78	0.11-5.56	0.81
Age	0.99	0.93-1.06	0.72
Sex	0.99	0.11-8.77	0.99
Smoking history	1.81	0.20-16.33	0.59
Heavy ETOH use	4.11	0.52-32.33	0.18
Episode type (primary or recurrent)	4.68	0.30-73.23	0.27
Time to post-op radiotherapy	0.98	0.95-1.02	0.32
Dose of post-op radiotherapy	1.31	0.99-1.74	0.06

In logistic regression analysis of the factors affecting the development of ORN, we found positive associations between smoking history ($p = 0.59$), heavy alcohol use ($p = 0.18$), episode type (primary or recurrent disease) ($p = 0.027$) and dose of post-op radiotherapy ($p = 0.06$) in the development of ORN (Table 3). These values, however,

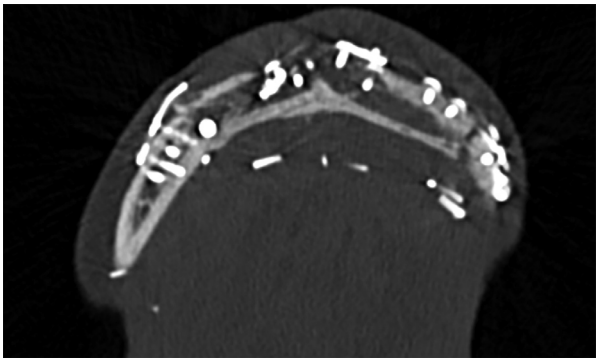

Figure 3 An axial slice from a CT scan of a patient with ORN of a free fibula flap following mandibulectomy.

are not statistically significant as their p-values are greater than 0.05, and their confidence intervals include 1.00. No statistically significant associations were demonstrated with regards to flap type ($p = 0.81$), age ($p = 0.72$), sex ($p = 0.99$) and time to post-op radiotherapy ($p = 0.32$).

With regard to other recipient site complications, three patients from the fibula group developed flap dehiscence, three patients developed orocutaneous fistulas, one patient required an unplanned return to theatre for revision of the anastomosis and one patient required a second free flap due to flap failure. Of the DCIA group, two patients developed flap dehiscence and one patient developed an orocutaneous fistula. Of the fibula group, Donor site complications for the fibula group included four patients with failed skin grafts, two patients with clawing of the great toe and one patient with significant stiffness of the ankle. Within the DCIA group, one patient had a transient femoral nerve palsy that self-resolved and one patient had a drain tube that became impacted and required surgical removal.

With regard to the patients who had free flap reconstruction for a recurrent malignancy ($n = 22$), 10 patients received radiotherapy pre-operatively (i.e. for their initial malignancy), 11 patients had post-op radiotherapy alone (i.e. for their recurrence but not their initial malignancy) and 1 patient had both pre-operative and post-operative radiotherapy (i.e. for both their initial and recurrent malignancies).

Discussion

ORN is a devastating complication that may follow radiotherapy (Figure 3). In the setting of head and neck cancer, this can cause significant morbidity, decreased quality of life and the need for further resection and reconstruction.[12] The purpose of this study was to compare the rates of ORN between two commonly used free flap reconstructions, which have not been explored in depth in the literature. Our results show no significant difference between ORN rates in free fibula flaps and DCIA flaps. Hence, ORN should not be a consideration when deciding the reconstructive technique for head and neck cancer defects.

The current pathophysiology of ORN was described by Marx et al.[13] in 1983 when they proposed the theory that radiation leads to hypoxic, hypovascular and hypocellular tissues resulting in tissue breakdown and chronic non-healing wounds. More recently, the fibroatrophic theory put forward by Dalanian and Lefaix[14] describes three distinct phases: a pre-fibrotic inflammatory phase, a constitutive fibrotic cellular phase and a matrix densification and remodelling phase. These phases result in more fragile tissue with a higher risk of late reactivated inflammation following trauma. Although the pathophysiology of ORN has been studied in the native mandible, there remains a gap in the literature regarding whether the bone and soft tissue of the free fibula and the free DCIA differ in terms of development of ORN.

Previous studies have compared the free fibula flap to the DCIA flap for mandibular reconstruction with respect to failure rates, donor site complications and recipient site complications; however, very few have explicitly assessed ORN as an outcome. Shpitzer et al.[15] and Mucke et al.[16] have previously compared free fibula flaps and DCIA flaps with regards to flap failure rates and complications with retrospective and prospective studies, respectively. Although Shpitzer et al.[15] found failure rates to be similar between both groups, Mucke et al.[16] concluded that DCIA flaps were associated with a significantly higher failure rate than free fibula flaps. These two studies, do, however, agree that DCIA flaps are associated with more complications. Shpitzer et al.[15] found a higher rate of intraoral skin flap complications and suture line breakdowns in the DCIA group while Mucke et al.[16] demonstrated a higher rate of delayed wound healing in the DCIA group. It was mentioned by Mucke et al.[16] that the rate of ORN within their cohort of free flaps was 20%; however, there was no distinction as to how these were divided among the two groups, and no comparison was made.

Lonie et al.[7], in a meta-analysis comparing free fibula flaps and DCIA flaps, also looked at flap failure and complication rates. No significant difference was found between the groups in terms of flap failure rates; however, recipient site complications, including delayed healing and suture line breakdown, were higher in the DCIA flap group. No significant difference was found between the groups in terms of donor site complications, though a trend was shown towards higher donor site complications in the fibula group. In terms of osseointegrated implants, the DCIA group was found to outperform the fibula group. Although Lonie et al.[7] do not include ORN as one of their investigated outcomes, there is a suggestion that free fibula flaps may tolerate an irradiated bed better than free DCIA flaps; however, our results show that both have similar rates of ORN, and so are likely similar in their ability to tolerate an irradiated bed.

