Analysis of the Outcomes of Micro-Vascular Reconstruction following the Management of Head and Neck Cancer

A Thesis Presented in the University of Dublin for the Degree

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Doctor in Medicine (M.D.)

By

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Declarations

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I declare that this thesis has not been submitted as an exercise for a degree at this university and is my own work. This thesis contains the published work of others, duly acknowledged in the text wherever included.

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Declaration and Statement of Plagiarism

I declare that the work presented in this thesis is my own. The co-authored publications included are the greater part my own work. The papers, on which my thesis will be based, are published in the British Journal of Oral and Maxillofacial Surgery (BJOMS). This is one of the leading journals in the field of Maxillofacial Surgery, with an impact factor of 2.018, and Eigenfactor and Article Influence factors of 0.005 and 0.438 respectively.

The papers are based on the single common theme of reconstruction in Head and Neck Cancer. This relates to my service in St James Hospital and furthermore is a cornerstone of the research theme I am developing, namely Quality of Life (QoL), Physical Functioning, and Patient Concerns Inventory (PCI) post Head and Neck Cancer ablation and reconstruction.

- Paper 1

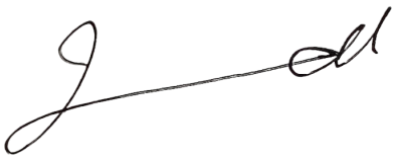
O'Connell JE, Brown JS, Rogers SN, Bekiroglu F, Schache A, Shaw RJ. Outcomes of microvascular composite reconstruction for mandibular osteoradionecrosis. Br J Oral Maxillofac Surg. 2021 Nov;59(9):1031-1035. PMID: 34531074.

I conceptualised and designed the paper. I undertook a comprehensive literature review and synthesised the evidence. RJS, SNR and I interpreted the findings in the clinical context. I prepared the first draft of the manuscript; all authors contributed to and approved the final paper.

- Paper 2

O'Connell JE, Koumoullis H, Lowe D, Rogers SN. A 31-year Review of Composite Radial Forearm Free Flaps for Head and Neck Reconstruction. Br J Oral Maxillofac Surg. 2022 Feb 18:S0266-4356(22)00064-X. PMID: 35382950.

I, along with SNR, conceptualised and designed the paper. I and HK undertook a comprehensive literature review. DL conducted the statistical analysis. I interpreted the data and prepared the first draft of the manuscript. All authors contributed to and approved the final paper.



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List of Abbreviations

ALT	Anterolateral thigh
AI	Artificial Intelligence
ASR	Age standardised ratio
CAI	Conversational Artificial Intelligence
CREST	Cancer Research Stimulus Awards
CRFFF	Composite Radial Forearm Free Flap
DCIA	Deep Circumflex Iliac artery
ELAF	Extended lateral arm flap
HNC	Head and Neck Cancer
HNSCC	Head and Neck Squamous Cell Carcinoma
HPV	Human Papilloma Virus
HRQOL	Health Related Quality of Life
LLMS	Large language models
LD	Latissimus dorsi
MSAP	Medial sural artery perforator
NLP	Natural Language Processes
OCSCC	Oral Cavity Squamous Cell Carcinoma
ORN	Osteoradionecrosis
PCI	Patient Concerns Inventory
PROMS	Patient Related Outcome Measures
RFFF	Radial forearm free flap
SCC	Squamous Cell Carcinoma
SJH	St James Hospital
TAP	Thoracodorsal artery perforator
TCGA	The Cancer Genome Atlas
TSJCI	Trinity Saint James Cancer Institute
VSP	Virtual Surgical Planning
ZIP	Zygomatic Implant Perforator

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I want to thank Professor John V Reynolds for his support and advice, not only during the supervision of this thesis, but also at earlier stages of my career. Always encouraging, but nonetheless rigorous, and with exacting standards.

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My service in St James Hospital, based primarily on the management of patients with Head and Neck Cancer, would not be possible without the support and encouragement of my consultant colleagues, especially Mr Conor Bowe who is an integral part of the Maxillofacial Cancer Service. Thank you.

It is a privilege to take care of patients burdened with Head and Neck Cancer. They are a vulnerable cohort, often in the lower socio-economic demographic of society. Notwithstanding the challenges their disease brings them, they are invariably willing to participate in research. Achieving better outcomes for patients is not possible without this. I admire their strength in adversity.

Finally, to my family. My wife, Jennifer, who is unwavering in her support and encouragement. Our boys; who give me perspective, and are the perfect anti-dote to any challenges work or life may bring. My father, John, and late mother, Nell, who emphasised the importance of education and hard work, and treating others with decency.

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Chapter 1: Introduction

1.1. Background

The oral cavity extends from the mucosal surface of the lips to the junction of the hard and soft palate. It does not include the soft palate, uvula, or tonsils, which form part of the oropharynx. Oral cavity cancer is the eighth most common cancer worldwide, with an estimated 350 000 cases arising annually. While there have been significant advances in the understanding and management of oral cavity cancer, the morbidity and prognosis associated with it have remained largely unchanged. The vast majority of Oral Cavity and indeed all Head and Neck malignancies, are squamous cell carcinomas (SCCs). In 2015, the estimated age-standardised ratio (ASR) of oral cavity cancer was 5.8 in men and 2.3 in women per 100 000. This 2:1 ratio has narrowed recently but still probably reflects the higher consumption of alcohol and tobacco by men worldwide. The incidence of oral cancer increases with age, with most cases occurring in those over 50 years. The mean age at presentation is 62 years, with a strong correlation between lower socioeconomic class and disease incidence. However, there is an increasing trend for cases affecting younger patients (45 years or younger), many of whom lack exposure to traditional risk factors. The 5-year survival rate for early-stage cancers is 80%. Despite recent advances, the overall 5-year survival for oral cancer has not markedly improved and remains at 50%.

Tobacco, alcohol, and betel quid (areca nut, catechu, slaked lime wrapped in a piper betel leaf) are long-established risk factors for oral cavity squamous cell carcinoma (OCSCC). There is a dose–response relationship between the use of tobacco, alcohol and betel quid and the development of oral cancer.

Transcriptionally active human papillomavirus (HPV) accounts for only a small percentage (approximately 5%) of OCSCCs, which is in stark contrast to oropharyngeal squamous cell cancers (OPSCCs), where 50–70% are caused by HPV. Although HPV-positive SCC has prognostic significance in the oropharynx, this survival advantage does not appear to be conferred within the oral cavity.

According to The Cancer Genome Atlas (TCGA), alterations in *p53* (83%) and *CDKN2A* (57%) are the two most frequent genomic mutations noted in HPV-negative cancers of the head and neck (of which oral cancer is an example). This contrasts with HPV-positive tumours, found most frequently in the oropharynx, which have a considerably lower mutational burden and consistently retain *p53* ‘wild-type’ status. It is, however, important to note that, as yet the current standard of care in head and neck squamous cell carcinoma (HNSCC), including oral

cavity cancers, is not based on or influenced by genetic profiling or molecular biology.

Surgery, with adjuvant radiotherapy (or chemoradiotherapy) if indicated, remains the mainstay for management of oral cavity cancer. While the desire to achieve surgical cure has remained the highest priority, the emphasis of surgery has "de-escalated" from being radical toward more function-sparing approaches that confer greater importance to reconstruction and rehabilitation. Reconstruction of post-ablative defects with an associated improvement in quality of life is a cornerstone of the surgical management of oral cavity cancer. This evolution in surgical management has been influenced by an improved understanding of tumour biology, more accurate staging investigations and microvascular free tissue transfer reconstruction. Overall and disease-specific survival, in patients with surgically resectable disease, is largely dictated by tumour biology, with features such as nodal metastases with (extra-nodal extension) ENE of greatest importance.

1.2 Reconstruction of Ablative Defects

Reconstruction following tumour ablation is a key component in the management of OCSCC. Decision making with regards to reconstruction should not influence the ablative procedure. Notwithstanding the importance of facial aesthetics, preservation or restoration of speech, chewing, swallow and oral continence are of paramount importance. The oral cavity is a unique site. It contains hard and soft tissues, including the dentition, is bathed in saliva and is anatomically complex. It is the opening to the aerodigestive tract and has a multitude of motor and sensory nerves. Like any defect, reconstruction of the oral cavity should aim to replace resected tissue with similar tissue.

A free flap is a portion of vascularized tissue harvested from a distant donor site and transferred to an area requiring reconstruction where its artery and vein are anastomosed locally, thereby providing an independent blood supply. The advent of microvascular free tissue transfer has revolutionized the management of head and neck malignancy. The ablative surgeon, safe in the knowledge that most defects can now be reconstructed satisfactorily, can resect with sufficient margins, thus increasing the chances of tumour clearance.

The variety and versatility of available flaps allows reconstruction of even the most complex defects. Most tissue types, including skin, fascia, muscle, tendon, and bone, can be harvested.

The choice of donor site is wide but is influenced by, among other things, the type and shape of tissue that needs to be replaced. Advantages of free flaps include flexible reconstruction that contains soft and osseous tissue tailored to ablative defect, independent blood supply, proven reliability, and robust tissue. Disadvantages include complex technique requiring specific training and experience, increased length of surgery, and need for more rigorous postoperative monitoring.

In oral cavity reconstruction, common soft-tissue flaps used include the radial forearm free flap (RFFF) and anterolateral thigh (ALT) flap. Alternative soft-tissue free flaps include rectus abdominis, latissimus dorsi, medial sural artery perforator and lateral arm flaps. The relative merits of these flaps are outlined in ***Table 1.1***.

The fibula is the most commonly used bone-containing (composite) flap globally, while the iliac crest (DCIA), scapula (including tip of scapula) and composite radial forearm flaps are also used, each carrying specific pros and cons. Chimeric flaps, where osseous and soft-tissue components are independently mobile (e.g., the thoracodorsal system of free flaps), are advocated for certain complex reconstructions. The relative merits of the more common composite flap donor sites are outlined in ***Table 1.2***.

Table 1.1: Relative Merits of common soft tissue free flaps.

Donor site	RFFF	ALT	MSAP	TDAP	Lateral arm	Rectus	LD
Donor site morbidity	+++	++	++	++	++	+++	++
Pedicle length	++++ 18 cm	+++ 12 cm	++ 10 cm	++++ 15 cm	+ 6 cm; increased with ELAF	+ 7 cm	++ 8.5 cm
Quality of vessels	++++	+++	+++	++++	++	++++	++++
Diameter	Artery: 3 mm Vein: 1.5 (3 mm if cephalic) No atherosclerosis	Artery: 2.1 mm Vein: 2.3 mm	Artery: 1.25 mm Vein: 2 mm	Artery: 2.7 mm Vein: 3.4 mm No atherosclerosis	Artery: 1.5 mm Vein: 2.5 mm	Artery: 3.5 mm Vein: 4 mm	Artery: 2.7 mm Vein: 3.4 mm No atherosclerosis
Soft-tissue paddle	++ 12 × 5 cm	++++ 16 × 8 cm	++ 10 × 5 cm	++++ 25 × 10 cm	++ 12 × 5 cm	+++ Muscle: 6 × 25 cm Skin: 13 × 25 cm	++++ Muscle: 35 × 20 cm Skin: 18 × 7 cm
Two-team operating	+++	++++	++++	+	++	+++	+

ALT, anterolateral thigh; ELAF, extended lateral arm flap; LD, latissimus dorsi; MSAP, medial sural artery perforator; RFFF, radial forearm free flap; TDAP, thoracodorsal artery perforator.

Table 1.2. Relative merits of composite flap donor sites.

