Adaptive Staged Surgical Protocol for Prosthetic Reconstruction for Osteoradionecrosis of the Jaws (ORNJ) and Comparison of its Functional Outcomes with Free Fibula Flap Reconstructions

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Abstract

Background: Reconstruction of full thickness mandibular defects with disarticulation due to ORNJ has traditionally been accomplished using vascularized free fibula flaps (FFF). But not all patients are candidates for FFF. A two-staged protocol (SPR) was developed taking into account the challenges of the surgical site and comorbidities of the patient utilizing custom prosthetics.

Methods: This study retrospectively analyzed 16 patients (13 males, 3 females) who developed stage III ORNJ subsequent to radiation and molar extraction (FFF n=4, SPR n=12). Postoperative surgical complications, maximal incisal opening (MIO), Pain Visual Analog Scale (VAS) at the different end points for the SPR and FFF group were analyzed.

Results: All patients demonstrated decrease in pain and increased mouth opening. Comparing Stage 1 SPR and FFF patients, there was a significant difference in pain, but not in function (1.89 ± 1.05 vs 0.25 ± 0.5, $p<0.01$ and 28.44 ± 8.10 vs 24.75 ± 1.26 $p>0.20$). After completion of the second stage surgery, there were significant differences in function, but not in pain in comparison to FFF patients (24.75 ± 1.26 vs 36.5 ± 8.37, $p<0.026$ and 0.25 ± 0.5 vs 0.17 ± 0.41, $p>0.779$).

Conclusion: Reconstruction of the temporomandibular joint with a custom prosthesis contributes to the significant improvement in function in the stage 1 SPR and in pain in stage 2 SPR versus the FFF.

Keywords: Osteoradionecrosis, Free fibula flap, Hemimandibulectomyt

Introduction

Head and neck cancer is a devastating disease with high rates of morbidity and mortality. Although there has been a recent upward trend in its occurrence in younger populations (HPV positive tumors - tumors positive for oncogenic forms of the human papilloma virus type 16), the majority of patients are of an advanced age and often burdened with multiple medical co-morbidities [1-3]. The negative sequela of adjunctive treatment of head and neck cancer are progressive and lifelong, the worst being osteoradionecrosis of the jaws (ORNJ). The most usual site of ORNJ is the posterior mandible due to a common need to extract a symptomatic posterior molar that lies in affected bone within the radiation field. Our clinical experience reveals that this is particularly true in patients treated for tonsillar and base of tongue tumors. Characteristics of Advanced/ Stage III ORNJ include a wide area of chronic, necrotic, infected bone, surrounding soft tissue that is often cellulitic, fibrotic and avascular, with intraoral and sometimes extraoral tissue breakdown and communication. ORNJ is a chronic disease process that initially develops over months after the surgical trauma and can fester over years of observation and conservative treatment, making the surgical field extremely compromised. Given these challenges, multimodal treatment includes a combination of medical and surgical therapies; hyperbaric oxygen (HBO), pentoxyphylline/Vitamin E and IV antibiotic therapy, are aimed to optimize the surgical field, which is followed by resection and reconstruction. Reconstruction of full thickness mandibular defects has traditionally been accomplished through single or double-barreled vascularized free fibula flaps (FFF) [4]. The FFF technique does two things: 1. It brings vascularized tissue to an otherwise poorly vascularized wound bed and encourages establishment of boney continuity and 2. FFF offers the chance for functional rehabilitation with dental implants, this being most true for cases that are being immediately reconstructed after cancer clearance. However, this reconstruction technique is challenging in ORNJ patients because the surgeon relies on the stability of a reconstruction plate secured to the distal and proximal segments of the mandible to support the fibula. Unfortunately, in ORNJ cases, the proximal segment is often compromised (chronic radiation injury) to the point where there can be plate/screw separation from the bone or fracture of the plate secondary to lack of fusion of the fibula to the proximal or distal segments. Further, achieving dental reconstruction is often not practical or realistic in ORNJ patients due to out-of-pocket costs, the uncertainty of implant integration, or restorative difficulties such as limited opening (fibrosis from radiation) or difficulties in peri-implant soft tissue management.

The SPR treatment protocol includes resection, an intermediate reconstruction using a custom bent stock plate and stock fossa prosthesis, to allow for soft tissue closure and then placement of a final custom extended fossa/eminence, tmj/ramus/body prosthesis (TMJ Concepts, Ventura CA). The SPR considers the bone proximal to the necrotic bone or pathologic fracture to be greatly affected due its proximity to the field of radiation and rather than rely on dead bone to support a reconstruction, the SPR assumes it is compromised and prescribes disarticulation of the joint and removal of the entire hemimandible. Experience has dictated that removal of the compromised proximal segment, including the joint, is more successful than leaving it and attempting to include it in the reconstruction. Further, in cases of full disarticulation, the SPR offers clear advantages in reconstruction of the TMJ, because both the temporary and final custom prosthesis are merely extended versions of the prosthetics used in traditional

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TMJ reconstruction strategies, offering greater fidelity to the form and function of the TMJ than can be achieved by any other reconstructive method.