A prospective study by Politi and Toro[17] has compared the fibula and DCIA flaps in terms of function and quality of life in the short-term and long-term. General morbidity, quality of life, function of the donor site, function of the oromandibular complex, aesthetic evaluation of the donor site and aesthetic evaluation of the face were evaluated at one month and one year. Politi and Toro[17] concluded that the DCIA flap was preferred for quality of life, mastication and aesthetics in dentate patients, and that the aesthetic appearance was better tolerated in the DCIA group, especially in women. Though some major complications were noted, including flap loss, femoral nerve palsy and clawing of the great toe, ORN was not an outcome measure.

Other studies have been conducted that compare the free fibula flap and free DCIA flap for the management of ORN. Lee et al.[18], in a systematic review, compared fibula flaps, DCIA flaps, radial forearm flaps, scapular flaps, anterolateral thigh flaps, latissimus dorsi flaps, rectus abdominis flaps, serratus anterior flaps and humerus flaps for the reconstruction of mandibular ORN. Lee et al.[18] concluded that the free fibula flap is the workhorse flap for reconstruction of mandibular defects, though evidence is limited. Chen et al.[19], however, found the free DCIA flap to be superior to the free fibula flap in the management of ORN in terms of post-operative healing and infection rates. Though our study did not examine the use of free fibula or free DCIA flaps in the management of ORN (as our primary outcome for investigation was the development of ORN), it is nevertheless worthwhile to consider the comparisons made by studies between the free fibula and free DCIA flaps for ORN reconstruction.

Limitations of this study include the following: unequal sizes of the study groups (127 patients in the free fibula group compared with 27 patients in the free DCIA group), the low number of patients with ORN (12 total), not analysing the details of the delivery of the radiotherapy, the retrospective nature of the study, the search methods for identifying eligible patients as well as potential selection bias and attrition bias.

The unequal sizes of the study groups may be attributable to the popularity of free fibula flaps as compared to free DCIA flaps in our hospitals. The free fibula flap, now considered the workhorse for mandibular reconstruction by many, benefits from its quality and length of bone, as well as its vasculature.[20] Previous studies may have also contributed to the popularity of the free fibula flap by showing the free fibula flap to have very low failure rates[21] and demonstrating that free DCIA flaps to have more donor and recipient complications.[15] This discrepancy between numbers of free fibula flaps compared with free DCIA flaps has also been seen in other studies comparing the two.[17]

The relatively small sample size and number of patients, who developed ORN, though comparable to other studies comparing the two flaps,[16] limit the statistical power of this study. The low incidence of ORN in this cohort (7.8%) does, however, correlate to reported rates.[8] Further studies and analyses may help to strengthen the conclusions of this study.

The delivery of radiotherapy was not investigated apart from the dosage and time to radiotherapy. Total dosage, the use of larger field sizes, delivery in higher doses per session and the use of a homolateral field have been implicated in the development of ORN.[22] Though our study found no significant difference in the rates of ORN between the free fibula and free DCIA flaps, we are unable to confirm or deny that the delivery methods of radiotherapy were similar between the two groups.

The search methods used to identify eligible patients was not uniform between the two hospitals and hence may have affected the results. Both The Royal Melbourne Hospital and St Vincent's Hospital Melbourne have different systems on which patient's data are stored; thus, no standardised search method could be used. For The Royal Melbourne Hospital, a query of the BioGRID system was used, and the outcomes were checked with the head and neck database records and a search through online patient records. In contrast, St Vincent's Hospital Melbourne did not have a database into which a query for bony free flaps could be entered. Hence, a manual search through previous audits was conducted. This introduces the potential for human error and selection bias.

A total of 8 patients, or 5.2% of the study cohort, were lost to follow-up as no records could be found following their reconstruction and radiotherapy, and there were no records of their death. These patients, nevertheless, had met the inclusion criteria defined by the study and hence were included in the final analysis. In this manner, selection bias due to loss to follow-up was reduced.

Strategies to reduce the incidence of ORN have been described in the literature and include the use of a multidisciplinary approach with a dentist experienced in oral cancer, pre- and post-irradiation dental evaluation, including radiographs, patient education surrounding oral hygiene, prophylactic or symptomatic extraction of teeth 2–3 weeks prior to radiotherapy, correct fitting of dentures, a review of patient medications such as bisphosphonates and systemic interventions such as hyperbaric oxygen or prophylactic antibiotics.[23, 24] Although there was no standardised guideline between our two centres for ORN prevention, these strategies were widely employed within both hospitals.

Our findings indicate that the decision of which bony flap to use should not be influenced by the potential risk of ORN and that in fact the rates are remarkably similar. Other considerations should be included in the decision-making algorithm such as quality of bone stock, length and position of defect, preservation of the temporomandibular joint, reliability of the skin paddle and complexity of the defect should guide the ultimate choice of flap.

Conclusion

The pre-operative decision of the type of reconstruction to use can be a challenging one. Many factors must be taken into consideration, such as patient factors, the type of defect needing to be reconstructed and the advantages and disadvantages of each particular reconstruction.

Our study shows that between the two most popular vascularised bony free flaps, the free fibula flap and the free DCIA flap, the incidence of ORN should not be a significant determining factor in choice of reconstruction.

Conflict of interest statement

No conflicts of interest declared.

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