Donor Site	Fibula	DCIA	Scapula	Thoracodorsal/tip of scapula	Composite RFFF
Donor site morbidity	++	+++	+++	+++	+
Pedicle length	+++	+	+	+++	++++
Quality of vessels	+++/+ (may be affected by atherosclerosis)	++ (potentially small diameter)	++++ (large, spared from atherosclerosis)	++++ (large, spared from atherosclerosis)	+++ (spared from atherosclerosis)
Volume of bone	++	++++	+++	++	+
Length of bone	++++ (14 cm)	+++ (12 cm)	++ (10 cm)	++ (6 cm)	+++ (12 cm)
Suitability for implants	+++	++++	+++	+	Not suitable
Soft-tissue paddle	+++ (Occasionally unreliable)	+ (internal oblique or DCIA perforator)	++++ (two soft-tissue flaps and/or chimera with LD or TAP)	++++ (allows chimeric flap with two independently mobile skin paddles with/without LD muscle)	+++ (reliable skin flap, but lacks bulk)
Two-team operating	++++	+++	+	+	+++

DCIA, deep circumflex iliac artery; LD, latissimus dorsi; RFFF, radial forearm free flap; TAP, thoracodorsal artery perforator.

1.3. **Reconstruction by Anatomical Sub-site**

1.3.1 Soft-tissue reconstruction

Intraorally this includes the tongue, floor of the mouth, buccal and retromolar mucosa as well as the soft palate. As outlined previously the most used soft-tissue flaps are the RFFF and ALT. The RFFF provides a thin, non-hirsute and pliable flap with a long vascular pedicle and so can be useful where significant bulk is not required. The ALT, however, owing to its increased bulk, is far more suited to tongue reconstruction where bulkiness is crucial in creating a seal between the oral cavity and soft palate during speech and swallowing. The ALT also facilitates multiple skin paddles and/or muscle components, where necessary.

1.3.2 Mandible reconstruction

Reconstruction with composite free flaps is now the gold standard for segmental mandibular defects. The choice of flap is varied and depends on factors including the site, size and complexity of the defect, patient comorbidities and indeed surgeon training and preference. While it is possible to leave small posterior sites unreconstructed, reconstruction of an anterior defect is particularly important, and challenging, to achieve satisfactory function for the patient.

In a systematic review reporting a total of 9499 cases of mandibular reconstruction with vascularised bone flaps over a 25-year period, 12% were composite radial forearm free flaps (CRFFF)[1]. The potential disadvantages of the CRFFF relate mainly to donor site morbidity, especially radius fracture, and the limited bone stock available. Radial fracture rates have been reported in the regions of 0% and 18%[2, 3, 4]. Fracture confers considerable morbidity in respect to delayed healing, joint stiffness, and osteoporosis owing to prolonged immobilisation[5]. In cases where fracture does not occur the morbidity of harvest is similar to the soft tissue radial[6, 4]. Modifications on the earliest harvesting techniques such as limiting the harvest to 40% of the radial radius[7,8,9,10,11,12] use of a keel shaped osteotomy to reduce points of stress, and prophylactic plating along with arm casting have led to a reported reduction in the incidence of fracture rates.

The CRFFF has limited bone stock compared to the fibula, DCIA, and scapula, however despite this, the flap has been described in management of mandibular osteoradionecrosis (ORN)[13],

and reconstruction of small volume maxillary[14, 15], lateral mandibular segmental defects[16], and to augment the zygomatic implants perforator flap (ZIP flap)[17].

Although there are previous articles reporting series of CRFFF [4, 5, 9, 17, 18, 19, 20] , the majority report relatively small numbers, typical between 4 and 86, with two studies reporting 155[16] and 167[10] cases respectively. The previous literature has tended to lack long-term follow up or in the information provided for the plating and casting management. Very few studies report on recipient vessels used in the neck.

1.3.3 Maxillary reconstruction

The main aims of maxillary reconstruction are to restore facial contours and aesthetics; separate sino-nasal cavities from the mouth; restore soft palate competence to facilitate speech and swallowing; and, finally, restore/provide for replacement of dentition.

A classification system for maxillary defects is useful for both treatment planning and discussion with colleagues. The most widely adopted classification is that proposed by Brown and Shaw[21] (**figure. 1**); this classification considers both the vertical and horizontal extent of the defect. Classes I–VI describe the increasing size in a vertical dimension, while the horizontal extent is described by the letters a–c. Although not absolute, one of the advantages of this classification system is that it implies management.

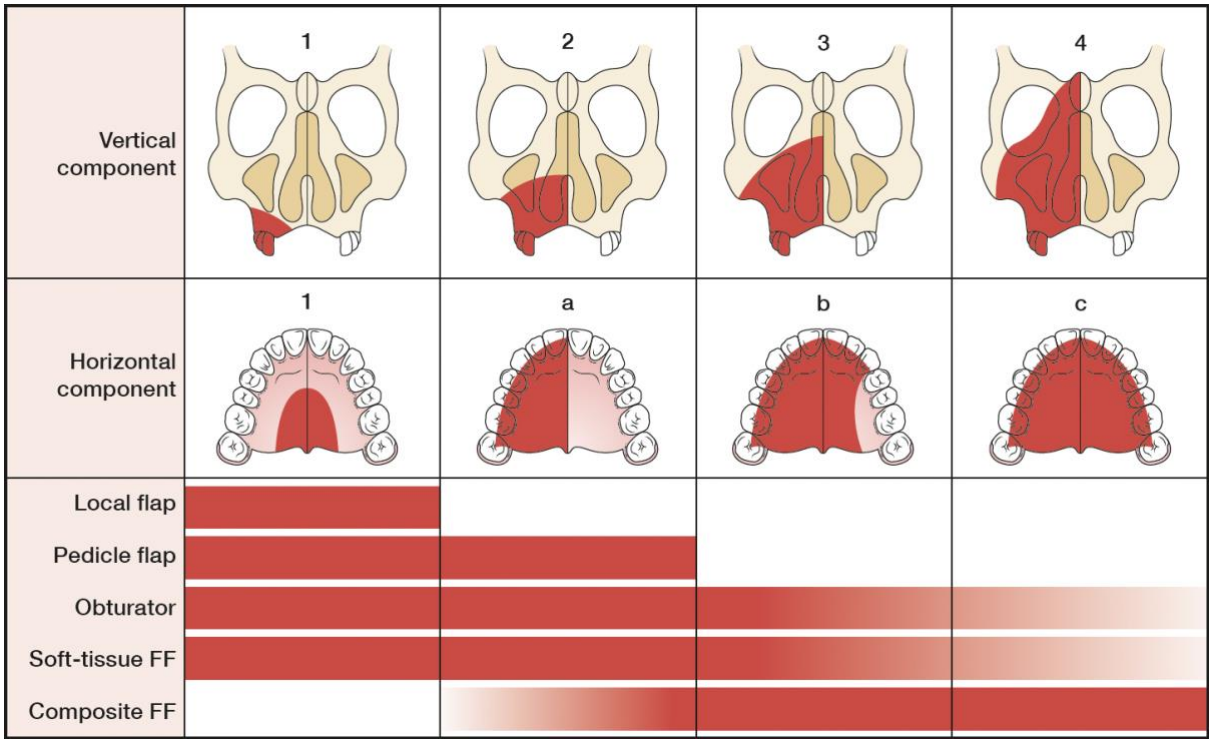


Figure 1. Maxillectomy defect classification and proposed reconstructions. Note that an updated version was published in 2010, but this diagram provides a useful visual representation of proposed reconstruction according to the class of defect. *Brown JS, Rogers SN, McNally DN, Boyle M. A modified classification for the maxillectomy defect. Head Neck 2000; 22(1): 17–26.*

Class I defects are easy to repair with the only reconstructive requirement being to separate the oral and nasal/antral cavities. Local flaps are often satisfactory, and the RFFF is the most commonly used free flap. Class II defects can be restored in a similar fashion to class I, especially when more posteriorly located. However, composite (bone-containing) free flaps are usually required for anterior defects, and class IIc defects, as well as situations where the existing dentition is not adequate to retain a prosthesis.

In classes III and IV, support for the contents of the orbit is lost, as well as support for the anterior cheek and alveolus. A prosthesis alone will provide a suboptimal result. The reconstructive goals are to support the orbital contents and facial skin, ensure bony continuity between the remaining alveolus and zygomatic buttress (ideally sufficient to facilitate endo-osseous implant placement), as well seal the oral and nasal cavities. Therefore, a composite free flap (e.g., the thoracodorsal free flap) is suitable for fulfilling these requirements.

Evolution in zygomatic implant technology can support prosthetic rehabilitation and restoration of low-level maxillectomy defects in combination with soft-tissue flaps. In select cases, this can remove the necessity for composite free flaps.

1.4. Zygomatic Implants and Zygomatic Implant Perforator (ZIP) Flaps, and Virtual Surgical Planning (VSP)

Zygomatic as well as oncological or co-axis implants, used in conjunction with a fixed or removable prosthesis, or indeed with a free flap, have improved our ability to quickly restore dentition post maxillectomy. Recently, the use of zygomatic implants that perforate a soft-tissue free flap (used to close an oroantral/oronasal communication) and placed immediately after tumour ablation has been described. In 2022, the Maxillofacial/Head and Neck team at St James hospital performed the first ZIP flaps performed in the Republic of Ireland[22].

The use of virtual surgical planning (VSP) in oral cavity reconstruction is increasing. Benefits include reduced operating time, greater accuracy and improved aesthetic/functional outcomes.

Patient-specific surgical stents and cutting guides for both the tumour and donor sites are made preoperatively, based on CT scans and software. The surgeon performs the surgery virtually; based on the resection and therefore the size and shape of reconstruction required, cutting guides are provided for both the oral resection and donor site harvesting.

Chapter 2 : Outcomes of Microvascular Composite Reconstruction for Mandibular Osteoradionecrosis

2.1. Definition, and Scale of the problem

Osteoradionecrosis (ORN) is exposed necrotic bone after radiotherapy in the absence of neoplasia. Affected patients suffer from malnutrition, opiate dependency, haemorrhage, infection, disfigurement, and reduced quality of life[23].

The reported incidence of ORN ranges from 2 to 22% (which may reflect the lack of consistency among definitions and classifications), with a steady decrease in more recent published series, which converge on a rate of 6-8% [24, 25, 26, 27, 28]. This decrease may be related to advances in radiotherapy (RT) techniques, in particular Intensity-Modulated Radiation Therapy (IMRT), and the recognition and mitigation of risk factors. However, the incidence of head and neck cancer [29, 30] is increasing, as is survival and use of radiotherapy. Therefore, the at-risk population is increasing. In 2019, the UK National Flap Registry Report showed that of the 1485 free flaps used in Head and Neck (H&N) Reconstructions between 2016-19, 6% were for radiotherapy induced defects. Additionally, vessel depleted necks (common in an ORN setting) accounted for 7-10% of all H&N defects.

Since it was first described in 1926 by Ewing as 'radiation osteitis'[31], a number of definitions and classification systems, as well as theories on pathophysiology, have been proposed.

There is no clear consensus on the need for clinical and/or radiological or indeed, histological examination[32, 33]. However, what is common to all definitions is the presence of devitalised or necrotic bone in irradiated tissue, in the absence of neoplasia[34].

Other variables that differ between definitions include duration of the lesion, extent of soft and/or hard tissue involvement, and the presence or absence of symptoms[35, 36, 37]. While dental extractions are often the precipitant, ORN can occur without trauma. Using existing definitions, a break in the mucosa of any size is required to diagnose ORN. However, it can present radiologically in the absence of ulceration[38], and this phenomenon is accounted for in the definition suggested by Store and Bysen[39].

Other classifications systems include those based on the response to hyperbaric oxygen and subsequent need for surgery, the amount and/or location (most commonly in relation to the inferior alveolar nerve) of bony involvement, and distinguishing between hard and soft tissue involvement[40].

Shaw et al[41], in a prelude to and as part of the protocol for the HOPON trial[42], sought to refine and objectify the definition of ORN. Most prior classifications were developed in order to aid clinical management of ORN as opposed to objectively measuring a specific trial end-point.

