Considerations for the use of alloplastic temporomandibular joint replacement in head and neck reconstruction: a review and case report presentation

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Dedication

To the loved ones that I have lost. I am who I am today because of you.

Acknowledgements

To my parents for all the love and support given to accomplish not only this present work, but also all these medical years, to my advisers, to my friends, and last but not least, to my boyfriend, I cannot describe how thankful I am for the kindness, love, support and patience.

Resumo

O cancro oral é o sexto cancro mais comum no mundo. Quando as queixas iniciam, a maioria já se encontra num estádio avançado da doença. Múltiplas modalidades terapêuticas são necessárias no tratamento do cancro oral, incluindo abordagens cirúrgicas e radioterapia/quimioterapia.

Uma das consequências mais conhecidas da radioterapia é a osteorradionecrose. A osteorradionecrose define-se pela exposição óssea e necrose, por um período mínimo de três meses. Esta entidade patológica produz efeitos tardios no suprimento sanguíneo tecidual, o que cria um ambiente difícil e inadequado para a reconstrução de deformidades ósseas e de tecidos moles remanescentes.
Vários estudos recomendam retalhos livres de peróneo como primeira opção de reconstrução para esses pacientes com grandes defeitos mandibulares e que sofrem de osteorradionecrose. No entanto, a incerteza surge quando os retalhos de perónio falham e os procedimentos de resgate não atingem o seu objetivo.

Neste presente trabalho é discutida a viabilidade da substituição aloplástica da articulação temporomandibular em pacientes pós tumores de cabeça e pescoço, quando são submetidos a radioterapia. Os efeitos da radioterapia estão associados a um maior risco de infeção e exposição pós-operatória, no entanto existem alguns casos de sucesso com próteses aloplásticas, mesmo quando a radioterapia é utilizada no tratamento desses pacientes. Além disso, é apresentado um caso clínico de um paciente com cancro de cabeça e pescoço. Este paciente, após resseção do tumor e radioterapia foi submetido a várias tentativas de reconstrução mandibular. Quando todas as técnicas falharam, uma substituição aloplástica da articulação temporomandibular foi proposta. Este trabalho pretende fazer uma revisão das técnicas de reconstrução em situação de radioterapia e propor uma nova abordagem através da apresentação de um caso clínico.

Palavras-chave

Substituição aloplástica da ATM;ATM;ORN;Radioterapia;Próteses aloplásticas

Resumo alargado

A prevalência do cancro da cabeça e pescoço está diretamente relacionada com consumos elevados de álcool e tabaco, sendo estes os principais fatores etiológicos da doença. Recentemente, tem sido notada uma correlação maior entre o desenvolvimento do cancro oral e o vírus Papiloma Humano (VPH). O carcinoma do pavimento celular (CPC) é o tipo celular mais prevalente e este tipo de neoplasia tem tendência a apresentar sintomatologia quando os doentes já se encontram numa fase avançada da doença. Nestes casos, o tratamento deve cumprir três principais objetivos, a erradicação do tumor, preservar ou restabelecer a sua forma e a função e prevenir qualquer recidiva. Assim, a principal terapêutica baseia-se na resseção cirúrgica do tumor e suas margens, combinado com terapêuticas adjuvantes, nomeadamente a radioterapia.

As consequências do tratamento podem ser devastadoras. A deformação das estruturas da faciais podem conduzir a problemas estéticos com redução da autoestima e problemas funcionais, influenciando o processo de mastigação, deglutição e fala.

A radioterapia, embora seja um tratamento adjuvante essencial que tem vindo a tornar-se numa estratégia imprescindível no combate à erradicação deste cancro, pode causar complicações severas tanto a curto como a longo prazo. A osteorradionecrose é das principais e mais temidas consequências da radioterapia e consiste na exposição de osso necrosado através de uma ferida durante um período mínimo de três meses.

A osteorradionecrose mandibular continua a ser difícil de gerir quando se trata doentes com cancro de cabeça e pescoço com radioterapia, com incidências entre 0,4% a 56%. A suscetibilidade da mandíbula como local preferencial para o desenvolvimento de osteorradionecrose, em comparação com os outros ossos da cabeça e pescoço, baseia-se no seu maior conteúdo mineral e, portanto, uma maior quantidade de radiação é absorvida. Além disso, o corpo mandibular, a sínfise e a região parassinfisária, são supridas principalmente pela artéria alveolar inferior, que é menor e mais predisposta a grandes riscos do que nos outros ossos faciais. A osteorradionecrose mandibular habitualmente manifesta-se com dor, formação de fístulas, drenagem de secreções purulentas com infeção local ou sistémica, disgeusia, padrões alternados de mastigação e de fala e fratura patológica.

Desta forma, o uso de radiação na região mandibular e da articulação temporomandibular parece ter um efeito negativo no tecido local e a potencialidade de prejudicar pequenos vasos e anastomoses microvasculares, o que pode conduzir a um estádio avançado onde o tecido poderá tornar-se necrótico e envolvido por infeção. Para além disso, cria um ambiente pouco seguro para a colocação de implantes

dentários, uma vez que a radiação prejudica a osteointegração dos implantes, através da diminuição da vascularização óssea, o que reduz o seu potencial de cicatrização. Nesses casos, a opção remanescente é a cirurgia radical com resseção segmentar das áreas envolvidas, que pode resultar em perda significativa da parte óssea e das partes moles, seguida de reconstrução primária dos grandes defeitos que afetam a estrutura da face.

A reconstrução da articulação temporomandibular pretende reestabelecer as funções e a estética facial, bem como a saúde psicológica dos doentes. O plano de reconstrução deve ter em consideração o defeito ablativo. Vários estudos já demonstraram que ao reconstruir tecidos previamente submetidos a tratamento radioterápico, ocorrem maiores taxas de complicações devido a um compromisso da cicatrização.

Em relação à reconstrução mandibular e da articulação temporomandibular e tendo em conta os resultados funcionais e estéticos, os retalhos livres vascularizados são os mais comumente utilizados, oferecendo características favoráveis como disponibilidade, biocompatibilidade, adaptabilidade e menor custo, sendo amplamente reconhecidos como a abordagem mais confiável para alcançar uma reconstrução eficaz da mandíbula. Assim, utilizam-se transferências de retalhos cirúrgicos tanto regionais como à distância para oferecer tecido bem vascularizado que não tenha sido comprometido pela exposição à radiação, permitindo um bom suprimento sanguíneo para a região, facilitando a cicatrização e possivelmente até estendendo a viabilidade do osso remanescente. O benefício fundamental das transferências de retalhos ósseos livres vascularizados assenta no facto de uma grande quantidade de osso poder ser transferida com segurança, mantendo o seu próprio suprimento sanguíneo. No entanto, em mandíbulas irradiadas, a reconstrução com retalhos livres pode ser desafiante. A escolha do local ideal para obter o retalho e a sua colheita exigem um alto nível de precisão e habilidade.

Outras opções de reconstrução incluem retalhos não pediculados, raramente usados pelo fluxo sanguíneo insuficiente na área irradiada. Uma vez que a radiação também implica redução permanente do suprimento sanguíneo, o enxerto ósseo não vascularizado em tecido irradiado associa-se a um sucesso mínimo. Também as placas de reconstrução e a restauração de tecidos moles sem osso podem ser usadas para reparar anormalidades mandibulares laterais. As placas de fixação de titânio são recentemente produzidas com tecnologia 3-D à medida do paciente, reduzindo a necessidade de moldagem intraoperatória. Apesar destas vantagens, não são aceitáveis para deformidades complexas envolvendo a região anterior da mandíbula e o côndilo. Adicionalmente, foram associados a uma taxa relativamente alta (50-80%) de fracasso devido a um risco aumentado de fratura, extrusão de placa ou luxação, sobretudo após radioterapia pós-operatória. Estas adversidades desencorajaram o uso de placas de reconstrução em pacientes submetidos a irradiação severa, bem como em doentes que desenvolveram osteorradionecrose. Na ausência de reconstrução óssea, a reabilitação dentária também deixa de ser viável.

Quando a articulação temporomandibular precisa de ser reconstruída, a reconstrução aloplástica, embora não seja uma opção habitual aplicada em casos de osteorradionecrose mandibular e osteorradionecrose da articulação temporomandibular, apresenta alguns benefícios. As próteses aloplásticas não requerem autoenxertos, podem ser desenhadas e produzidas adaptando-se à estrutura anatómica do doente e necessitam de menos tempo cirúrgico, uma vez que não há necessidade de recolher um retalho à distância. Aqui surge uma questão importante. Se as próteses aloplásticas puderem ser uma opção em casos selecionados de pacientes com cancro de cabeça e pescoço, quais são os riscos associados à radioterapia e qual é o período mais adequado para iniciar a radioterapia, considerando os seus riscos inerentes? Complicações como hipersensibilidade ao material, exposição e infeção da prótese por diminuição da vascularização e fibrose nos tecidos circundantes podem estar relacionados à exposição de radiação pré-operatória. Assim como a infeção, exposição, fratura e aumento considerável da dose de radiação no tecido devido à radiação retroespelhada pelos componentes metálicos da prótese podem estar associados à radioterapia pós-operatória.

De acordo com os resultados encontrados durante esta revisão da literatura, várias conclusões podem ser retiradas. Vários estudos confirmam que o retalho microvascular de peróneo é a opção de primeira-linha, principalmente se o defeito envolver o arco anterior. O peróneo é ideal pela qualidade de osso acessível, sendo que é vascularizado, resiste à reabsorção, tem uma capacidade considerável de restauração de contorno com múltiplas osteotomias sem comprometer a sua viabilidade, oferece tecido mole para restaurar defeitos complexos e uma camada dupla de osso cortical adequada para implantes dentários. Os vasos têm um calibre adequado para as anastomoses. Também é adequado pela quantidade de osso disponível, uma vez que uma quantidade significativa de defeitos de tecidos moles da pele facial/pescoço requer mais de 12 a 15 cm de osso e o peróneo dispõe da possibilidade de ser colhido até 25 a 27 cm de comprimento. Além disso, a secção distal do peróneo pode ser usada para obter até 12 a 15 cm do pedículo vascular. Um pedículo longo pode fornecer mais possibilidades de vasos recetores, incluindo vasos cervicais contralaterais, sem necessidade de enxerto de uma veia. Isto é crucial porque identificar vasos recetores suficientes no pescoço ipsilateral em pescoços severamente irradiados pode ser difícil.

Ainda assim, os retalhos ósseos não estão livres de complicações e posteriores insucessos, sobretudo quando os doentes são submetidos a radioterapia. A osteorradionecrose é uma complicação bem conhecida após a reconstrução com retalhos livres. Doses superiores a 60 Gy estão cientificamente associadas a maior risco de complicação e desenvolvimento de osteorradionecrose, assim como o estádio e a localização do tumor, a extração de dentes e o historial de cirurgias prévias para ablação do tumor. Apesar da extensa ressecção mandibular de todo o osso necrótico e completamente inviável e da reconstrução com osso vascularizado adequado para qualquer defeito, até 25% dos doentes podem apresentar osteorradionecrose residual ou recorrente. A exposição à radiação tanto no pré como no pós-operatório prejudica a integridade da vasculatura do recetor e tem impacto negativo sobre a viabilidade dos retalhos livres, conduzindo à sua perda. Como resultado, as reconstruções após osteorradionecrose têm maiores taxas de complicações do que as reconstruções primárias após neoplasia de cabeça e pescoço. Embora a transferência de retalhos livres tenha provado ser uma abordagem de reconstrução bem-sucedida, a sua aplicação em áreas altamente irradiadas tem o potencial de causar mais dificuldades e contribuir para piores resultados. Complicações locais como hematomas, seromas, congestão venosa e necrose da pele ou eventos microvasculares como trombose podem resultar em perda até 14% de retalho livre, necessitando de reoperação. O insucesso do retalho exige uma revisão e, na maioria dos casos, um segundo retalho livre de localização doadora diferente. Desta condição resulta um aumento da morbidade e maior tempo de internamento, o que dita uma maior necessidade de conhecimentos sobre os mecanismos que contribuem para a perda do retalho. Consequentemente, nem todos os doentes são bons candidatos para a reconstrução com retalho livre de perónео.

A necessidade de uma segunda abordagem cirúrgica, assim como o tempo prolongado de internamento, a dificuldade na fixação do enxerto, má oclusão e anquilose recorrente motivaram a procura por uma nova opção cirúrgica. Vários sistemas de próteses aloplásticas para a restauração da articulação temporomandibular têm sido desenvolvidas recentemente. Quando comparado a outras técnicas reconstrutivas, o uso de prótese da articulação temporomandibular reduz o tempo cirúrgico, minimiza a morbidade ao eliminar a necessidade de área doadora de retalho, reduz o tempo de internamento e proporciona imediata função da articulação temporomandibular após a reconstrução. No entanto, a falha da prótese por perda de parafuso ou fratura da prótese por fadiga do metal, o ajuste estreito da prótese ao local do defeito, a perda de lateralidade e de movimentos de protrusão e os custos elevados são todos potenciais problemas com estas próteses.

As próteses aloplásticas são essencialmente feitas em titânio. O titânio possui qualidades fortes, resistentes à corrosão e facilmente manipuláveis, daí ser o metal de escolha para a produção dos principais componentes das próteses da articulação temporomandibular, considerando a sua biocompatibilidade, estabilidade, facilidade de manuseio e biointegração.
Placas e próteses de titânio para a reconstrução são propensas a infeção e exposição, principalmente após radioterapia pós-operatória, uma vez que a radiação dificulta a reconstrução tardia devido ao suprimento sanguíneo permanentemente reduzido da área, o que pode conduzir ao desenvolvimento de osteorradionecrose. Além disso, os metais implantados podem induzir um aumento da dose de radiação nas interfaces osso-metal e tecido-metal no lado da entrada do feixe por um mecanismo de retroespelhamento da radiação nos componentes metálicos da prótese.
Tratamento com radiação pré-operatória pode causar compromisso sensorial pós-cirúrgico na mucosa fina do paciente, xerostomia, infeção, limitação dos movimentos da língua e menor amplitude mandibular. Assim, antes da cirurgia, os tecidos destes doentes devem ser avaliados, de modo a determinar a viabilidade dos mesmos antes da reconstrução.

Neste trabalho é também apresentado um caso clínico. Um paciente do sexo masculino de 65 anos foi encaminhado ao Instituto Português da Face para avaliação e reconstrução da articulação temporomandibular e mandíbula. O paciente foi submetido noutro centro a várias cirurgias de reconstrução após a remoção cirúrgica de um carcinoma pavimento celular da cavidade oral. Quando clinicamente avaliado, apresentava uma mordida cruzada exuberante, com incapacidade para se alimentar adequadamente, atingindo apenas 63 Kg de peso e com uma queixa principal de dor. Os seus antecedentes médicos incluíam cirurgias prévias para remoção das amígdalas, litíase renal e abordagem a uma hérnia discal. Além do diagnóstico do carcinoma pavimento celular, o seu historial médico não era significativo para nenhuma outra doença. Quanto à sua história social, foi fumador de longa data (1,5 maços/dia durante 30 anos) e consumia moderadas quantidades de álcool. Não apresenta hábitos tabágicos desde 2018, data do diagnóstico do carcinoma do pavimento celular, e reduziu drasticamente o consumo de álcool. O início da sua história clínica começou em 2017, e é marcado por uma dor oromandibular contínua à direita. Após realizar uma biópsia, foi estabelecido o diagnóstico de neoplasia mandibular de estágio T4N0M0. A primeira cirurgia foi realizada com ressecção do tumor e reconstrução primária com um retalho de peróneo esquerdo. No pós-operatório, em abril de 2018, iniciou radioterapia durante 2 meses com 60 Gy sobre o local da cirurgia e mais 40 Gy nos linfonodos direitos. Devido à radioterapia, foi necessário desbridamento cirúrgico um mês depois por infeção fúngica. Posteriormente, a avaliação clínica revelou parotidite induzida pela radiação e uma espícula mandibular exposta. Foi então realizada uma parotidectomia mais nova osteotomia segmentar mandibular, seguida de reconstrução com placa de osteossíntese com encerramento com plastia gengival. Desenvolveu-se uma nova infeção local e o doente foi reoperado em 2019 para retirar todo o material. Decidiu-se por uma tentativa final de reconstrução, no Instituto Português da Face, onde o presente orientador deste trabalho, o cirurgião principal, propôs uma reconstrução aloplástica customizada da articulação temporomandibular. Para prosseguir com esta estratégia de reconstrução, foi realizada uma ressecção hemimandibular direita. Em seguida, uma prótese da marca TMJ Concepts produzida à medida do doente foi colocada na região mandibular e da articulação temporomandibular. Após 2 anos de acompanhamento, este doente apresenta uma notável melhoria da estética facial, dos movimentos mandibulares, dos níveis de dor e da qualidade de vida em geral. Hoje em dia, este doente consegue alimentar-se com uma dieta progressiva, possibilitando o regresso ao seu peso habitual, também é percetível uma evolução na dicção, mesmo com apenas uma sessão de terapia da fala e exercícios de treino em casa, e um quase regresso à sua vida normal foi alcançado. No entanto, algumas complicações foram notadas. Os movimentos cervicais laterais são limitados até determinados ângulos, consequência de uma fibrose marcada da zona cervical pós radioterapia; uma neurite facial pós-cirúrgica afetou ligeiramente o seu equilíbrio e consequentemente a sua capacidade de andar e também são relatadas algumas queixas. A opinião deste doente em relação à sua função e resultados estéticos é de que a reconstrução aloplástica foi um grande sucesso.

Em conclusão, considerando os defeitos após a ressecção cirúrgica e radioterapia no tratamento do cancro da cabeça e pescoço, a reconstrução mandibular deve ser realizada tendo em vista restabelecer a função e a capacidade estética do doente. Quando o retalho livre de perónеo falha, próteses aloplásticas podem ser tidas em consideração. Os efeitos da radiação antes e após a reconstrução aloplástica não estão suficientemente descritos na literatura. Há pouca experiência com o uso de próteses aloplásticas como substitutos mandibulares específicos para cada doente não candidato à reconstrução com retalhos livres. Embora as próteses de titânio possam ser uma alternativa viável para a reabilitação das funções perdidas, a sua segurança ao interagir com a radiação ainda não foi estabelecida. Igualmente a radioterapia pré e pós-operatória apresentaram resultados tanto positivos como negativos, não permitindo escolher uma estratégia preferencial sobre quando a radioterapia deve ser realizada. Por fim, a decisão entre um segundo enxerto ósseo vascularizado com as suas morbilidades inerentes ou uma prótese aloplástica com as suas complicações devido à radioterapia ainda não totalmente descritas e devidamente investigadas, fica ao critério do paciente e da equipa cirúrgica.

Em relação ao caso clínico apresentado, este doente apresenta um caso de sucesso da reconstrução aloplástica após várias tentativas falhadas, inclusive de retalho livre de peróneo, e radioterapia pré-operatória. Tendo em mente que esta é uma abordagem cirúrgica nova e com pouca experiência, os resultados encorajadores deste doente podem ser o ponto de partida para desenvolver novas investigações e tratamentos semelhantes quando todas as outras alternativas de resgate falharem.