They performed a systematic review of both definition and classification of ORN, and where definition is concerned found that most were based on 3 published versions;
Harris[43] defined mandibular ORN as ‘‘exposed irradiated bone that fails to heal over a period of 3 months in the absence of local tumour”, while Marx[15] described it as ‘‘an area greater than 1cm of exposed bone in a field of radiation that has failed to show any evidence of healing for at least 6 months”. Store and Boysen[17] include radiological change without exposed bone, something that is specifically excluded by Harris & Marx.
Given that there are multiple published definitions of ORN, it is therefore not surprising that there is more than one classification system. Most were developed based on institutional retrospective reviews, and some on response to a prior treatment. The classification described by Notani et al[44] is simple, easy to use, and widely adopted. It does not refer to response to previous treatments, nor is it based on progression or improvement of the condition. In stage I ORN is confined to alveolar bone, stage II ORN is limited to the alveolar bone and/or above the level of the inferior alveolar canal and stage III ORN is under the lower part of the inferior alveolar canal, with fistula or bone fracture.

2.2 Risk Factors

Risk factors for the development of ORN include tumour related factors such as size, location, and bony invasion; patient/systemic factors including immunodeficiency, peripheral vascular disease, malnutrition, and alcohol and tobacco use[4, 45,46]; and treatment factors such as RT technique including total dose, and area of mandible irradiated[47]. In addition, dental extraction(s) pre- and post-radiotherapy is a risk factor. Interestingly, pre-RT extraction has been reported as an independent risk factor[26], and moreover, prophylactic extractions did not reduce the risk regardless of the condition of the patients’ teeth[48,49]. There is a three-fold increased risk for ORN in dentate versus edentulous patients[50].
In one large retrospective review[51], the median time to the development of ORN from the end of RT was 0.9 years (range, 0.2-8.2 years). The actuarial rate of ORN of the mandible was

3% at 1 year, 5% at 3 years, and 7% at 5 years. To investigate additional variables that may contribute to the development of ORN, the authors performed a detailed analysis of matched cohorts of patients with ORN versus controls without ORN. The presence of cardiovascular comorbidities, the use of bisphosphonates, and pre-RT dental extractions each were found to have statistically significant associations with ORN. Additionally, those receiving a neck dissection were at increased risk. In keeping with aforementioned studies, patients with ORN were found to have a higher rate of pre-RT dental extractions compared with the cohort without ORN. It should however be considered that the need for pre-radiotherapy dental extraction could be viewed as a surrogate for worse dental hygiene, smoking, and comorbidities, which may predispose these patients toward a higher risk of ORN from inadequate healing.

The generation of acute mucosal wounds also can be increased by concomitant chemotherapy and altered fractionation, although these variables were not found to significantly contribute to the incidence of ORN.

There is some evidence supporting a genetic basis for ORN, with a variant allele within the TGF- β1 gene associated with this phenotype[52]. Brooker at al[53] sought to identify a panel of common genetic variants which can predict ORN. They identified single nuclear polymorphisms associated with ORN. This may, in-time, help with the formation of patient specific radiotherapy protocols.

Radiotherapy related risk factors are well described. A total mandibular dose of greater than 60Gy is associated with the development of ORN. A reduction in the prevalence of ORN could be attributed to the refinements in radiotherapy techniques from conventional two-dimensional (2-D) RT to three-dimensional (3-D) conformal RT, and to the current use of IMRT[12]. When comparing 3-D conformal RT to IMRT, Tsai et al demonstrated a reduction in ORN from 13% to 6%[4].

2.3 Pathophysiology

The pathophysiology of ORN remains unclear. Early theories suggested that it was a manifestation of osteomyelitis due to radiation-induced devitalisiation, and subsequent infection, of the bone[54, 55, 56]. Watson and Scarborough in 1938 identified three crucial factors in the development of ORN, namely radiation, trauma, and infection[57]. The inability to easily identify micro-organisms using conventional techniques in bone affected by ORN undermined this theory; however Støre and colleagues[58], using DNA-DNA hybridization, detected a multitude of bacterial species, most of them anaerobic. Porphyromonas gingivalis was the most predominant organism, followed by Fusobacterium nucleatum subspecies polymorphum. All samples contained Actinomyces, Prevotella and F. nucleatum. The authors concluded that bacteria, particularly anaerobes, are not merely surface contaminants and in fact may play a greater pathophysiological role than previously thought. That same group, in a subsequent study[59], demonstrated bacteria in osteoradionecrotic bone using scanning and transmission electron microscopy.

Marx subsequently challenged the sequence of radiation, trauma, and infection and instead proposed the Hypoxia, Hypocellular and Hypovascular theory[15], which formed the basis for hyperbaric oxygen therapy. His theory was based on the clinical data from 26 consecutive cases of ORN from which 12 en-bloc resection specimens were cultured and stained for micro-organisms. This, of course, was before the advent of the routine use of DNA hybridization. Marx, nonetheless, went on to state that microorganisms play only a contaminant role in osteoradionecrosis and that trauma is only one mechanism of tissue breakdown leading to the condition. He proffered the Hypoxia, Hypocellular, and Hypovascular theory as an alternative and that it lead to reduced healing capacity and remodelling potential, resulting in the formation of a chronic non-healing wound.

However, the presence of tissue hypoxia in post-irradiated tissue has yet to be demonstrated. Delanian and Lefaix[60] proposed the fibroatrophic theory, where fibroblast activation and dysregulation results, ultimately, in the replacement of hard and soft tissue with a fibrous matrix with reduced cellularity and vascularity. They hypothesized that this may occur in 3 phases namely ‘pre-fibrosis’ which is essentially chronic inflammation, followed by an ‘organised’ phase of fibrosis, and finally a ‘fibro-atrophic’ phase in which there is gradual loss of bone marrow cells. The authors suggested that there may be two pathways to this

radiation-induced fibrosis. The first pathway is one of gradual hypoxia, not unlike Marx's theory. The second pathway is the stromal theory, which suggests that radiotherapy increases reactive oxygen species in the bone, which then dysregulate fibroblasts and induce metaplasia to myofibroblasts. This theory has formed the basis for the use of anti-oxidants and anti-fibrosis medications[61, 62].

2.4 Treatment

2.4.1 Non-Surgical

While there are ongoing and completed prospective randomised multi-centre clinical trials looking at strategies for the management of ORN, there is currently no established standard of care.

Conservative management for asymptomatic patients (*Notani Stage I disease)* is widely adopted. Sequestrectomy, with closure of adjacent mucosa, is also advocated.

The use of hyperbaric oxygen (HBO) in the management of ORN, as proposed by Marx, was based on its neovascularization potential[15]. He developed a treatment protocol, the Wolford Hall HBO protocol, in which patients underwent 30 dives of 100% oxygen at 2.4 atmospheres for 90 minutes. This was followed by sequestrectomy or debridement for stage II, or resection for stage III ORN cases, followed by a further 30 dives. Resection with reconstruction was reserved for refractory patients. Marx described good results; however similar results have not been replicated by other authors. One study demonstrated worse results after reconstruction in ORN patients who have had previous HBO compared to those who have not[63]. However, this should be interpreted with caution as only 3 of 30 included patients received perioperative HBO. Another similarly looked at free flap reconstruction for management of ORN and reported no significant differences in complication rates between 2 patient cohorts, one of whom had received pre-operative HBO[64]. The authors did however state that there was increased infections in the patients with a history of HBO therapy.

It should also be noted that HBO is not without its own potential complications[65.] and many side effects have been described, mainly caused by barotrauma (e.g., hearing loss, visual changes, and seizures).

The use of hyperbaric oxygen therapy (HBOT), in order to stimulate neo-angiogenesis, fibroblast proliferation, and collagen synthesis in order to prevent or treat ORN has been the subject of large randomised trials. The HOPON trial[6] examined the benefit of HBO in the prevention of ORN after high-risk surgical procedures in the irradiated mandible. It randomised patients into a 1:1 ratio, with half receiving HBO, and the primary outcome measure was ORN at 6 months. The incidence of ORN at 6 months was 6.4% and 5.7% for the HBO and control groups, respectively. The trial investigators ultimately concluded that the low incidence of ORN makes recommending HBO for dental extractions or implant placement in the irradiated mandible unnecessary. Their findings and indeed recommendation were in contrast to a recently published Cochrane review[66] and previous trials reporting rates of ORN (non-HBO) of 14% to 30% and challenge a long-established standard of care.

More recently[67], investigators combined data from the two randomized clinical trials DAHANCA-21 and NWHHT2009-1, and concluded that HBO did not significantly improve the healing outcome of ORN after surgical removal of necrotic bone as compared to standard care (70% vs. 51%).

The work of Delanian and Lefaix has led to the use of Tocopherol and Pentoxyphylline, along with the bisphosphonate Clodronate, as medical management of ORN. In addition, others have suggested the use of an antimicrobial at the outset of medical therapy, in order to reduce super-imposed infection. These strategies are, however, not based on prospective randomised trials.

Pentoxifylline (a vasoactive xanthine derivative) was suggested to improve blood viscosity and flow, thereby improving the vascularity of affected tissues. Tocopherol (a vitamin E analogue) is an antioxidant and was thought to scavenge reactive oxygen species. Finally, clodronate, a first-generation non-nitrogenous bisphosphonate, was added in non-responsive cases and to promote osteoblast differentiation and osteogenesis. The benefits of PENTOCLO were first described in a case of sternal ORN in a female patient who had previously under-gone radiotherapy for breast cancer[68].

In a trial by Delanian et al, all patients had failed conservative therapies such as antibiotics, HBO, and/or sequestrectomy[69]. Ten patients received a daily combination of 800 mg of pentoxifylline and 1000 IU of vitamin E for at least 6 months and then for as long as clinical regression was observed. An additional eight patients received the above combination of

pentoxifylline and vitamin E, along with 1600 mg of clodronate daily, 5 days a week, after the group noted success in the treatment of ORN of the sternum with this combination. Treatment was again administered for at least 6 months, until mucosal coverage was obtained. Sixteen of the 18 patients recovered completely, and of these, 14 experienced rapid complete recovery.

The efficacy of combined pentoxifylline-tocopherol treatment in superficial radiation induced fibrosis was confirmed by the same group in a randomised clinical trial, and then in successful phase II trials especially in uterine fibroatrophy and osteoradionecrosis[70].

A UK based group retrospectively reviewed the outcomes of patients with ORN who were prescribed Pentoxyphylline and Tocopherol, without clodronate[71]. They could not replicate the results reported by Delanian and colleagues.

While the use of Pentoxyphylline and Tocopherol, in the setting of ORN, was initially described of the management of early stage ORN, its successful use in more advanced cases is reported[37]. Breik et al[72] in 2019, described successful cases of bony union after the use of pentoxifylline and tocopherol to manage Notani grade III ORN of the mandible. Both patients had pathological fractures with orocutaneous fistulas and were deemed unsuitable for surgery. Delanian and colleagues[73] described six patients, among a larger cohort, who had pathological fractures, and five showed an improvement in staging, with resolution of the pathological fracture.

A recent systematic review and meta-analysis[74], looked at the use of pentoxifylline and tocopherol in the management of ORN. A total of 211 patients were included in the review. Of these, 126 patients (60%) recovered fully or improved significantly enough with the use of the combination of tocopherol and pentoxifylline (with or without clodronate), to not require further surgical or medical intervention. Most of these patients had already failed other therapies such as antibiotics, HBO, or surgical debridement. ORN remained the same for 60 patients, with disease progression in 15 patients, all requiring surgical intervention.

In the context of this present study, where we are looking at the management of advanced stage ORN and more specifically the surgical management of same, it is interesting to note that in those included studies which reported on advanced ORN[75, 76, 77, 78], the majority favoured resection with free flap reconstruction in advanced ORN with pathological fracture. The authors of this systematic review ultimately concluded that their results suggest that there is a role for the medical management of ORN, as evidenced by disease resolution and

or cessation of progression with clinical symptom improvement for all stages of ORN. They further concluded that the recommended dose regimen would be that initially described by Delanian et al., which includes 800 mg of pentoxifylline and 1000 IU of vitamin E daily for at least 6 months and then for as long as regression is observed. They do, however, state that owing to a lack of consistent reporting and indeed nomenclature used across reports and studies, a well-designed prospective study is required to better delineate the role for medical management, including PENTOCLO, in the management of ORN.

To date, there has been no randomized trials, or trials making a comparison of PENTOCLO against control treatments. To that end, the Liverpool Clinical Trials centre is currently recruiting to the NIHR funded (Award ID: 131050) Randomised Controlled Trial of PENTOCLO in Mandibular Osteoradionecrosis (RAPTOR). It is an unblinded randomised controlled trial where patients in the control arm receive standard supportive care dependent on symptoms including antibiotics, analgesia and antiseptic mouthwash. In the treatment arm, patients additionally receive PENTOCLO. The aim of this trial is to establish the value of the PENTOCLO in treating osteoradionecrosis of the mandible. The target population is patients who have previously been cured of head and neck cancer that have received radiotherapy and who have osteoradionecrosis of the mandible. Approximately 15 research sites are to be opened to recruitment, with the target recruitment number of 120 patients.

The potential therapeutic role for mesenchymal stem cell (MSC) derived exosomes in the management of ORN has recently been explored[79]. Exosomes are extra-cellular membrane-bound phospholipid vesicles with a cup-shaped structure derived by all eukaryotic cells. They can potentiate angiogenesis, immunomodulation, bone regeneration, and ferroptosis regulation[80].

Ferroptosis is an iron-dependent form of nonapoptotic cell death, providing a new possible theory for ORN[81,82]. During radiotherapy, ionizing radiation generates reactive oxygen species (ROS) and induces the expression of long-chain acyl-CoA synthetases 4 (a lipid metabolism enzyme), which leads to lipid peroxidation and ferroptosis[83]. If ferroptosis occurs in the osteoblasts, osteoporosis will and osteonecrosis may occur[84].

Another group investigated the preventive effects of tonsil-derived mesenchymal stem cells on osteoradionecrosis, albeit in a rat model, and found that these MSCs can be effective for bone regeneration in ORN, particularly when applied immediately after dentoalveolar trauma or surgery[85]. Jin and colleagues[86] investigated the effect of rat mesenchymal stem cells (rMSCs) and bone morphogenetic protein-2 (BMP-2) on the osseous healing of osteoradionecrosis in the rat mandible and found that healing after post-irradiation trauma in rats was enhanced immediately after dentoalveolar trauma by application of BMP-2, whereas the combined application of rMSCs and BMP-2 was most effective after osteoradionecrosis occurred.

2.4.2 Surgical

Notwithstanding the importance of the above conservative measures, as well as preventative strategies such as meticulous oral hygiene and more contemporary RT techniques, surgical resection with free flap reconstruction remains the mainstay for advanced ORN (*Notani Stage III*), in particular where pathological fracture, with or without an extra-oral fistula, as well as symptoms (such as intractable pain) unresponsive to conservative measure have occurred.

2.4.2 (a) Early Stage ORN: Surgical Intervention and Periosteal Flaps

However, there is no clear consensus on the role for surgical intervention in Notani stages I and II (i.e. without pathological fracture and/or exposed bone above the level of the inferior alveolar nerve where the mandible is involved); and indeed those refractory to conservative management. The potential for ORN progression to a more advanced stage, requiring more complex surgery with an associated increased morbidity and risk, has led to some groups advocating for surgery at an earlier stage. Beauvillain de Montreuil et al were one of the earliest groups to advocate for early surgical intervention[87]. They recommended the use of periosteal free flaps, thereby bringing bony growth factors and progenitor cells that could trigger increased osteogenic[88] and neoangiogenic responses[89] to the ORN process.

The osteogenic properties of periosteal flaps were first described over 40 years ago[90], in both healthy and irradiated bone[91]. Masquelet[92] described the successful use of the free osteoperiosteal medial femoral condyle flap in the treatment of post-traumatic or infectious limb pseudo-osteoarthritis.

Beauvillain de Montreuil et al[87] hoped to stop ORN progression by providing periosteal bone vascular supplementation thereby reducing the risk for progression to a situation where the bone fractures; a situation likely requiring composite free flap reconstruction. The authors hypothesised that the placement of healthy vascularised tissue without irradiated cells is a biological response (counterbalance) to the hypoxia, hypocellularity, and hypovascularisation of ORN. Furthermore, they highlight the advantages of providing a reconstruction which does not require the use of metallic osteosynthesis materials (essentially plates and screws), which in an irradiated field may cause local complications in up to 50% of patients, some requiring further surgery.

In 2009, D'Hauthuille et al[93] reported eight patients with ORN treated by periosteal free flaps that healed completely, including two with secondary radiological evidence for osteoconduction, and one histological proof of the osteoconductive capacity of the periosteal free flap. This highlighted the potential for periosteal free flaps in the management of ORN. In 2019, Bettoni et al[94] reported on the management of Notani I-II with 13 periosteal flaps in 11 patients. They used inner femoral condylar periosteum in four patients, iliac crest in one, external brachial with humeral periosteum in one, and radial forearm with radial periosteum in seven patients. Their surgical protocol involved resection (as opposed to simple curettage/debridement) of the area affected by ORN until apparently healthy and bleeding bone was encountered. They then harvested the periosteal free flap and performed a micro-vascular anastomosis in standard fashion, based on the available neck vessels. With a mean follow-up range of 83-months, only one patient developed further/progressive ORN. Furthermore, the authors provided dental rehabilitation for all patients six months postoperatively in the absence of recurrence or progression of ORN. Interestingly, three of these patients had dental implants inserted without development of any new ORN. The authors have, over time, favoured use of the radial periosteal flap as opposed to the iliac crest or internal femoral condyle, as it has a relatively long vascular pedicle which is often required given that, by definition, these patients have an irradiated neck (and possible previous neck dissection) which potentially obligates the use of vessels remote from the site of resection, for example the contra-lateral neck. However, the authors do also highlight that all cases of osteoconduction occurred only when the internal femoral condyle flap was used for reconstruction.

Prevost et al[95], expanded further on the use of periosteal flaps and reported on their use in more advanced (Notani III) ORN cases. They describe in detail 10 cases of advanced ORN, all of whom had either a pathological fracture or ORN below the level of the inferior alveolar nerve, managed with a free periosteal medial femoral flap.

The authors defined a primary endpoint of 'success' as the presence of osteogenesis (bone callus formation) and bone stability at postoperative follow-up, in addition to no further surgery. By this strict definition, 50% of patients had a successful outcome. They reported 3 absolute failures, i.e., requiring removal of the flap (2 for vascular/anastamotic reasons, and another because of infection requiring flap removal). Of note, 3 additional patients required another procedure, namely hardware removal. Another patient underwent post-operative hyperbaric oxygen treatment for the management of skin necrosis. However, of the seven patients presenting re-operatively with a pathological fracture, four successes (bone union/consolidation) and two partial successes were recorded, thus avoiding a potential segmental mandibulectomy. Ultimately, the authors conclude that periosteal flap surgery (using a medial femoral condyle flap) with debridement can be considered as an alternative to segmental resection with composite flap reconstruction, in cases of advanced ORN including those with a pathological fracture.

Gigliotti et al in 2021[96], sought to evaluate if mandibular debridement and coverage with a fascio-cutaneous free flap (Radial Forearm), without harvest of periosteum, via minimal access incisions would result in ORN resolution and symptom amelioration in patients with intermediate stage (Notani II) ORN. The authors hypothesized that in patients with progressive treatment-resistant ORN not requiring segmental mandibulectomy, debridement of necrotic bone with mandibular preservation in combination with vascularized soft tissue coverage would result in durable symptom and disease resolution. Additionally, they sought to explore if patients treated with a microvascular reconstruction for intermediate stage ORN would experience a faster recovery with fewer complications than patients treated with advanced stage ORN. They retrospectively reviewed and compared two groups of patients with ORN; one a mandibular preserving approach with a fasciocutaneous forearm flap for progressive treatment-resistant intermediate stage (Notani III) ORN to mandibulectomy and vascularized bone flap reconstruction for advanced stage (Notani III) ORN. The primary outcome was ORN resolution. One-hundred percent of patients undergoing a mandibular

preserving approach experienced ORN resolution compared with 83.3% in the segmental mandibulectomy and composite free flap reconstruction group; albeit the difference was not statistically significant. Additionally, patients in the mandibular preservation group experienced a shorter hospitalization, decreased length of surgery, and less delayed healing requiring local wound care. The comparative results are not surprising but what is interesting is the fact that 100% of patients (albeit a relatively small cohort, n=11) with Notani II ORN, managed with debridement and a radial forearm flap had complete resolution of ORN. The authors conclude that the findings of their study suggest that not waiting until the development of stage III ORN and intervening earlier with a microvascular intervention has generally superior outcomes and can shorten the disease course.

In a case series of 8 patients, Haffey et al[97] reported a similar approach to early and intermediate stage ORN using an anterolateral thigh fascia lata flap covered by a full thickness skin graft for mandibular coverage. In their series, 1 patient developed flap failure requiring another ALT fascia lata flap. However, there were no other peri-operative complications. All patients maintained intra-oral wound integrity and symptom control. Remarkably, the mean in-patient hospital stay was 3 days (range, 1-7 days). Imaging up to 4 years postoperatively demonstrated no evidence of ORN progression, with several cases demonstrating an increase in the radiographic bone density. Interestingly, one patient who had a limited mandibular height pre-operatively but in whom medical co-morbidities precluded the use of a composite free flap, developed a mandibular fracture post-operatively. However, this was managed conservatively and the mandible remained covered intra-orally at 3-years post-operatively. The authors believe that use of an independently vascularised flap, thereby bringing nutrient blood to at risk bone, helps re-establishes vascular supply, improves tissue oxygenation, increases the clearance of free radicals, and aids in the ability to deliver antibiotics and fight infection. The also cite the fact that this surgery does not preclude or complicate further reconstructive procedures (e.g. fibula flap) should progression of disease mandate a segmental resection.

Of course, it is not surprising that a mandibular preserving approach with soft tissue free flap coverage only versus free tissue transfer utilising a composite free flap for advanced stage ORN is associated with a higher rate of ORN resolution, and a lower rate of perioperative complications and flap loss. Notani II and Notani III are 2 distinct groups. For example, the

presence of a cutaneous fistula in stage III ORN necessitates a more complex reconstruction requiring either cutaneous reconstruction with an external skin paddle or cervical relining with primary closure of the excised fistula. In Notani II, neck access incisions can be minimal, along with limited intra-oral periosteal stripping, and there is no requirement for the use of hardware.

Notwithstanding this, some authors advocate the use of segmental resection and composite free flap in less advanced ORN. Als Deek[98] has proposed that in patients with recalcitrant early to intermediate stage ORN, segmental resection with composite flap reconstruction should be the preferred approach and similar to the approach to advanced stage ORN. He suggests that segmental resection reduces the risk for further ORN, permits dental rehabilitation, and does not exhaust vessels in patients with vessel-depleted necks. Of course, this is not supported by the above cited studies where the development of future ORN in cases managed with debridement/marginal mandibulectomy was not inferior to segmental resections.

2.4.2. (b) Advanced ORN: Resection with Free Flap Reconstruction

Although free flaps remains the gold standard for reconstruction, simple resection without reconstruction is appropriate for selected patients. Furthermore, the use of pedicled flaps and a second stage reconstruction with cortico-cancellous bone grafts remains an option. However, free flap reconstruction offers significant advantages relative to multi-stage hard and soft tissue surgery. It allows reconstruction of both soft and hard tissues at a single surgery, where non-irradiated tissue, with an independent blood supply, is used to reconstruct a defect.