Abstract

Oral cancer is the sixth most common cancer in the world. When the complaints initiate, most of these cancers are already in an advanced-stage disease. Multiple modalities are often required in the treatment of oral cancer, including surgical approaches and radiotherapy.

One of the most well-known consequences of radiotherapy is osteoradionecrosis. Osteoradionecrosis is when irradiated bone becomes exposed and necrotic through a wound and persists for a minimum of three months. This condition produces late effects on the tissue blood supply, which creates a difficult and inappropriate environment for reconstruction of remaining bone and soft tissue deformities.
Several studies have recommended fibula free flaps as the first reconstruction option for these head and neck patients with major mandibular defects and suffering from osteoradionecrosis. Nonetheless, uncertainty emerges when fibula free flaps fail, and salvage procedures do not achieve their purpose.

In this present work is discussed the feasibility of alloplastic temporomandibular joint replacement in head and neck patients when submitted to pre- or post-radiotherapy. The effects of radiotherapy in both cases are associated with a higher risk of postoperative infection and exposure, meanwhile there are some successful cases with alloplastic prostheses, even when radiotherapy is used in these patients' treatment. Additionally, a case report of a head and neck patient is presented. This patient was submitted to several attempts of mandibular reconstruction after mandibular resection and radiotherapy. When all the efforts have failed, an alloplastic temporomandibular joint replacement was proposed. This present work intends to review reconstruction techniques in radiotherapy treatment situations and offer a new approach through a case report presentation.

Keywords

Alloplastic TMJ replacement;TMJ;ORN;Radiotherapy;Alloplastic prostheses

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List of Acronyms

RT	Radiotherapy
TMJ	Temporomandibular Joint
ORN	Osteoradionecrosis
FFF	Fibula Free Flap
ATMJR	Alloplastic Temporomandibular Joint Replacement
HPV	Human Papilloma Virus
SCC	Squamous Cell Carcinoma
UHMWPE	Ultra-high Molecular Weight Polyethylene

Chapter 1

Introduction

The prevalence of head and neck malignancies is mostly related with tobacco and alcohol use and presents a high mortality rate due to its late diagnosis (1). When the complaints begin, the tumor has most likely ranged a significant size and produced large facial defects, both functional and esthetic (2).

Salvage attempts require surgery along with radiotherapy (RT), especially when it comes to advanced stage disease. Major consequences can arise from this combined treatment. Ablative surgeries such as mandibulectomy cause the loss of mandible continuity (3) (4), architectural form distortion and functional dysfunction, particularly when temporomandibular joint (TMJ) is implicated (5). The side-effects of RT can be devastating since it is the main risk factor for developing osteoradionecrosis (ORN) and this risk is greater in patients with tumors of advanced stage. ORN is caused by poor wound healing, however according to recent investigations, ORN-affected tissue revealed the presence of bacteria, what suggests that bone may get infected consequently (6). In these cases, the remaining option is resection of necrotic areas, which may result in significant bone and soft tissue loss, requiring primary mandibular and TMJ reconstruction of the defects distressing the framework of the face and affecting the functions that were previously lost (7).

Fibula free flaps (FFF) remain the gold standard in mandibular reconstructions (3). However, when ORN develops due to RT, several complications arise leading to FFF failure. Therefore, when FFF fails to restore both functional and aesthetic capabilities, a salvage reconstruction must be accomplished.

There are various options to perform mandibular reconstruction, including vascularized bone grafts, titanium plates and alloplastic prostheses.

Considering the effects of RT, this present work purpose is to identify the considerations for the use of alloplastic temporomandibular joint replacement (ATMJR) in head and neck patients. The feasibility of alloplastic prostheses submitted to RT before and after mandibular reconstruction will be discussed and a clinical case report will be introduced as a successful experience of ATMJR.

1.1 Head and Neck Cancer

Head and neck cancer, the sixth most common cancer worldwide representing about 2.8% of all cancers, includes tumors of the oral cavity, sinuses, larynx and pharynx, salivary glands, thyroid and skin, soft tissue, and bone tumors of this area. The etiology of this cancer is well known, being tobacco use and alcohol consumption the most common etiologic agents (1). According to the Portuguese Order of Dentists, 8 in each 10 patients diagnosed with oral cancer smoke or used to smoke tobacco. However, recent studies have demonstrated the role of other pathogenic mechanisms. The Human Papilloma Virus (HPV) have been strongly correlated with the oral cancer. Squamous cell carcinomas (SCC) are the most predominant ones and account for over ninety percent of all oral primary malignant neoplasms (1). With the progress of the disease, patients can suffer facial distortion, occlusion disarrangement, TMJ disorder, and diffused orofacial pain (8).

Therapeutic Approach

The main goal of treatment of head and neck neoplasm is to eradicate the cancer, preserve or reestablish form and function and prevent any cancer relapse (1).

The choice of treatment relies on three major factors. Tumor factors, such as its location, dissemination to regional lymph nodes, primary size, bone involvement (nearness to mandible or maxilla), previous treatment, and histology are imperative to select the initial treatment. Depth of invasion, determined by histology, is a crucial feature to determine treatment and further prognosis, as thicker lesions have an increased risk of lymph node metastases. The need to stipulate the proximity of the tumor to the mandible or maxilla is mandatory since the possibility of bone invasion requires different surgical approaches. Patient factors, such as genetic, life-style habits, geographic differences, and the ability to tolerate the therapeutic program also play a vital role in treatment selection. Habits of smoking and alcohol consumption can lead to further complications and increase the risk of several primary tumors. A previously intervention and radiation therapy delivered in the same area requires an adaptable surgical planning, especially when considering pos-operative reconstruction with free flaps or free tissue transfer. Surgical expertise is considered an important factor in head and neck reconstruction. Experienced and multidisciplinary teams are required to obtain successful outcomes when appropriate surgery followed by reconstruction is embarked (1).

Although initial and definitive treatment is most frequently surgical, introduction of radiation as a non-surgical approach became an important method of treatment for selected oral cancer. However, in most cases of advanced neoplasm, using surgery simultaneously with radiation is an available and more effective option. SCC significantly predominates in the oral cavity and, as the majority of primary malignant tumors in this area except for lymphoma, is treated by surgery through a wide resection with negative margins (1). The tumor extension will dictate the magnitude of the resection (7).

Consequences of Surgical and Radiation Therapies

As result, malignant tumors can lead to tissue defects of mandible (2), requiring ablatives surgeries such as mandibulectomy, which cause the loss of mandible continuity and can result in functional sequelae, self-esteem reduction, (3)(4)(9) and to end-stage TMJ pathology, leading to anatomical distortion and physiological dysfunction (5).

Although postoperative radiation therapy has demonstrated to improve disease control and overall survival of patients with advanced stage disease, it has a wide range of consequences on regular tissues, in particular radiation-induced necrosis of soft tissue and bone. ORN can be a late complication of radiation treatment. It is a condition where irradiated bone becomes exposed and necrotic through a wound that extends beyond skin or mucosa and persists for over a three-month period due to failed healing after several efforts of conservative treatment (10)(11)(6)(12). Within a previously irradiated zone, cell damage causes stimulation and deregulation of fibroblastic activity, resulting in atrophic tissue. This triggers a biochemical cascade that destroys endothelial cells by releasing cytokines and free radicals. The formation of thrombi by leukocyte attachment to endothelial cells or the expansion of endothelial cell colonies can block the arterial lumen and cause vascular thrombosis, resulting in microvessel necrosis, local ischemia, and tissue loss. Fibrin leaks into tissue due to damage to the vasculature and the production of vasoactive cytokines, increasing collagen deposition (10)(13). Besides that, after irradiation, the bone matrix in the mandible is replaced by fibrous tissues due to a combination of osteoblast loss, failure of the osteoblasts to repopulate, and excessive proliferation of myofibroblasts (13).

Mandibular ORN remains a serious struggle of RT for head and neck cancer (14)(6), with reported incidences ranging from 0.4% to 56% (12), with many cases taking place within the first 3 years after treatment (15). Susceptibility of the mandible as preferable location for development of ORN, compared to the other bones in the head and neck, is based on its higher mineral content and thus a larger sum of radiation dose is absorbed. Also, discarding the ramus and condylar parts, mandibular body, symphysis and parasymphyseal portions are mainly supplied by the inferior alveolar artery, which is fewer and more predisposed to major risk than that in other facial bones (16)(6).

Mandibular ORN commonly manifests with pain, fistula formation, drainage of purulent discharge with local or systemic scattering infection, dysgeusia, changed patterns of mastication and speech and pathologic fracture (13)(15)(6). Dental extraction preceding radiation, poor oral hygiene, total radiation dose, genetic susceptibility, and comorbid circumstances often precede the onset of ORN (10)(14). Mandibular previous surgeries also add further risk (16), however spontaneous ORN reaches 10% to 48% of cases (6).

Therefore, the use of wide-field radiation in mandibular and TMJ area seems to have a negative effect on local tissue, and the potential to harm the integrity of tiny vessels and microvascular anastomoses, which can lead to an advanced stage where tissue becomes necrotic and surrounded by infection. This creates an unsafe environment for implant placement since radiation impairs osseointegration of implants by lowering bone vascularity, which reduces healing potential, (17)(18) and makes it unlikely to respond to conservative treatments e.g., local debridement with antiseptic solutions, and have few restorative options (13)(10)(17). In these cases, the remaining option is radical surgery with segmental resection of involved areas, which may result in significant bone and soft tissue loss, followed by primary reconstruction of large soft tissue, skin and bony defects distressing the framework of the face.