However, vessel depletion, fibrosed tissues, and increased susceptibility to infection and wound breakdown all make reconstruction with a free flap more challenging. Historically, reconstruction of irradiated tissues carried a higher risk of complications, including flap failure[99, 100, 101, 102]. Deutsch et al[103] 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. Contrera et al[104], in 2021, looked at the morbidity associated with surgical management of ORN. All patients (n=76) included in their

retrospective review had a segmental resection and most had a free flap reconstruction. One observation made was that compared to patients with complications, patients without complications had a significantly shorter median time from radiation therapy to surgery. Notably, 65% of patients had a post-operative complication requiring a return to theatre.

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[105].

Others have reported that radiotherapy does not affect the rate of complications associated with free flaps[106]. More recently, the reported free flap success rate in the management of ORN ranges form 86-100%[107]. The UK Flap Register reported a flap success rate of ninety-one percent for ORN versus ninety-six percent for other indications.

2.4.3 Vessel Depleted Neck and Virtual Surgical Planning

Not only does radiotherapy potentially affect the quality of tissues and vessels in the site of ORN resection, it sometimes obliges the reconstructive surgeon to look-for suitable vessels (for anastamotic purposes) in sites remote from the radiotherapy fields, for example the contra-lateral neck or thyro-cervical area. This increases the complexity of surgery, and therefore potential complications.

Owing to the increasing incidence of and improved survival in oro-pharyngeal cancer, and with more widespread application of chemo-radiotherapy, surgeons are increasingly likely to be faced with the challenge of performing free flap surgery in the hostile environment of a vessel depleted neck (VDN). Options to surmount this include a corlett loop which is a temporary arteriovenous fistula, the subclavian or transverse cervical vessels, internal mammary vessels, and the superficial temporal vessels as suitable recipients outside the field of radiation and surgery[108, 109, 110, 111]. Kerai et al[112], in 2023, described the successful use of robot assisted harvesting of the internal mammary vessels in the management a patient with Notani III grade ORN affecting the anterior mandible and a vessel depleted neck. Reconstruction of the mandibular defect was done with a virtually planned composite fibular free flap and microvascular anastomosis of the peroneal vessels to the left internal mammary artery and left internal mammary vein. Significantly, there were no thoracic complications.

Scaglioni and colleagues[113]described the use of internal mammary perforator vessels as recipient vessels in combination with a chimeric antero-lateral thigh (ALT) flap to reconstruct a floor of mouth defect in a patient also with a VDN.

The use of virtual surgical planning (VSP) in head and neck tumour ablation with reconstruction is increasing[114], and indeed becoming the standard of care. This leads to reduced operating time, greater accuracy, improved bony contact and improved aesthetic/functional outcomes[115].

However, use of VSP in the setting of ORN can be challenging. Conventionally, in ORN, resection margins are guided by the findings at operation and resection is essentially continued until clinically apparent normal bleeding bone is encountered. Some authors have described using tetracycline as a fluorescent marker to discriminate between vital and necrotic bone[116].

In VSP, the resection margins must be defined pre-operatively to facilitate fabrication of patient specific cutting guides.

However, we know that the risk of ORN is higher in the posterior mandible and if more than 60 Gy have been delivered[117], and that the risk is reduced if the mandible has received less than 50 Gy[4].

The MD Anderson Symposium working group[118] looked at dosimetric parameters associated with osteoradionecrosis (ORN) in oropharyngeal cancer patients in the IMRT era and demonstrated that a wide range of dose-volume histogram parameters in the intermediate and high beam path were all significantly higher in ORN patients. Using DCE-MRI, differences in vascular leakiness can be measured between affected and healthy bone tissue[119]. This information could potentially be used to guide virtual resection margins.

Recently, a map of the radiotherapy dose delivered to the mandible has been utilised to help guide resection margins and fabrication of cutting guides, as one would with routine VSP. It involves superimposition of previously delivered radiation dosimetry data on to the virtual mandible[120, 121]. This technique allows the surgeon to identify the dose of radiotherapy delivered to specific anatomical locations of the mandible which, when combined with clinical assessment, can allow for better estimation of the surgical resection margins, and reduce the

risk of mal- or non-union and indeed further ORN. Ultimately, the goal is to avoid resection in an area of the mandible that has received a high dose of radiotherapy.

2.5. Retrospective Clinical Audit

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.

2.5.1 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[122], 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[123].

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 in this audit is as in a previous publication on mandible reconstruction[124].

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

2.5.2 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 2.1.*

	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* • *Class II* • *Class III* • *Class IV*	 37 (76%) 7 (14%) 3 (6%) 2 (4%)	 29 (60%) 13 (26%) 6 (12%) 1 (2%)	 31 (63%) 11 (23%) 7 (14%) 0
Donor Site • *DCIA* • *Fibula* • *Radial* • *Scapula*	 17 (35%) 18 (37%) 12 (24%) 2 (4%)	 16 (33%) 19 (39%) 12 (24%) 2 (4%)	 18 (37%) 18 (37%) 11 (22%) 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* • *2000-2004* • *2005-2009* • *2010-2015*	 4 7 17 21	 4 7 17 21	 4 7 17 21
Osteotomy in osseous component of Free flap (%)	32 (66%)	28 (57%)	28 (58%)
Method of fixation (%) • *Reconstruction plate* • *Mini-plate* • *Both*	 49 44 7	 71 29 0	 54 46 0

Table 2.1. Groups according to ORN/Radiotherapy status

All complications, including partial and complete flap failure, are outlined in *Table 2.2.*

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

The distribution of donor sites for the ORN cases is outlined in *figure 1.*

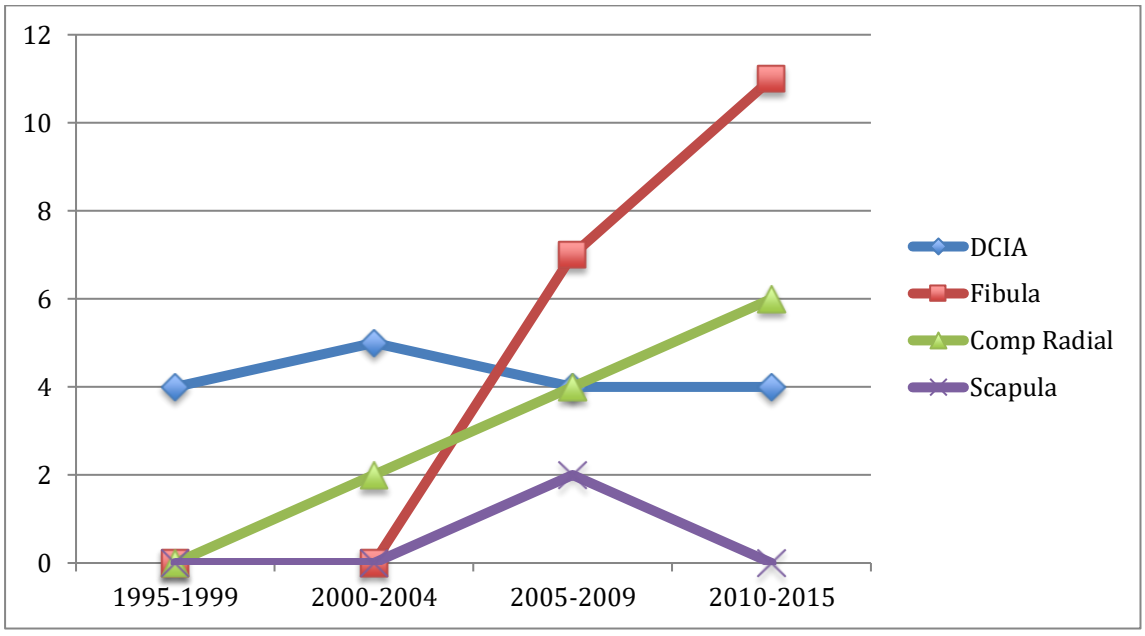


Figure 2.1. Donor sites for ORN reconstructions

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.

2.6 Discussion

These 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.

This study/audit 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[2,94, 125]. 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[126].

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. 2*) 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.

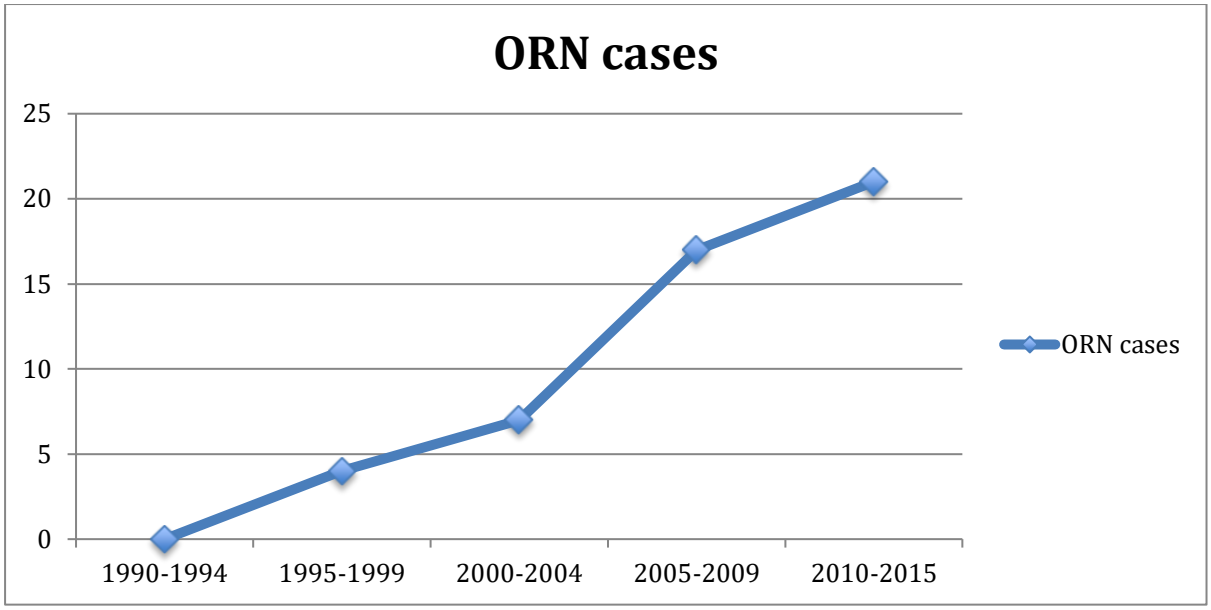


Figure 2.2. Number of ORN cases per 5-year period.

The other notable trend has been for an increased reliance on the fibula donor site for ORN cases (*figure. 1*). 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[127].

Lee et al[128], 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 favourably to this. In addition, it compares favourably 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[102], 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[129], 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[130] 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[131], in 2004 found a significantly increased rate of local complications in ORN cases, when compared to non-ORN but irradiated patients.

While we now routinely use in-house Virtual Surgical Planning (VSP) [the benefits of which are well described] for all composite mandibular reconstructions including ORN resections; it was not available during the majority of the 25-year time period on which this audit is based. Several published studies have included VSP in the setting of an ORN diagnosis[132, 133]. However, case numbers have been small and many reported series do not discriminate between ORN and other pathologies. Johal et al[134], in a series of 29 cases including seven cases of ORN, found ORN to be a risk factor for less accurate results. Recently, Annino and colleagues[135], in one of the largest published series, retrospectively looked at 26 cases where VSP was utilised. They reported substantial improvement in preoperative symptoms, no flap failures, an acceptable complication rate, and a high level of accuracy in execution of the virtual plan. While they did report having to extend the resection margin intra-operatively owing to gross ORN at the margin; they did not however report on the incidence of further ORN in follow-up.