Mandibular and Temporomandibular Joint Reconstruction Options

The mandible provides a characteristic shape of the face and defines the framework of the facial lower third. It plays an essential role in protecting the airway, supporting the tongue, the lower teeth, and the muscles of mastication (19) allowing diverse functions when articulated with the TMJ. The TMJ is an atypical diarthrodial synovial joint that performs translation and rotation movements and links the temporal bone to the mandible condyle. It is composed by the mandibular condyle and glenoid fossa of the squamous part of the temporal bone and divided into upper and lower cavities by an articular fibrocartilaginous disc (20). Their function and form are necessary for the acts of chewing, speaking, deglutition, breathing, and for facial aesthetics, psychological development, and quality of life (21).

The mandibular and TMJ reconstruction aims to restore these functions and facial esthetics, as well as the psychological health of the patients. The reconstructive effort must take into consideration the ablative defect owing to ORN, the underlying pathology, and the needs of each patient (7)(9). It has previously been demonstrated that when reconstructing tissue that has already been subjected to radiation treatment, increased complication rates occur, due to intrinsic poor wound healing in this tissue (12).

Regarding mandibular and TMJ reconstruction, reconstructive modalities with respect to functional and aesthetic outcomes, fibula, iliac, radial forearm, and scapula are the most common osseous donor sites (22), offering characteristics as availability, biocompatibility, adaptability, and lower cost (21). Vascularized bone grafts are widely acknowledged as the most dependable approach for achieving single stage, effective reconstruction of the jaw (13)(11)(21)(7)(23). This has resulted in the utilization of regional and distant surgical flap transfers to offer well-vascularized tissue that has not been compromised by radiation exposure, improving blood supply to the region, facilitating healing, and perhaps extending the viability of the remaining bone. The fundamental benefit of vascularized free bone transfers is that a large amount of bone can be safely transferred while maintaining its own vascular supply. Bone can also be combined with muscle or skin to create a composite repair if necessary. Because the bone loss is frequently accompanied by a considerable soft tissue deficiency, selecting a flap that can be used as a composite flap is critical (14). Nonetheless, in the irradiated jaw, free flap repair is challenging. Choosing the optimal donor site and harvesting a suitable flap necessitates a high level of precision and ability (12).

Non-pedicled flaps, on the other hand, have been proven to be unreliable and to give insufficient blood flow to the irradiation bed. Once radiation also implicates permanent reduced blood supply, non-vascularized bone grafting into irradiated tissue has been associated with minimal success (14).

Options without osseous flaps containing soft tissue only combined with the use of fixation devices such as reconstruction plates are available. Plate fixation and soft tissue restoration without bone can be used to repair lateral mandibular abnormalities. Titanium fixation plates are recently produced as 3-D modeling custom-made or patient precise plates that do reduce the need for sizing or bending intraoperatively, and they achieve premorbid mandibular contour (22). The theory behind this treatment approach is to use a hard plate to bridge and stabilize the mandibular segments in patients who are not interested in undergoing a lengthy and invasive procedure. Despite these advantages, they are not acceptable for complex deformities involving the anterior mandible and those including the condyle unit. In addition, they are not the preferred hypothesis since they have been reported to be associated with a relatively high failure rate, ranging between 50–80% (24), due to an increased risk of fracture, plate extrusion or dislocation and other complications (4), in particular following postoperative RT. These adversities discouraged the resorting of reconstruction plates in patients undergoing severe irradiation as well as those with osteoradionecrosis. In the absence of a bone repair, dental rehabilitation is likewise not viable (22).

When the TMJ needs to be reconstructed, alloplastic reconstruction, although not a usual criteria option applied in cases of mandibular ORN and TMJ ORN, shows some benefits. ATMJR devices do not require a donor site, they can be designed and produced adapting to the anatomical structure of the patient, and they are expected to necessitate decreased surgery time, since there is no need to harvest a distant flap. Also, patients can begin physical therapy right after the ATMJR device is implanted, speeding up the process of mandibular function recovery. According to current research, ATMJR devices have a 10- to 20-year lifetime (21). This is where an important question emerges. If ATMJR devices can be an option in selected cases of head and neck patients, what are the risks associated with radiation therapy and when is the most suitable period to implement radiation therapy, considering its inherent risks? Consequences such as material hypersensitivity (21), prosthesis exposure and infection due to diminished vascularization and fibrosis in the surrounding soft tissue (25) can be related to preoperative RT. As well as infection, exposure, fracture, and a considerably higher dose enhancement in the soft tissue due to the backscatter radiation from the metallic components (26) can be associated with postoperative RT.

1.2 Case Report - Presentation

A 65 years-old male patient was referred to Instituto Português da Face for evaluation and reconstruction of TMJ and mandible. The patient was submitted to several reconstruction surgeries after surgical removal of SCC. He presented with an exuberant crossbite, inability to have proper feeding, achieving only 63 Kg, and a chief complaint of pain.

His medical history included previous surgeries for removal of tonsils and kidney stones and approaching to herniated disc (S1-S2). Other than his cancer history, his medical history was not significant for any other illnesses. His social history was positive for long-term tobacco (1,5 packs/day for 30 years) and alcohol consumption. Nowadays he does not have tobacco habits since quitting in 2018 after SCC diagnosis, and he has abruptly reduced his alcohol consumption.

In the year of 2017, this patient presented with continuous right oromandibular pain, which lead him to search for medical assistance. After biopsy, diagnosis of stage T4N0M0 SCC of the mandible was established. The first surgery was performed, with tumor resection and primary reconstruction with left FFF.

Postoperatively, in April 2018, the patient initiated RT for two months with 60 Gy on the surgical site and more 40 Gy on the right lymph nodes. Because of radiation therapy, surgical debridement was required one month later due to fungal infection.

Afterwards, clinical evaluation revealed mumps owing to RT and exposed mandibular spike. Parotidectomy plus mandibular osteotomy was carried out, followed by reconstruction with osseous integration plate and a gingival closure. A new local infection developed, and the patient was reoperated in 2019 for removal of all material.

A decision was made for a final reconstruction attempt on Instituto Português da Face, where this present work adviser, the main surgeon, proposed a custom-made ATMJR.

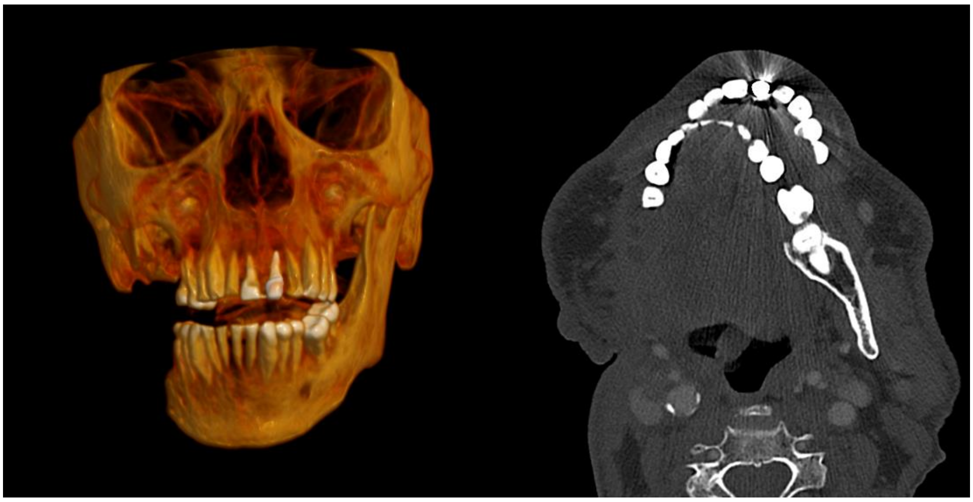

Figure 1 – Initial mandibular defects

Figure 2 – Initial dental closure

Chapter 2

Methods and Materials

2.1 Literature Search Strategy

Literature research was performed up to the February of 2022. The strategy used to browse the articles included the following electronic databases: Pubmed (MEDLINE), SCOPUS and Web of Science, with aim to identify articles about the considerations for the use of ATMJR, published between the years 2000 and 2022.
The word descriptors “temporomandibular joint replacement”, “TMJ prosthesis”, “TMJ alloplastic reconstruction”, “mandibular reconstruction”, “replacement arthroplasty”, “cancer of head and neck”, “radiotherapy”, “mandible” and “titanium” were search within mesh terms. Two general search keys were created to perform this literature research (Table 1).

Table 1 – General Search Key

General Search Keys	
#1	temporomandibular joint replacement
#2	TMJ prosthesis
#3	TMJ alloplastic reconstruction
#4	mandibular reconstruction
#5	replacement arthroplasty
#6	cancer of head and neck
#7	radiotherapy
#8	mandible
#9	titanium
#1 OR #2 OR #3 OR #4 OR #5 AND #6	
#7 AND #8 AND #9	

Relatively to idiom, only articles published in English and Portuguese were chosen. In Pubmed, the search strategy was performed without subject area or type of search restriction, and it was limited to humans with nineteen or more years of age, resulting in 638 articles. In SCOPUS database, 426 articles were obtained using the word descriptors to search within “article title, abstract and keywords” and “Medicine” as subject area of reference. In Web of Science database, 855 articles were obtained using the word descriptors to search within “author keywords”. No articles were included to this list by searching through the article’s references.

2.2 Eligibility Criteria

It was identified articles relevant to develop the considerations for the use of ATMJR, adding up a total of 1919 articles. A broad strategy was used, regarding the types of studies or reviews found. These total number of articles were then submitted to four distinct phases of evaluation.

In the first phase, the inclusion manual criteria to choose the articles through analyzing the titles included, as underlying pathology, the head and neck cancer, the defects affecting the jaw area and the management of osteoradionecrosis and the effects of RT. The ones mainly concerning the pediatric population or not presenting an abstract were removed.

Then, in the second phase, it was conjugated the results obtained through the research in all different electronic databases and eliminated those with repeated titles between databases.

In the last phases, articles were selected based on these eligibility criteria and then screened by abstract reading, following full-text reading and analysis. Those that did not meet the inclusion criteria or had exclusion criteria were removed.

2.3 Study Selection and Data Processing

The first literature research yielded a total of 1919 articles, where 1790 were excluded after the first phase of evaluation for presenting other than the relevant research topics for this review, resulting in 129 selected articles within the three databases. Of these, 23 were duplicated and therefore, eliminated in the second phase of evaluation. From the 106 articles remaining, 42 were excluded in the third phase of evaluation, after abstract reading, and 27 in the fourth one after full-text analysis, summing up a total of 37 eligible articles.

A data base board was created, where all the information gathered was included.

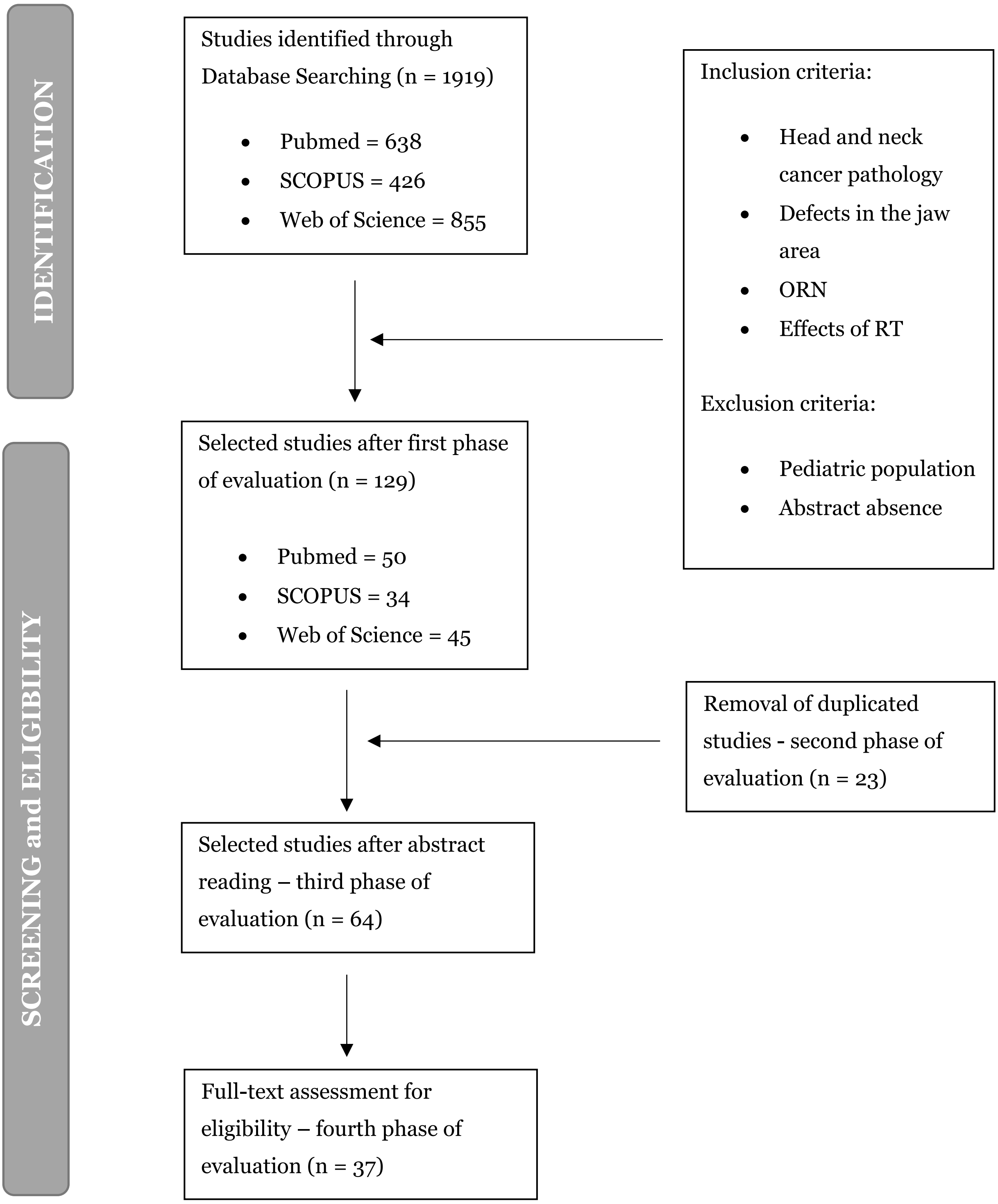

Figure 3 – Flowchart of articles' selection phases

2.4 Patient Selection

This patient was first introduced by this present work adviser. Considering the complexity and outcomes of this case report, the idea of exploring mandibular and TMJ alloplastic reconstructions in head and neck cancer emerged. Once the main theme question was established, the patient was interviewed to access his clinical history and present outcomes. The patient's informed consent was obtained.

Chapter 3

Results

The following articles assessed the preferred material to reconstruct mandibular and TMJ areas after developing mandibular ORN and its main complications.

Table 2 – Characteristics of included studies assessing the preferred material for mandibular reconstruction in patients developing ORN

Author, Year	Follow -up	Population	Diagnosis	Reconstruction Materials	Main complications	Conclusion
Suh et al. 2010 (13)	- 5,5 to 82 months	40 patients	- 38 SCC - 1 Adenoid cystic carcinoma - 1 Epimyoepithelial carcinoma	- 36 Fibula - 3 Latissimus dorsi/serratus anterior/rib - 1 Iliac crest - Reconstruction plates	- 55% (n=22) wound complication - 43% (n=17) hardware infection or extrusion - 25% (n=10) recurrent or residual ORN - 18% (n=7) skin infection or breakdown - 15% (n=6) fistula - 5% (n=2) pathologic fracture - 5% (n=2) donor site complication	Microvascular free flaps are trustworthy for advanced mandibular ORN treatment
Baumann et al. 2011 (15)	- 3 to 72 months	63 patients 88 flaps	-	- 75 Free flaps - 13 Pedicled flaps	- (n=4) flap loss - (n=6) fistula - (n=8 neck infection - (n=2) hematoma	Advanced ORN deficiencies can be successfully repaired with a free flap reconstruction

Chang et al. 2001 (14)	- 5 months to 7 years and 8 months	29 patients	- 19 SCC - 4 Adenocystic carcinoma - 4 recurrent SCC - 1 Mucoepidermoid carcinoma - 1 Salivary duct carcinoma	- 83% (n=24) Microvascular bone plus pedicled flaps - 17% (n=5) Soft tissue	- 14% (n=4) flap loss - (n=2) skin paddle necrosis	The FFF is the first choice of reconstructive procedure for a significant mandibular lesion
Sandel IV et al. 2007 (10)	- 1 to 49 months	14 patients 16 flaps	-	- 2 Iliac crest, - 1 Radial forearm, - 1 Transverse rectus abdominis, - 6 Fibula - 2 Latissimus dorsi with associated rib - 2 Scapula	- 6,2% (n=1) skin paddle breakdown - 12,5% (n=2) fistula - 14,2% (n=2) persistent ORN - 6,2% (n=1) partial flap failure	Free flap reconstruction should be used to treat advanced radionecrosis of the bone or soft tissue.
Celik et al. 2001 (16)	-	27 patients	- SCC	- Free fibula osteoseptocutaneous flap - Inferior genicular artery osteoperiosteal cutaneous flap	- (n=2) partial skin graft failure - (n=1) arterial insufficiency - (n=3) fistula	Once ORN has been established, the optimal treatment strategy is to replace dead bone with a vascularized bone transfer. If the bone defect is bigger than 5cm, a fibula flap reconstruction is the best option.

Lee et al. 2015 (12)	-	368 free flaps	- 83% SCC	215 fibula flaps - 43 iliac crest flap - 31 radial flap - 18 scapula flap - 18 anterolateral thigh flap - 16 latissimus dorsi flap - 12 rectus abdominis flap - 10 serratus anterior flap - 5 humerus flap	- (n=36) fistula -(n=27) wound infection - (n=26) thromboses - (n=2) skin paddle necrosis - (n=26) hardware plate exposure - (n=5) haematomas - (n=2) carotid artery rupture	The fibula is the workhorse free flap for reconstruction in mandibular ORN.

Suh et al. 2010 (13), reviewed 40 patients treated by segmental mandibulectomy followed by reconstruction, after failing to respond to conservative treatment or presenting pathologic fracture of the mandible due to ORN. All patients received RT after head and neck cancer diagnosis, and 12 patients received simultaneously chemotherapy. The most common bone flap used for mandible reconstruction was FFF along with reconstructive plates. There were no cases of flap failure.

Baumann et al. 2011 (15), examined data from 63 patients subjected to debridement of necrotic tissue, due to ORN, followed by free flap reconstruction. At the time of tumor removal, 17 individuals had already undergone flap reconstruction. Patients received radiation therapy and the mean dose was 66.5 Gy. A total of 32% of surgeries resulted in complications, what led to 5% of complete flap loss. A total of 5 flaps were necessary for the salvage of a neck infection, hematoma, and fistula and additional 3 flaps were required to treat fistulas. Late complications such as neck contracture (n=3), recurrent ORN (n=2) and exposed mandibular hardware (n=2) also required surgical procedures.