Challenges with the use of VSP, include the fact that it does not account for a vessel depleted neck, nor does it consider the possible soft tissue constraints which may not facilitate optimal placement or projection of a bone segment. Furthermore, defining a resection margin pre-operatively can be difficult and may result in the need for alteration intra-operatively and/or potentially increase the risk for further ORN post-operatively.

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[136] 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[137]. 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[138] reported a recurrence rate of 14.5% within 1 to 41 months following mandibulectomy.

The advent of dosimetry guided virtual surgical planning (VSP) in the reconstruction of mandibular osteoradionecrosis has the potential to reduce the incidence of further ORN, post ORN resection and reconstruction. This hypothesis (which it is in the true sense of the word, giving the limited available supporting evidence) is based on the fact that the risk for ORN is greater when >60Gy is delivered to the mandible. If surgeons can avoid placing a resection margin in a high-risk area, the potential for further ORN may be diminished. However, currently there is insufficient data on the relationship between the received RT dose and the ideal location for bone cuts. A better delineation of this relationship may help to give a figure or dose in Gy above which the risk for further ORN is high. In 2022, an international consortium of centres collected retrospective data on patients who underwent segmental mandibular resection as treatment for ORN[139]. Thirty-three patients were included in their study, of which 5 developed further ORN. No recurrence was observed with margins placed in the mandibular volume exposed to less than 56 Gy.

However, results of this study ultimately showed that the volume of radiated bone was not predictive for risk of progression. Nonetheless, the authors concluded that as recurrent ORN occurred with bone resection margins within the 56 Gy isodose volume, this could serve as a starting point for the pre-operative planning of reducing the risk of ORN recurrence.

Nonetheless, ORN is a multifactorial disease, and basing resection margins solely on dosimetry data should be done with caution. Other considerations include quality of adjacent soft tissue and muscle insertions, tumour site, prior head and neck surgery, adjuvant chemotherapy, smoking status, dental health, and of course findings at operation.

A large multi-centre prospective study, sufficiently powered to draw significant conclusions, comparing the long-term outcomes of dosimetry-based resection margins with those based on clinical findings at operation, is required to better delineate the benefit of this technique.

2.7 Conclusion

The incidence of ORN, 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 favourably. The main benefits of resection with reconstruction are relief of pain, closure of an oro-cutaneous fistula, and possible return to a per oral diet. However, it must be acknowledged that many of these patient develop progressive trismus, worsening of swallow and speech function and a consequent reduction in quality of life.

Chapter 3: Composite Radial Forearm Free Flaps for Head and Neck Reconstruction

3.1 Abstract

The aim of this study was to report the patient characteristics and radial fracture rates in a consecutive series of composite radial forearm free flap (CRFFF) for head and neck reconstruction over a 31-year period. The patients were identified from between 1990 to 2020 inclusive from theatre records and records from previous analyses at the Unit on free flap outcomes. Electronic case notes were accessed where available, to gather information on the operation, histopathology, and radiographs. Patients were categorized into three groups for analysis: (1) new oral cancers with a composite radial being the first choice of flap, (2) new oral cancers with a composite radial being the choice of flap following compromise of another bony flap, (3) osteoradionecrosis (ORN) cases. There were 103 CRFFF cases, median (IQR) age 69 (59-80) years, comprising 78 (Group 1), 5 (Group 2) and 20 (Group 3). The CRFFF failure rate was 6% (6/103) and the radius fracture rate was also 6% (6/103), both with 95% confidence interval 2.2-12.2%. Of the 6 radius fractures, 1 underwent surgical management (rush nailing), 1 died in hospital and the others managed with cast immobilisation. Two-year overall survival after surgery for the103 patients was 54% (SE 5%), while 5-year survival was 40% (SE 5%). In conclusion, in spite of the familiarity with other bone flaps such as fibula free flap, DCIA, scapula, and the limited bone stock and potential fracture related morbidity associated with the CRFFF, this flap still has a place in the surgical reconstructive armamentarium.

3.2 Introduction

In a systematic review reporting a total of 9499 cases of mandibular reconstruction with vascularised bone flaps over a 25-year period, 12% were composite radial forearm free flaps (CRFFF)[140]. The potential disadvantages of the CRFFF relate mainly to donor site morbidity, especially radius fracture, and the limited bone stock available. Radial fracture rates have been reported in the regions of 0% and 18%[141, 142, 143]. Fracture confers considerable morbidity in respect to delayed healing, joint stiffness, and osteoporosis owing to prolonged immobilisation[144]. In cases where fracture does not occur the morbidity of harvest is similar to the soft tissue radial[145, 4]. Modifications on the earliest harvesting techniques such as limiting the harvest to 40% of the radial radius[146,147,148,149,150,151] use of a keel shaped osteotomy to reduce points of stress, and prophylactic plating along with arm casting have led to a reported reduction in the incidence of fracture rates.

The CRFFF has limited bone stock compared to the fibula, DCIA, and scapula, however despite this, the flap has been described in management of mandibular ORN[152], and reconstruction of small volume maxillary[153, 154], lateral mandibular segmental defects[155], and to augment the zygomatic implants perforator flap (ZIP flap)[156].

Although there are previous articles reporting series of CRFFF [4, 5, 9, 17, 157, 158, 159] , the majority report relatively small numbers, typical between 4 and 86, with two studies reporting 155[16] and 167[10] cases respectively. The previous literature has tended to lack long-term follow up or in the information provided for the plating and casting management. Very few studies report on recipient vessels used in the neck.

The aim of this present study was to report the patient characteristics and outcomes, including radius fracture rates, use of recipient vessels, flap utilisation and survival in a consecutive series of CRFFF used in the reconstruction of head and neck defects over a 31-year period. This data serves to put into current context the place of the CRFFF as a reconstructive option following head and neck cancer.

3.3 Methods

This was a consecutive series of all oral HNC patients having composite radial forearm free-flap (CRFFF) resections undertaken at the Head and Neck Cancer Centre, Liverpool, UK over a 31-year period from 1990. Cases were identified by theatre logs and previous analyses on free flap outcomes. Electronic case notes were accessed where available to gather information on the operation, histopathology, and radiographs.

Data included patient demographics, TNM staging[160], HNC site, diagnosis, Oral cancer-histology type or ORN, date of operation, use of radiotherapy, composite radial free flap as first or second reconstruction choice, length of radial bone harvest, donor site hand side, recipient vessels of anastomosis on the neck, overall free-flap success, radius fracture, treatment of radial fracture, length of hospital stay and date of death.

Patients were categorized into three groups for analysis: (1) new oral cancers with a composite radial being the first choice of flap, (2) new oral cancers with a composite radial being the choice of flap following compromise of another bony flap, (3) osteoradionecrosis (ORN) cases. Fishers Exact test was used to compare patient groups regarding categorical variables and the Mann-Whitney (2 groups) or Kruskal-Wallis (>2 groups) test for numerical variables. Kaplan-Meier methods were used to report overall survival, with follow-up of patients either to death, last clinic known to be alive or to 12-2-2021; the log rank test was used to compare survival curves. Statistical significance was regarded as $p<0.05$ and the analyses were performed using SPSS v25.

Audit approval was granted by the hospital Clinical and Audit Management System (CAMS No. 9727).

3.4 Results

There were 103 CRFFF cases from 1990 to 2020, median (IQR) age 69 (59-80) years and 58% (60) were male. The CRFFF failure rate was 6% (6/103) and the radius fracture rate was also 6% (6/103), both with 95% confidence interval 2.2-12.2%; one patient had both a radius fracture and a failure of the CRFFF. Of the 6 radius fractures, 1 underwent surgical management (rush nailing), 1 died in hospital and the others were managed with cast immobilisation. Two-year overall survival after surgery for these 103 patients was 54% (SE 5%), while 5-year survival was 40% (SE 5%); 6 patients died in hospital.

There were 78 patients with new oral cancers for whom the first choice of flap was a composite radial (Group 1), comprising 75 squamous cell carcinomas and 3 adenocarcinomas. In addition, there were 5 patients for whom the choice of flap was not a composite radial (1 DCIA, 4 fibula) and where there was flap compromise, and a composite radial was used as a second reconstructive option (Group 2). There were also 20 ORN patients (Group 3) who had a composite radial used to reconstruct the resection in the ORN; 2 of these patients previously had another bony flap (1 DCIA, 1 fibula) which failed, and the second reconstruction involved a composite radial. Comparison of these three groups by patient demographics, treatment details and outcomes is shown in Table 1. Group 2 (2^{nd} reconstruction) new patients stayed longer in hospital (median 71 days) compared with Group 1 (1^{st} reconstruction) new patients (median 19 days) or Group 3 ORN patients (median 12 days), p=0.007. Almost all (4 of 5) of Group 2 cases were before 2010, compared with 56% of Group 1 cases and 30% of ORN cases, p=0.046. Patients in Groups 2 and 3 were younger on average (median 67 and 61 years respectively) than for Group 1 patients (median 75 years), p=0.005. There was also a differing mix of recipient vessels of anastomosis in the neck, p<0.001. The facial artery was the recipient artery for 80% (4/5) of Group 2 second reconstructions and 91% of Group 1 first reconstructions but for only 30% for ORN patients, with the transverse cervical artery involved for 55% of the ORN group. The internal jugular vein was the recipient vein for 75% (3 of 4) of Group 2 second reconstructions, while the most common veins for Group 1 first reconstructions were either the internal jugular (50%) or common facial (29%) and for ORN cases it was either the transverse cervical venous system (45%) or common facial vein (25%). Further details of the 6 flap failures are summarized in Table 2.

For Group 1 new case first reconstruction patients involving a composite radial, flap failure was 5% (2/44) for operations during 1990-2009 and 9% (3/34) during 2010-2020, p=0.65; radius fracture rates were 9% (4/44) and 3% (1/34), p=0.38. Stays in hospital became shorter over time, p=0.001, median (IQR) of 24 (14-38) days for 1990-2009 and 14 (10-23) days for 2010-2020. Patients selected for CRFFF were younger during 1990-2009 at a median (IQR) 67 (55-78) years compared with 79 (70-84) years for 2010-2020, p=0.001. During 2010-2020 only 3 of 34 patients were aged under 65 compared to 22 of 44 during 1990-2009. Figure 1 shows Kaplan-Meier survival curves by time period for Group 1 patients aged 65 years and over. Overall, two and five-year survival during 1990-2009 (n=44) was 51% (SE 8%) and 36% (SE 8%) respectively, and for 2010-2020 (n=34) was 41% (SE 9%) and 26% (SE 9%), log rank test of survival curves p=0.15. Kaplan-Meier survival curves for patient groups 1 and 3 by time period are shown in Figure 2. There was a significant difference (log rank test chi-squared = 6.4, p=0.01) between group 1 (n=78) and group 3 (n=20) with ORN patients having the better survival.

Table 3.1. Patient demographics, clinical status and outcome for the three groups.