Chang et al. 2001 (14), assessed 29 head and neck patients who went through resection and reconstruction with free flaps, after failing to respond to conservative treatment or presenting pathologic fracture of the mandible due to ORN. Patients received radiation therapy and the mean dose was 67.4 Gy. The diagnosis of ORN was evaluated by clinical and radiographs findings. Complications occurred in 21% of the patients among the 24 vascularized bone free flaps. There was a loss of 14% free flaps due to venous thrombosis and wound infection, and in 2 of these patients, second free flaps were necessary. Nevertheless, all patients had complete resolution of ORN symptoms, and no recurrence was detected.

Sandel IV et al. 2007 (10), reviewed 14 head and neck patients who presented with radiation-induced tissue injury and, therefore, were treated with microvascular reconstruction, but only 9 patients had mandible involvement. Patients received radiation therapy and the mean dose was 6967 cGy. Within the radiation damaged zone, anastomosis was performed in 14 flaps, whereas 2 flaps were performed outside of that zone. Including the initial reconstruction, 5 patients required several free flaps attempts. Complications described in Table 2 required surgical interventions. There were no total flap failures, and one partial flap failure was salvaged by thrombectomy.

Celik et al. 2001 (16), evaluated 27 patients who underwent tumor resection followed by RT with a mean dose of 5900 ± 1300 cGy and, consequently, developed mandibular ORN. After resection of necrotic bone and soft tissue, patients underwent flap reconstructive procedures. One case of fistula formation required revision operation. There were 2 partial skin grafts failures in the fibula donor site and one total flap failure, due to arterial insufficiency.

Lee et al. 2015 (12), performed a systematic literature search that included 378 free tissue flap transfers used for ORN treatment. Patients received radiation therapy and the mean dose was 67.71 Gy. One quarter of the patients who reported to be treated with adjuvant treatment, received adjuvant chemotherapy. There were 146 sequelae after surgery. A total of 5.4% donor site complications were reported. There were 36 flap failures that demanded revision procedures. Of those that have failed, 5 developed fistulas, 3 turned into infections, 10 developed vessel thromboses, and 2 developed skin paddle necrosis.

The subsequent studies illustrate main complications after vascularized bone flaps, mainly FFF, in head and neck patients who developed ORN due to radiation therapy.

Table 3 – Characteristics of included studies assessing main complications after mandibular reconstruction with vascularized bone flaps in patients developing ORN

Author, Year, Country	Follow -up	Popula tion	Diag nosis	Reconstruction Materials	Main complications	Conclusion
Store et al. 2002 (24)	57 months	16 patients 20 flaps	-	- 5 upper lateral arm flap - 1 radial forearm flap - 4 iliac crest flap - 7 fibula flap - rigid plates	- 3 intraoral or skin exposure with bridging plate failure - 2 exposure and infection with grafts losses	Inserting materials into a damaged tissue bed raises the likelihood of complications and failure.

Etezadi et al. 2013 (11)	-	1 patient	- Tonsillar SCC	- FFF - pectoralis major myocutaneous flap - latissimus dorsi flap	- dehiscence of the wound - heavy scar formation - intraoral soft tissue breakdown	More study is needed to develop an accurate approach for determining the amount of soft tissue excision required in an irradiated patient.

Store et al. 2002 (24), reviewed 16 patients who went through mandibular reconstruction due to ORN. All patients developed ORN after RT with a mean dose of 75 Gy. One of the patients received a second course of RT after tumor recurrence, adding a total of 90 Gy dose of radiation. Overall success rate was 75%. Nonetheless, all 3 bridging plates failed due to intraoral or skin exposure and 2 fibula flaps were lost as a result of dehiscence and infection.

Etezadi et al. 2013 (11), reported a single case of a left tonsillar SCC patient treated with radical resection and neck dissection. Surgery was followed by chemotherapy and RT, with a mean dose of 7000 cGy to the left neck and mandible. The patient presented with exposed necrotic bone in the left mandible, pain, trismus, and intraoral purulent drainage. Debridement of the necrotic bone and segmental resection was performed. Nevertheless, dehiscence of the skin complicated with a fistula led to skin incision breakdown and oral wound. FFF was used to replace the mandibular defect and the skin paddle to closure the wounds. Postoperatively, skin paddle remained workable, but wound dehiscence and intraoral soft tissue breakdown occurred. More 2 remediations of necrotic debridement followed by autologous flap reconstruction were attempted.

The following studies evaluated the viability of alloplastic procedures before radiation therapy for head and neck cancer.

Table 4 – Characteristics of included studies assessing main complications of alloplastic procedures before radiation therapy for head and neck cancer patients developing ORN

Author, Year	Follow-up	Population	Diagnosis	Reconstruction Materials	Main complications
Maurer et al. 2010 (27)	- 6 to 98 months	102 patients	- 63% SCC - 4% recurrence of SCC - 5% ORN	- Titanium reconstruction plates - TMJ prosthesis - Titanium miniplates - Free bone grafts	- 26% oral exposures with inflammation - 5% loss of osteosynthesis screws - 5% plate fracture
Wang et. Al 2005 (28)	- 12 to 58 months	66 patients	- 60% SCC - 3% Adenoid cystic carcinoma - 2% Mucoepi dermoid carcinoma - 1% Verrucous carcinoma	- Titanium plate - Vascularized flaps	- 8% chronic local infection - 6% plate exposure
Pederson et al. 2021 (25)	-	1 patient	SCC	- Total mandibular joint prosthesis	- None

Maurer et al. 2010 (27), assessed 102 patients mainly with head and neck cancer diagnosis. Titanium reconstruction plate was used in 73 patients, 4 of whom required TMJ titanium endoprosthesis. Free bone grafts fixed with titanium miniplates were the chosen materials to reconstruct 29 patients. A total of 53 patients received RT after alloplastic procedures and 9 of those experienced plate exposure. The overall success was 64%. The success rate for patients treated with postoperative RT was 56% (<50Gy) and 52% (>50Gy), compared with 71% of success for patients who did not receive RT.

Wang et. al 2005 (28), evaluated 66 oral cavity cancer patients treated with mandibular resection and reconstructed with vascularized flaps along with titanium reconstruction plates. Postoperative RT was administrated to 34 patients, with a mean dose of 55 Gy. Complications occurred in 29,4% of patients who received RT, compared to 18,8% treated with surgery alone. Therefore, the plate was removed in 20,6% of patients who got RT, compared to 12,5% of individuals who received surgery alone.

Pederson et al. 2021 (25), analyzed one patient diagnosed with SSC treated with total parotidectomy and resection of the mandibular ramus, condyle, and adjacent lymph nodes. A Biomet stock total mandibular joint prosthesis was implanted. Postoperative RT was administered, with a mean dose of 64 Gy to the parotid area and 54.4 Gy to lymph nodes. After 1 year of follow-up, the patient had no sign of recurrence or symptoms and presented a good joint function with a small deviation toward the operated side.

The following studies assessed the feasibility of alloplastic procedures after radiation therapy for head and neck patients.

Table 5 – Characteristics of included studies assessing main complications of alloplastic procedures before radiation therapy for head and neck cancer patients developing ORN

Author, Year	Population	Diagnosis	Reconstruction Materials	Results
Maroulakos et al. 2017 (17)	1 patient	SCC	- Implant-supported fixed mandibular prosthesis	At 3-year follow-up, the prostheses and implants were stable
Elhelow et al. 2018 (29)	1 patient	SCC	- 2-piece magnet-bearing substructure bonded to a silicone prosthesis	At follow-up visits the patient's overall health was good, both physically and mentally, with no recurrences or diseases.
Qassemyar et al. 2017 (23)	2 patients	- Ameloblastoma - SCC	- Titanium prosthesis	The cosmetic and panoramic radiography outcomes were both satisfactory.

Maroulakos et al. 2017 (17), reported a single case of head and neck cancer patient treated with right lateral resection of the mandible and unilateral neck dissection and followed by FFF reconstruction. Prior to the cancer therapy, several teeth were extracted. RT was applied after mandibular reconstruction, with a mean dose of 60 Gy to the mandible and 50 Gy to the lower neck. Due to postradiation and postsurgical complications, such as xerostomia, infection, and reduction range of mandibular motion, an implant-supported fixed mandibular prosthesis was chosen.

Elhelow et al. 2018 (29), described a unique case of a patient with a history of oral carcinoma lesions treated with surgery and radiation therapy. Afterwards, he was newly diagnosed with SCC with mandibular invasion. Tumor ablative surgery and neck dissection were performed. Two reconstruction efforts were made on the patient, the first with latissimus dorsi flap, which was complicated by necrosis and subsequent infection and the second one with pectoralis major myocutaneous flap, which was complicated by plate exposure. A dehiscence bone exposure was noticed and surgically debrided. Then, with an infection-free defect, a 2-piece magnet-bearing substructure bonded to a facial silicone prosthesis was selected.

Qassemyar et al. 2017 (23), analyzed 2 oral cavity cancer patients. One patient had vascular contraindications that ruled out free flap bone surgery. The patient with SCC diagnosis was reconstructed with a local flap and treated with postoperative RT. Due to ORN, the patient developed mandibular pathologic fracture. Due to vascular sequalae, bone free flap was rejected as salvage procedure. Thereafter, both patients were reconstructed with custom-made porous titanium prosthesis.

Chapter 4

Discussion

4.1 First-line Mandibular and Temporomandibular Joint Reconstruction

In mandibular reconstruction, especially if the defect involves the anterior arch, the microvascular fibular flap is still the gold standard (3) (Table 2). The fibula donor site is optimal for the quality of accessible bone (23), because it gives a length of good-quality vascularized bone that resists resorption, has a considerable capacity for contour restoration with multiple osteotomies without compromising its viability, offers soft tissue to restore composite defects and provides anastomosis with a large vessel and offers a double layer of cortical bone, which is suitable for osseointegrated dental implants (7). It is also appropriate for the amount of available bone, because significant quantity of soft tissue defects of the facial/neck skin require more than 12–15 cm of bone (22), and the fibula can be harvested up to 25–27 cm long. Furthermore, the distal section of the fibula can be used to get up to 12 to 15 cm of the vascular pedicle. A lengthy vascular pedicle may provide more recipient vessel possibilities, including contralateral neck vessels, without the need for a vein graft. This is crucial because identifying enough recipient vessels in the ipsilateral neck in severely irradiated necks can be difficult (14).

4.2 Fibula Free Flaps Failure

ORN is a well-known complication after free flaps reconstruction, as shown in Table 10, even when head and neck patients do not experience radiation therapy. O'Dell et al. 2011 (6) report indicates that ORN patients with advanced-stage cancers outnumbered those with early-stage tumors by 4.7 times. The development of ORN is influenced by surgical methods that gain access to the tumor during surgery, radiation dose, and concomitant chemotherapy. Dental extractions done during or after radiation have been linked to an increased incidence of ORN (11) (Table 6).

Table 6 – ORN's risk factors, adapted from (6)

Risk Factors	Increased Risk of ORN
Location of primary tumor	Tongue, floor of mouth, alveolar ridge, retromolar trigone, tonsil
Stage of cancer	Stage III/IV
Dose of radiation	Doses >60Gy
Prior surgery for primary tumor	Mandibulectomies or osteotomies before radiation

Oral hygiene	Periodontal disease, oral hygiene also influences response to treatment
Dental extractions	Extraction after radiation exposure
Alcohol use	Continued use during and after radiation therapy
Tobacco use	Continued use during and after radiation therapy
Nutritional status	Poor nutrition affects wound healing

Also implant survival is linked with RT since implants in non-irradiated bone were more likely to survive, whereas implants in irradiated bone were more likely to fail (18). Thereby, when RT is chosen to be one of the effective treatments along with surgery, major and direst complications arise (Table 2). Despite aggressive mandibular resection of all necrotic and completely unviable bone and adequate vascularized bone for any size defect, 25% patients in Suh et al. 2010 (13) study experienced residual or recurrent ORN in unresected regions of the jaw. Radiation exposure, both pre- and post-operatively, damages the integrity of recipient vasculature and has a deleterious impact on the viability of free flaps (12), as reflected in Chang et al. 2001 (14) study with a total of 14% flap loss, which evidences the necessity of locating suitable recipients. The chronicity of ORN, infection, radiation damage on soft tissue and bone, severe fibrosis, and scarcity of recipient arteries are all factors that contribute to a higher complication risk (15).
As a result, ORN reconstructions are likely to have higher complication rates than primary head and neck reconstructions (15)(13) (Table 7).

Table 7 – Recent studies of vascularized head and neck reconstruction, adapted from (13)

Author	Date	Number of flaps	Flap survival	Prior RT	Reconstructive complication
Nuara et al	2009	300	99,7%	28,7%	17,3%
Pohlenz et al	2007	202	97,1%	40%	25,7%
Suh et al	2003	400	99,2%	37%	19%
Singh et al	1999	200	98%	33%	15%

Although free tissue transfer has proven to be a successful approach of repair, its application in heavily irradiated areas for radiation necrosis has the potential to cause more difficulties and contribute to poorer outcomes. Twelve patients with ORN were repaired with vascularized fibular osteoseptocutaneous flaps. One patient required reexploration due to partial flap failure, one had a fistula, one had partial skin paddle disintegration, and two had recurrence malignancy following repair. Bone transplant survival rates can be minimal, especially in irradiation wounds, with complication rates as high as 80% in certain studies (10). Sandel IV et al. 2007 (10) study concluded that a higher rate of skin paddle breakdown and fistula formation was found in the radionecrosis group, where two patients had persistent ORN that necessitated further therapy with multiple sequential free flaps. In irradiated tissue, the risk of wound infection and associated healing issues is well documented (14). Local wound problems or other microvascular events, such as thrombosis, can result in partial or total free flap loss. Flap failure demands a revision procedure and, in most cases, a secondary free flap from a different donor location. This results in increased morbidity and a longer hospital stay, necessitating attempts to gain a better knowledge of the mechanisms that contribute to flap loss (12).

Consequently, not all patients are good candidates for fibula flap reconstruction (Table 3). The Store et al. 2002 (24) study concluded that all 3 bridging plates failed due to intraoral or skin exposure and 2 fibula flaps were lost as a result of dehiscence and infection. They also deduced that due to increased morbidity from intractable pain and recurring infections associated with trismus, one third of the patients may eventually require a segmental resection. Suggesting that, regardless of the fact that microvascular surgery is now a standard operation, the repair of radionecrotic tissues can still provide some obstacles (24). Hematoma, seroma, venous congestion, and flap skin necrosis were among the complications seen in Etezadi et al. 2013 (11) study with the use of free flaps in the restoration of ORN defects. The rate of flap failure has varied from 4.5% to 14%, with partial or total flap loss necessitating reoperation.
These patients with recent lower extremity trauma or surgical treatments, as well as those with significant peripheral vascular disease affecting the lower limbs, should be assessed carefully (14).

4.3. Alloplastic Temporomandibular Joint Replacement

For several years, autografts for TMJ restoration were performed utilizing autogenous bones. Unfortunately, there are a number of drawbacks and difficulties involved with this operation (30). The necessity for a second surgical site, as well as the extended time of hospitalization, the difficulty of graft setting, malocclusion, and recurrent ankylosis, among other issues that could result in therapeutic failure, prompted the quest for a new surgical option. With this in perspective, numerous alloplastic prosthetic systems for TMJ restoration have been developed recently (20)(31)(32).
Some evidence suggests that using alloplastic joints as an end-stage treatment for certain individuals who have exhausted all other medical or surgical options may have a beneficial outcome (33). When compared to other reconstructive techniques, using a TMJ prosthesis shortens surgical time, minimizes morbidity by eliminating the necessity

for a donor site, reduces inpatient time, and gives instant function without the need for postoperative intermaxillary fixation (32)(20). Swallowing and articulatory function and quality of life have all been found to improve with facial prostheses, and these functionalities are regulated by defect size and radiation therapy history (9). Patients who have had multiple procedures appear to have more uncertain surgical outcomes (33).

Device failures have hampered TMJ prosthetic restoration in the past, including heterotopic bone growth and fibrosis, facial nerve damage, alveolar nerve injuries, neuropathic pain, loss of skin sensitivity, hearing issues, infection, and foreign body formations (33). Massive bleeding, facial nerve paralysis, and inappropriate prosthesis implantation are all possible significant consequences of ATMJR (30)(31). Lack of predictability for surgical revision, prosthesis failure due to loosening of a screw or fracture of the prosthesis due to metal fatigue, narrow fit of stock prostheses, loss of laterality and protrusion movements due to lateral pterygoid muscle disconnection, and high cost are all potential issues with TMJ prostheses (20).

Currently, only three TMJ prosthetic systems are available, TMJ Concepts, TMJ Implants/Christensen, and the Biomet/ Lorenz Microfixation TMJ Replacement System. Biomet/Lorenz Microfixation TMJ replacement system is a stock prosthetic system made up of three main components: an ultra-high molecular weight polyethylene (UHMWPE) fossa (temporal) component; a cobalt chromium alloy mandibular component that replaces the mandibular condyle and is coated with titanium plasma spray for increased bony integration; titanium fixation screws (20). In the TMJ Concepts prosthesis, the TMJ implant mandibular component is comprised of a condylar head fabricated from cobalt-chromium-molybdenum alloy and a mandibular body fabricated from titanium alloy. The TMJ implant glenoid fossa component consists of a fossa bearing fabricated from ultra-high-molecular-weight polyethylene and a mesh backing fabricated from unalloyed titanium (31). When compared to the TMJ Concepts and Biomet/Lorenz systems, the prosthetic TMJ Implants/Christensen system's metal-on-metal interface looks to be a disadvantage. Due to significantly greater quantities of cobalt and chromium in the body, potential difficulties with metal-on-metal prostheses, such as excessive frictional torque that could result in releasing the wear debris, are potentially harmful (20).

Alloplastic prothesis are mainly made of titanium. Titanium possesses strong, corrosion-resistant, ductile, and machinability qualities. Titanium is the metal of choice for the fabrication of the principal components of ATMJR devices because of its biocompatibility, stiffness, stability, ease of handling, and biointegration (5). Another significant benefit is the simplicity with which the condyle may be precisely positioned intraoperatively, as well as the ability to endure the tension associated with the mandible's physiological function (19).

Postoperative Radiotherapy Complications

Reconstruction titanium plates and prostheses are prone to infection and exposure, especially after postoperative radiation therapy (Table 4), since radiation makes delayed reconstruction more difficult due to the area's permanently reduced blood supply, which can lead to ORN. Even though the immediate restoration of joint function is possible with the implantation of a whole joint prosthesis, the danger of prosthesis exposure and ORN due to diminished vascularization of overlying soft tissue and fibrosis should be considered (25).

Some experiences revealed that implanted metals can induce backscatter radiation in RT, resulting in a dose increase at the bone-metal and tissue-metal interfaces on the beam entering side. Radiation-induced erythema, mucositis, and other salivary gland problems are more prevalent in these tissues. Research shows that backscattering just adjacent to the metal causes an increase in radiation dose in front of the metal (26) and decreased dose behind the metal over 2 to 3 mm (28).