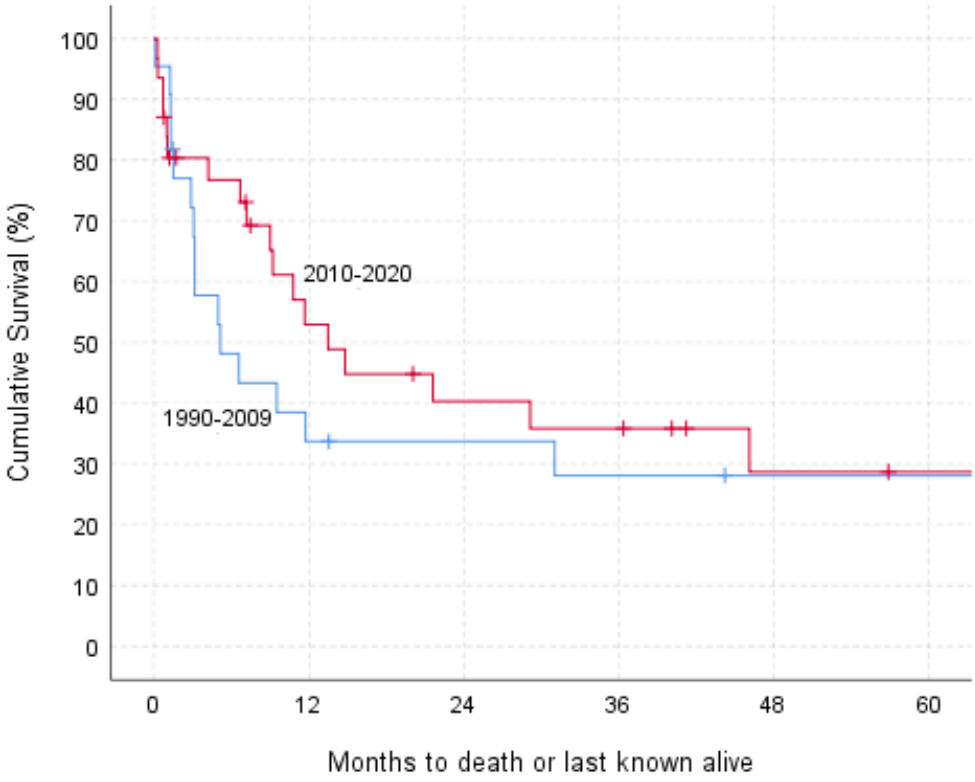
		Group 1, New Ca, 1st reconstruction		Group 2, New Ca, 2nd reconstruction		Group 3, ORN		P Value*	All cases	
		%	n	%	n	%	n		%	n
	No. of Patients	100	78	100	5	100	20		100	103
Gender	Male	55	43	40	2	75	15	0.20	58	60
Age at surgery	<65	32	25	20	1	65	13		38	39
	≥65	68	53	80	4	35	7		62	64
	Median (IQR)	75 (62-81)		67 (na)		61 (54-67)		0.005	70 (59-80)	
Year of surgery	1990-2009	56	44	80	4	30	6	0.046	52	54
	2010-2020	44	34	20	1	70	14		48	49
Dental status	Edentulous	39	27/70	50	1/2	17	2/12	0.30	36	30/84
Site	Anterior Mandible	17	13	0	0	5	1	0.11	14	14
	Body of mandible	55	43	60	3	90	18		62	64
	Retromolar	21	16	40	2	5	1		18	19
	Maxilla	8	6	0	0	0	0		6	6
Overall stage (Pathology)	Early 1-2	14	11	0	0		-	>0.99	14	11
	Advanced 3-4	86	64	100	5		-		86	69
	Not known		3		0		20			23
Radiotherapy	Yes	58	40/69	40	2	100	20	<0.001	66	62/94
Forearm used	Left	94	73	100	5	85	17	0.46	92	95
	Right	6	5	0	0	15	3		8	8
Length of radial Flap taken (mm)	<60	26	18	40	2	29	5		27	25
	60-69	14	10	20	1	6	1		13	12
	70-79	23	16	20	1	53	9		29	26
	≥80	36	25	20	1	12	2		31	28
	Not known		9		0		3			12
	Median (IQR)	70 (57-80)		60 (na)		70 (57-71)		0.60	70 (57-80)	
Recipient artery	External carotid (ECA)	3	2	0	0	15	3	<0.001	6	5
	Facial (FA)	91	60	75	3	30	6		77	69
	Transverse cervical (STA/TCA)	6	4	25	1	55	11		18	16
	Not known		12		1		0			13
Recipient vein	Transverse cervical venous system (SCV/TCV)	2	1	25	1	45	9	<0.001	12	11
	Facial (CF/FV/RMV)	29	19	0	0	25	5		27	24
	Ant/ Ext jugular (AJV/EJV)	15	10	0	0	15	3		14	13
	Internal jugular (IJV)	50	33	75	3	15	3		43	39
	EJV+IJV	5	3	0	0	0	0		3	3
	Not known		12		1		0			13
Flap Outcome	Success	94	73	100	5	95	19	>0.99	94	97
	Failure	6	5	0	0	5	1		6	6
Radius fracture	Fracture	6	5	0	0	5	1	>0.99	6	6
Died in Hospital	Yes	6	5/77	0	0	5	1	>0.99	6	6/102
LOS (discharged)	<14 days	31	22	20	1	63	12		36	35
	14-27 days	42	30	0	0	21	4		35	34
	≥28 days	28	20	80	4	16	3		28	27
	Median (IQR)	19 (12-30)		71 (na)		12 (9-18)		0.007	17 (11-30)	
Overall survival	One year	59% (SE 6%)		20% (SE 18%)		90% (SE 7%)		0.013		
	Two year	47% (SE 6%)		20% (SE 18%)		90% (SE 7%)				
	Five years	33% (SE 6%)		20% (SE 18%)		74% (SE 12%)				

*Fishers Exact test apart from Kruskal Wallis test for age, length of radial forearm and length of stay in hospital and log rank test to compare overall survival curves. P values computed after excluding any missing data. Any percentages stated in the table also omit missing data from the denominators. na: Interquartile range (IQR) not computed for denominators less than 10

Year	Group	Age	Diagnosis	Location	Fracture	LOS	Recipient artery	Recipient vein	Comment
1993	1	80	SCC	Body of mandible		46	FA	IJV	Venous failure day 1. Second surgery: Pec Major with 6th rib. Persistent fistula in the neck. Died in hospital day 46.
2008	1	83	SCC	Anterior Mandible		35	ECA	EJV	Arterial failure day 3. Second surgery: local tissue used with previous Pec Major, mandibular swing and no fistula.
2010	1	80	SCC	Body of mandible		11	FA	EJV	Venous failure day **3.** Secondary surgery: Buccal fat pad and local tissue advancement, mandibular swing and no fistula. patient unwilling for another free flap
2010	1	86	SCC	Retromolar		30	FA	IJV	Venous failure day 6. Secondary surgery: Local advancement including tongue flap to close the oro-cutaneous fistula, mandibular swing and no fistula
2019	3	67	ORN	Anterior Mandible		12	ECA	EJV	Venous failure day 1. Secondary surgery: Local advancement including tongue flap to close the oro-cutaneous fistula, mandibular swing and no fistula
2019	1	79	SCC	Body of mandible	Radius fracture	Died in hospital	ECA	RMV	Arterial failure day 7 as anastomosis breakdown due to neck infection.. Secondary surgery: Local advancement including tongue flap to close the oro-cutaneous fistula, mandibular swing and no fistula

Table 3.2. Further details of 6 flap failures. RT: radiotherapy; LOS: length of stay in hospital; NK: Not known

Figure 3.1 Kaplan-Meier survival by time period for group 1 patients aged 65 years and over

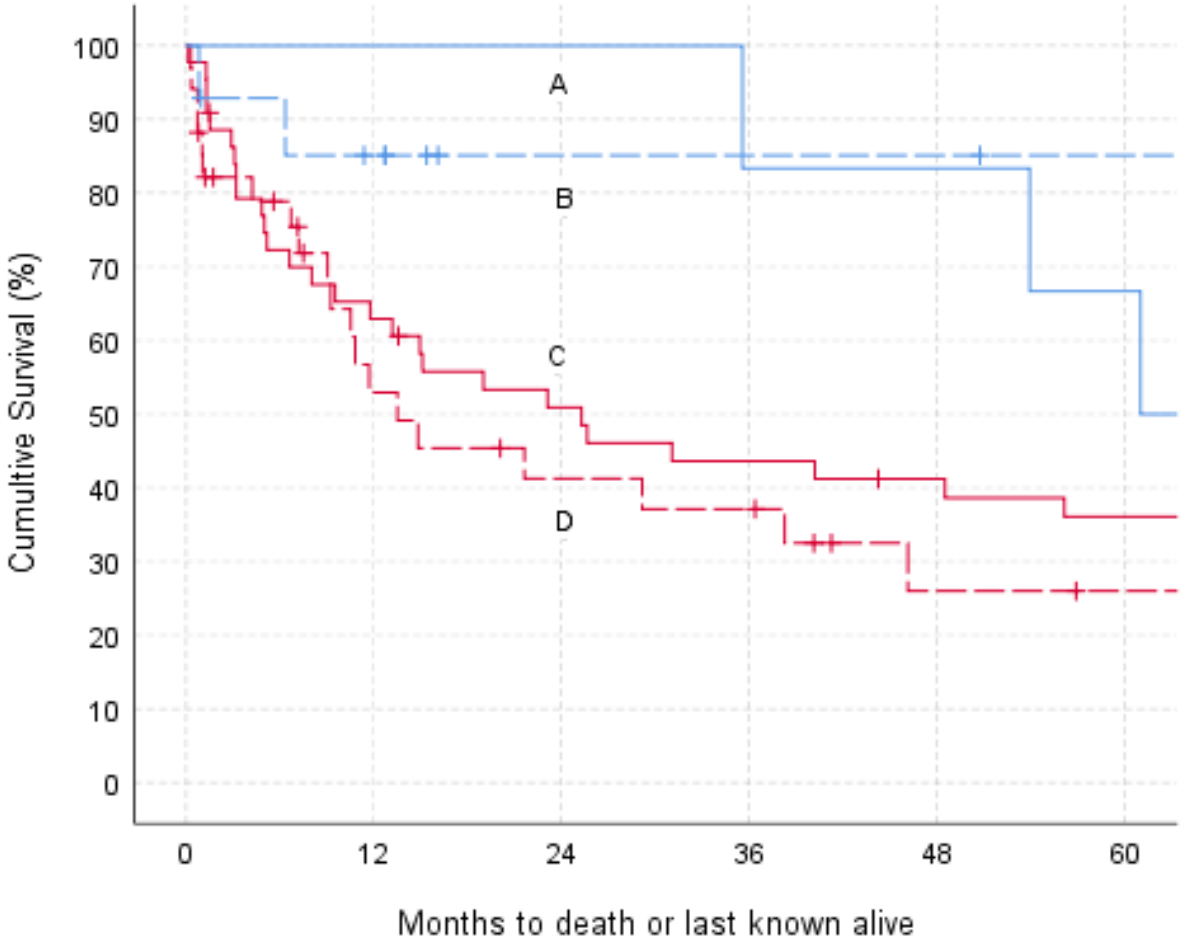


Log-rank test chi-squared value =0.11 p=0.74

1990-2009 median (IQR) age 78 (77-83), n=22

2010-2020 median (IQR) age 80 (73-84), n=31

Figure 3.2 Kaplan-Meier survival by patient group and time period



Footnote:

A: ORN, 1990-2009, n=6

B: ORN, 2010-2020, n=14

C: Primary tumour without salvage, 1990-2009, n=44

D: Primary tumour without salvage, 2010-2020, n=34

3.5 Discussion

The composite radial forearm free flap remains an important reconstructive option following head and neck cancer surgery. Although our Unit has previously published its experience on free flaps[13, 161, 162], we have never previously focused on the CRFFF specifically. Previous papers on free tissue transfer have allowed accurate historical records which for this consecutive series has been updated by more recent electronic patient case notes. Although this study has a considerable number of patients collated over a 31-year period, it has certain limitations. It has not been possible from this historical series to report osteotomy rate, non-union, fistula rates, oral rehabilitation details or health-related quality of life. The findings of this study compare similarly with other large series[10, 163], and this current paper details the recipient neck vessels, something which is lacking in other previous similar studies.

In this series six patients (6%) suffered a radius fracture, most of whom were managed with cast immobilisation. This rate compares favourably with the literature [2, 4, 5, 164, 165, 166]. Given the predominance of elderly patients in our cohort, likely with osteoporosis, it is perhaps surprising that fracture rates were not higher. In our two cohorts, namely 1990-2009 and 2010-2019, there was a reduction in fracture rates in the later period. It is difficult to be certain about the reason for this reduction, and the low number of fractures means that statistical significance cannot be inferred. Nevertheless, it is important to point out that we have changed our practice between the two time periods. Since 2010, we routinely prophylactically plate the radius with a 2.4mm volar reconstruction plate, together with a two-week above elbow, followed by a two-week below elbow cast immobilisation protocol. The use of prophylactic plating to prevent radius fracture has previously been well described in the literature[167].

This current paper highlights the utility of the CRFFF for primary reconstruction of composite oral defects (Group-1), particularly in elderly edentulous patients. The median age of these patients was 75 years. Interestingly, there is a significant shift in the median age of patients in this group between our two time periods, with half of the 1990-2009 cohort under 65 years compared with 9% of the 2010-2020 cohort. This reflects the change in choice of composite flaps in our Unit over the last 30 years. However, it also serves to highlight the continued utilisation and usefulness of the CRFFF in the elderly population. The CRFFF has a role in

providing additional support in selected cases of maxillectomy where reconstruction is by zygomatic implants (ZIP flap)[17]. With this technique there is very early rehabilitation prior to commencement of adjuvant therapy should it be required.

A two-team approach reduces operation time and in the older patient this can be an important consideration when balancing up fitness for major surgery, and complexity of other flaps such as a fibula, scapula or DCIA. The CRFFF can provide adequate restoration of mandible continuity with relatively low attendant morbidity[168]. With an ever-increasing elderly population with comorbidity, and increased risk for peripheral vascular disease in older patients, often precluding the use of a fibula as a donor site, the CRFFF continues to be a viable option. Notwithstanding this, the difficulty in placement of endosseous implants into a CRFFF remains.

The second group in this series is where the CRFFF was used for flap salvage when the initial composite flap failed. In our unit the reported overall flap failure rate is 2%, with a rate of up to 7% when applied to composite flaps only[13, 23]. Hence in this series the number of CRFFF (five patients) is small and difficult to draw any firm conclusions. Nonetheless, it should be pointed out that, all flap salvage cases utilising a CRFFF were successful and is demonstrates that this flap is a reliable salvage option.

The third studied group were patients with Osteoradionecrosis (ORN). Radiotherapy is a commonly used modality both as primary treatment and following surgery. The number of patients with ORN are likely to increase as there is evidence of improved survival in HPV positive tumours. As a consequence, surgeons will be faced with the reconstructive challenges following ORN, hence the importance of the data concerning the CRFFF in this situation and its place in relation to other flaps [13].

A notable outcome of this study was the recipient vessels in the neck particularly in ORN cases. As far as we are aware, there is only one other study[169] reporting recipient vessels in the neck for ORN, where the authors reported a series of 33 cases. The recipient vessels used were the Facial Artery (23 cases), Superior Thyroid Artery (9 cases) and the Lingual Artery (1 case). In our present study 55% of the ORN cases had a successful arterial anastomosis at the Transverse Cervical Artery (TCA) with 45 % at the Transverse Cervical Venous (TCV) system.

This is of significant relevance with regard to pre-operative planning and choice of flap. We have demonstrated that the Transverse Cervical vessels can be reliably and safely used in selected cases of ORN requiring reconstruction. However, use of these vessels mandates the use of a flap with a reliably long pedicle, such that it can reach the infra-clavicular area. The CRFFF with a pedicle length of up to 18cm can predictably do this. Additionally, use of the CRFFF also facilitates utilisation of contra-lateral vessels should that be required.

3.6 Conclusion

The CRFFF remains an very useful flap for reconstructive head and neck surgeons to have in their armamentarium and in light of its potential limitations, particularly in terms of fracture rates and limited bone stock, appropriate training in both harvesting technique and case selection is important.

Chapter 4: Discussion

4.1. Introduction

Despite an improved understanding of the biology and more accurate staging of Oral Cavity and other Head and Neck Cancers, overall and disease-specific survival, in patients with surgically resectable disease, is largely dictated by tumour biology. Surgery, in the form of tumour ablation followed by reconstruction is the gold-standard for management of Oral Cavity Squamous Cell Carcinoma (OCSCC). The use of free-tissue transfer ('free-flaps') is a cornerstone of contemporaneous reconstruction and is crucial for QoL for this group of patients. This, of course, is in the context of the fact that the overall 5-year survival across all OCSCC is less that fifty percent, and radical surgery is often ultimately palliative but with an initial curative intent. This thesis has examined outcomes following the use of free tissue transfer in post oncologic ablative defects.

Oncological resection of the oral cavity often results in a complex defect which can be a challenge to optimally reconstruct and provide rehabilitation and function. There are several reconstructive options including local tissue flaps, prosthetic obturation, the use of osseointegrated implants, as well as soft tissue and composite free tissue transfer. Multiple factors influence the choice of reconstruction including the site of defect, the requirement for hard tissue replacement, patient preference, and surgeon/institution experience and training.

Patients with advanced stage disease or disease with adverse features which increase the risk for loco-regional recurrence, often receive adjuvant radiotherapy following surgery.

Osteoradionecrosis (ORN) is a feared and problematic side effect of radiotherapy. Late-stage ORN typically and increasingly requires a segmental resection with formal reconstruction. Post-radiotherapy surgical fields represent a unique and challenging environment for the head and neck ablative and reconstruction surgeon.

4.2. Contribution to existing Surgical Practice and Literature

The research on which this thesis is based centres on the common theme of outcomes following free flap reconstruction of post-oncologic defects of the Head and Neck. The first study, *Outcomes of Microvascular Composite Reconstruction for Mandibular Osteoradionecrosis,* demonstrates that mandibular osteoradionecrosis (ORN) may be predictably managed with free flap reconstruction, albeit with an increased (local) complication rate. While the overall incidence of ORN in HNC patients (in patients receiving primary or adjuvant radiotherapy) is low, at 6%, the 'at-risk' population is increasing, especially given that HPV associated cancers are increasing and that primary radiotherapy is now the treatment of choice.

Osteoradionecrosis (ORN) often results in a very poor quality of life (QoL). Advanced stage disease causes intractable pain, poor speech and swallow, increasing analgesic requirements, and oro-cutaneous fistulae. Head and Neck reconstructive surgeons are increasingly likely to encounter patients with ORN and an evidence based approach to management is imperative. Despite the unique and hostile environment that post-irradiated tissues presents, our findings suggest that advanced mandibular ORN may be safely and predictably reconstructed with composite free flaps, and that free flap survival rate compares favourably to matched control groups. The main benefits of resection with reconstruction are relief of pain, closure of an oro-cutaneous fistula, and possible return to a per oral diet.

The second study, *Composite Radial Forearm Free Flaps for Head and Neck Reconstruction*, sought to put into current context the place of the Composite Radial forearm Free flap (CRFFF), as a reconstructive option following Head and Neck Cancer (HNC) surgery. Given the unique and varied reconstructive challenges often faced following HNC ablation, it is important that a wide armamentarium of options is available and that there is evidence to support their respective strengths and indeed weaknesses. This study demonstrated the continued usefulness of the CRFFF, particularly in the elderly population, in Osteoradionecrosis, and in vessel depleted necks where access to the trans-cervical vascular system, and/or the contra-lateral neck mandates the use of a long vascular pedicle.

The use of free tissue transfer has of course revolutionised the surgical management of HNC. Notwithstanding this, it is no longer sufficient to remain satisfied with replacing lost tissues and rehabilitating patient. It is incumbent on clinicians to measure the benefit for patients derived from our interventions, not only overall and disease specific survival but also the attendant changes in Quality of Life (QoL).

Cancer survivorship, in a Head and Neck Cancer context, not only pertains to surveillance for recurrence and early detection of second primary cancers, but also assessment and management of physical and psychosocial long-term and late effects of HNC and its treatment. The authors of the recently published *European Head and Neck Society recommendations for head and neck cancer survivorship care*[170] performed a literature review to provide an evidence base for their recommendations. However, they state that the data to support some of the recommended interventions is limited, and that they are therefore necessarily based on expert experience. Our ongoing and current research aims to address some of these deficits within our service.

4.3. Future Research: Patient Reported Outcomes and Data Driven Service Improvement

Patient reported outcome measures (PROMS) and Health-Related-Quality of life (HRQOL) are key outcomes in cancer care. For HNC survivors, identification of and addressing needs is hugely influential in HRQOL. It is influenced not only by tumour site, stage and treatment[171] but shaped by patient–clinician relationship, identification of needs, participation in therapeutic alliance, and quality of the rehabilitation service provision[172].

While there are many HRQOL and un-met needs measures, none are tailored specifically for HNC. The Patient-Concerns-Inventory[173] (PCI-HN) was developed as a tool to improve the HRQOL for HNC treatment survivors by helping patients outline and express their needs and concerns. It helps focus consultations, guides referral to ancillary services, and allows patients to express issues of concern to them. Furthermore, it can be used as a screening tool for adverse HRQOL[174]. However, currently it is only used by patients at the out-patient department (via either electronic device or hard cop format).

While use of the PCI-HN will allow our service to identify those issues concerning patients, it does not allow patients to highlight issues as and when they occur. Furthermore, it does not have the ability to guide patients to trusted resources.

In St James Hospital, our research group are currently trailing a web application, eAltra, which is based on the PCI-HN. The significant benefit, initially, is that the application is available to patients at all times, and therefore will allow patients to report concerns if and when they happen.

In time, it will allow our service and institution develop a large database of information, pertaining to patient concerns, and this will then inform service improvements and in particular identify areas where patients needs are unmet. Furthermore, it will allow us to direct patients towards approved resources and sources of information.

Survivorship programmes in Head and Neck Cancer (HNC) patients are less well explored relative to many other cancers. HNC is regarded as one of the most debilitating of all cancers and survivors are considerably more frail and have greater impairments in mobility than those with other solid malignancies[208]. Notwithstanding this, and given that there is strong evidence to support the fact that HRQoL early post-treatment is a key predictor of longer-term outcome, we are currently exploring interventions to improve the functional/physical outcomes in the early post treatment part of a survivorship journey. This is a collaborative effort between the Maxillofacial/Head and Neck Surgery Unit and the Department of Physiotherapy at St James Hospital. Our aim is to run a multi-centre randomised trail comparing different physical interventions aimed at HNC patients in the early survivorship phase, and ultimately improve their functional outcomes and treatment related side-effects.

4.4. Limitations

The papers, on which this thesis is based, are retrospective in their nature. This carries certain limitations. While we did utilise a prospectively maintained database for both studies, some information was not available to us, and so case-notes, theatre records, and histopathology reports were also used to complete our dataset. We focus on complications associated with free flap reconstruction of the head and neck. It is possible and indeed likely that minor complications (e.g. delayed wound healing), not requiring a return to the operating theatre (and so therefore not strictly documented), have not been accounted for. Furthermore, some treatment associated side-effects (e.g. trismus) can be progressive and these outcomes as not necessarily captured in a longitudinal fashion.

Nevertheless, major surgical outcomes for donor and recipient sites, we believe, are complete and accurate.

Oral rehabilitation (for oral cavity cancer), HRQoL (for all cancers), and patient reported outcomes are now considered key outcome measures. This information was not available to us in these studies and this is an obvious and important limitation. However, this is not lost on us, and ongoing survivorship research in St James Hospital is heavily focused on these outcome measures. We feel that this is a natural progression and improvement in the central theme of our research group, namely survivorship in patients requiring surgery for management of their head and neck cancer.

Appendix-Published Papers

Paper 1

Available online at www.sciencedirect.com
ScienceDirect
British Journal of Oral and Maxillofacial Surgery 59 (2021) 1031–1035
BRITISH Journal of Oral and Maxillofacial Surgery
www.bjoms.com

Outcomes of microvascular composite reconstruction for mandibular osteoradionecrosis

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Paper 2

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A 31-year review of composite radial forearm free flaps for head and neck reconstruction

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