Maurer et al. 2010 (27) revealed a much lower success rate following radiation, as shown in Table 8:

Table 8 – Results after postoperative RT, adapted from (27)

Radiation	Number of patients	Success rate (%)
None	49	71
<50 G	9	56
50 G or more	44	52

Although it is claimed that using adjuvant RT increases the risk of problems and plate failure, Wang et. al 2005 (28) demonstrated that postoperative RT had no effect on the titanium plate's osseous integration, risk of complications or plate failure. Of those who received RT, 29.4% had complications compared with 18.8% treated with surgery alone (Table 9):

Table 9 – Compared complications of Surgery + Postoperative RT and Surgery alone, adapted from (28)

Complication	Surgery + Postoperative RT (n=34)	Surgery alone (n=32)	Total (n=36)
Infection and plate exposure	4	2	6
Local infection alone	3	2	5

Plate exposure alone	2	2	4
Plate loosening	1	0	1
Total (%)	29,4%	18,8%	24%

TMJ total joint prostheses could be a viable alternative for cancer patients undergoing reconstruction, even if adjuvant radiation therapy is required. Pederson et al. 2021' (25) patient reconstructed with Biomet stock total mandibular joint prosthesis revealed an uncomplicated surgical course, with appropriate soft tissue healing and no infection. The patient's joint function was good, with an adequate mouth opening and a minor deviation toward the operated side, but no local symptoms in the jaw.

Preoperative Radiotherapy Complications

Effects of RT on bone and soft tissues are well-known. The biological ability of bone to remodel, heal, and turnover are affected in irradiated tissues (29). ORN can lead to bone exposure and necrosis through a wound that extends beyond skin or mucosa and makes it unlikely for TMJ replacement to survive.
Post radiation therapy in Maroulakos et al. 2017 (17) study caused postsurgical sensory impairment in the patient's thin mucosa, xerostomia and carious infection, the tongue movement was compromised, and TMJ evaluation exhibited a lower range of mandibular motion without pain.

Despite these discoveries, the SCC patient of Qassemyar et al. 2017 (23) study was able to perform normal function without pain or noticeable scarring, after 3D custom-made porous titanium prosthesis.

Before surgery, the patient's tissues must be evaluated, with special attention paid to the symphysis region, which is more vulnerable to such exposure. For patients who cannot have bone free flaps, the use of an alloplastic mandibular body replacement is a novel and intriguing option (Table 5).

4.4 Case Report – Resolution

The idea of a custom-made ATMJR emerged when several attempts of TMJ replacement failed. To pursue this reconstruction strategy, a right hemimandibular resection was accomplished. Afterwards, a custom-made TMJ Concepts prosthesis with a titanium mesh was placed in the mandibular and TMJ area.
After 2 years of follow-up, this patient presents remarkable improvement of facial aesthetics, mandibular motion, pain levels and overall quality of life. Nowadays this

patient is able to feed himself with a progressive diet, which enabled him to return to his normal weight, progress in his utterance is also noticeable, even with only one session of speech therapy and physical therapy exercises at home, and almost back to normal life was achieved.

Nonetheless, some minor complications were detected. Cervical lateral movements are restrained in certain angles, post-surgical facial neurite complication affects his equilibrium and consequently influences his ability to walk, and complaints of pain worsening with emotions are also reported.

This patient's opinion concerning his function and aesthetics outcomes is that ATMJR was a major success.

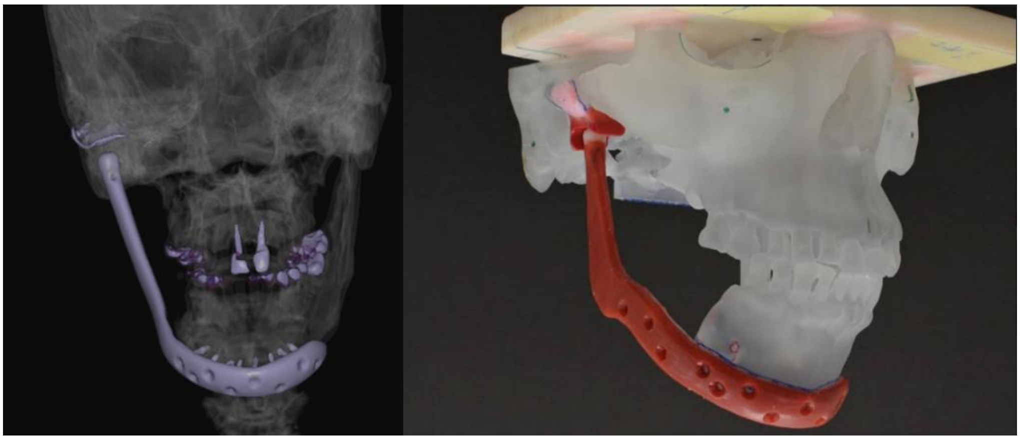

Figure 4 – Alloplastic TMJ prosthesis

Figure 5 – Final dental closure

Chapter 5

Conclusion

Ablative surgeries followed by RT in head and neck patients lead to major complications due both facial function distortion, infection and ORN. RT can be an effective but harmful treatment for these patients. Post RT bone and soft tissue necrosis can be associated with reduced blood supply, implicating further complications in head and neck reconstruction and unknown effects with different materials have been reported, for example dental implant survival (34), since it is not advised to perform dental implants on irradiated tissues when RT is used with a mean dose of 60 Gy (17). Considering the defects after surgical resection and RT, mandibular reconstruction must be performed, aiming to restore the patient's function and aesthetic. FFF is the gold standard reconstruction option for these cases. Nevertheless, when FFF fails its purpose, other reconstruction options must be considered.

ATMJR titanium devices, although not a consensual option in RT patients, can be designed to adapt to the exact anatomical structure of the patient and be a viable option in these end-stage disease patients.
Radiation's effects before and after alloplastic reconstruction are not sufficiently described in the literature. There is little experience with using alloplastic prostheses to design patient-specific mandible substitutes for those who aren't candidates for vascularized bone flap surgery. Although the titanium device can be a feasible alternative for improving mastication, deglutition, speech, and aesthetics rehabilitation, its overall safety when interacting with RT remained to be established. Some complications such as infection and exposure, mostly in postoperative RT, were described in this present work. Equally pre- and postoperative RT had both great and unpleasant results, and it cannot be chosen as a preferable strategy on when RT must be performed. Finally, the decision between a second vascularized bone graft with its inherent morbidity consequences and an ATMJR with its intrinsic complications due to pre- or postoperative RT, is up to the patient's and the surgical team's decision.

Regarding the case report, this patient presents a successful case of ATMJR after several attempts of surgical reconstruction, including FFF, and preoperative RT. Bearing in mind that this is a new and insufficiently experienced surgical approach, this patient's outcomes can be the first step to develop further investigations and experiences when all the other salvage alternatives have failed.

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Appendix

Table 10 – Characteristics of included studies assessing the main complications after mandibular reconstruction in head and neck patients

Author, Year, Country	Follow-up	Population	Diagnosis	Reconstruction Materials	Main complications
Gemert et al. 2018, Netherlands (2)	- 2 to 148 months	76 patients 79 Flaps	- 74 SCC - 1 Chondrosarcoma - 1 Osteosarcoma - 1 Osteoradionecrosis - 1 Osteomyelitis	- Titanium fixation plates - FFF	- 8 arterial insufficiency - 3 hematomas - 5 skin Island necrosis - 9 wound dehiscence - 14 infection - 4 plate fracture - 4 ORN - 1 nonunion
Zender et al. 2012, USA (35)	-	65 patients	• Advanced oral cancer (T4) - 94% SCC - 1% Verrucous - 3% Mucoepidermoid - 2% Adenocarcinoma	- 83% FFF - 9% Radial - 8% Iliac	- 15% wound breakdown - 15% hardware issues - 11% fistulas - 14% osteomyelitis/ORN - 3% hematoma - 8% cellulitis
Walia et al. 2021, USA (36)	- 2 to 123 months	266 patients	- Malignant tumor - ORN - Other not specified	- 66,2% FFF - 16.5% Scapula - 19 Osteocutaneous radial forearm flaps - 7 Anterolateral thigh flaps - 12 Fasciocutaneous radial forearm flaps	- 11,3% (n=30) wound dehiscence - 9,4% (n=25) fistula - 8,6% (n=23) / 4,51% infection - 9% (n=24) arterial insufficiency - 26,7% plate exposure - 7,14% ORN

				- 1 latissimus dorsi flap - 4 rectus abdominis flaps	
Swendseid et al. 2020, USA (37)	- 23 months	238 patients 250 Flaps	- 70% (n=177) Cancer - 20% (n=49) ORN - 10% (n=24) Benign cyst or trauma	- 80% (n=202) FFF - 11% (n=27) Radial forearm free flap - 9% (n=22) Scapula free flap	- (n=15) skin paddle necrosis - (n=13) flap failure - (n=15) ORN - (n=10) donor site morbity - (n=32) infection - (n=42) wound breakdown
Parise et al. 2018, Brazil (3)	-	43 patients	• 58,1% (n=25) Malignant lesions - 60% (n=15) SCC - 8% (n=2) cases of Fibroblastic osteosarcomas, Chondroblastic osteosarcomas, Ewing's sarcomas, and Fibrosarcoma, in each person - 4% (n=1) cases of Mucoepidermoid carcinomas and Osteosarcomas, in each person • 35,9% Benign lesions - 53% (n=9) Ameloblastomas - 23% (n=4) Myxomas - 12% (n=2) ORN • 6% (n=1) cases of Juvenile ossifying fibroids and Bone dysplasia in each person	- Microvascularized fibula flap - 5% (n=2) reconstruction plates - 95% (n=41) miniplates	- 2,3% (n=1) loss of FFF - 9,3%(n=4) exposure of miniplates - 2,3% (n=1) resorption of the flap - 6,9% (n=3) intraoral fistulas - 2,3% (n=1) pathological fractures - 9,2% tumor recurrence, infection, seroma and trombocytopenia