The SPR is realistic. The end goal is for placement of a custom prosthesis. But occasionally, that may not be achievable due to infection, plate exposure or exacerbation of medical comorbidities. In the cases where further surgery is not possible, then the protocol is designed so the patient can remain in the intermittent reconstruction and remain functional, aesthetic and pain free. In other instances, it is necessary to remove the hardware altogether and allow the patients to function free (due to plate exposure and infection). The limited times this has been done, it has been by patient choice, further reconstruction options are always offered. Our experience with the protocol tells us that being flexible with this population of patients is the best way to manage them.

The main driver of patients seeking out treatment for stage III ORNJ is pain, which spikes after a pathologic fracture. Doing the resection resolves the cause of their pain. So, the choice for reconstruction is then based on determining which technique leads to the most improved quality of life and function. We believe that better function is achieved with contemporary custom TMJ reconstruction techniques compared to the FFF.

The purpose of this manuscript is to introduce an adaptive staged treatment protocol aimed to clear the compromised bone and provide for an as stable and functional result as possible. To help the reader compare the utility of this approach, this manuscript retrospectively evaluates and compares the surgical results in a group of 16 patients with ORNJ who underwent either SPR or FFF reconstruction between November 2005 and May 2018 at two institutions. This introduction is not meant to be a rigorous scientific comparison between the two techniques, but only to put the two approaches side-by-side, so that the reader can appreciate the rationale used to develop the SPR.

Adaptive Staged Protocol

An adaptive staged protocol *(Table 1)* allows for resection of the involved mandible, healing of the intraoral and extraoral sites over temporary hardware, and final placement of a customized extended TMJ prosthesis, thus ensuring that the definitive prosthesis is placed in a healthy and sterile environment. This protocol anticipates complications and provides a contingency plan should one step of the surgical process fail. Being able to adapt and have a fallback treatment is necessary in this group of patients that often present with multiple medical comorbidities and locally compromised tissue beds. The three possible endpoints achievable with this protocol have all been found to be functional, esthetic and leave patients with an optimized quality of life given the situation [5].

The Staged Prosthetic Reconstruction (SPR) Protocol

Pre-surgical procedures

Execution of the SPR protocol is initiated well before the

Table 1. *The Prosthetic Reconstruction (PR) algorithm.*

Optimization	**-Optimization of comorbid conditions (CHF, diabetes, etc.)**	**Variable time frame**
Pretreatment and Surgical Planning	-HBO therapy	30 HBO dives
	-Vitamin E, Pentoxifylline (optional adjunctive therapy)	
	-Antibiotics, if needed	PEG placement 1 week prior to surgery
	-PEG tube placement	
	-VSP session to design the pre-bent plate	
Stage 1: ORNJ Resection and Intermediate Reconstruction	-Arch bar system	1 OR Session
	-NIM electrodes for facial nerve monitoring	
	-Disarticulation of joint	
	-Resection of ORN	
	-Closure of oral communication	
	-Placement of a stock polyethylene Biomet TMJ fossa prosthesis	
	-Placement of pre-bent plate and temporary add-on condyle	
	-Pectoralis major flap to add soft tissue for closure over the plate, if needed	
	-Short-term maxillomandibular fixation (MMF) to prevent dislocation	
Healing Phase	-Infectious Disease consultation	6 weeks of IV antibiotics
	-PICC line placement	
	-Additional HBO	
	-Physical therapy	
	-No food by mouth	
	-Obtain new CT	
	-Design TMJ Concepts extended-ramus prosthesis	
Stage 2: Placement of the Custom Extended-Ramus TMJ Prosthesis	-Explantation of initial pre-bent reconstruction plate with add-on condyle, and Biomet fossa	1 OR Session
	-Placement of TMJ Concepts custom joint prosthesis	

patient is taken to the operating room. After a diagnosis of advanced stage mandibular ORN is confirmed, patients are typically scheduled for hyperbaric oxygen [6]. Most patients receive 30 dives preoperatively, but this is left to the discretion of the HBO physician. Vitamin E and pentoxifylline are given preoperatively to further optimize blood flow and healing capabilities of the tissue bed [7,8]. The PTX-Vit E protocol takes advantage of the antioxidative actions of Vitamin E, while pentoxifylline has been shown to significantly decrease the duration of non-healing ulcerations by increasing erythrocyte flexibility and causing vasodilation, both of which improve the red blood cells ability to navigate the fibrotic vasculature and increase the delivery of oxygen to the irradiated tissue. The combination of PTX-Vit E demonstrates drug-synergy and creates an overall anti-fibrogenic environment and has become an accepted treatment adjunct for ORNJ, but this is without general consensus because these studies are insufficiently powered to recommend them as definitive [9-11]. A typical regimen is Vitamin E 400 IU BID and pentoxifylline 400 mg BID. To this regimen, an antibiotic with good bone penetration may be added if purulence is noted. An oral antibiotic with high bioavailability is an alternative to parenteral therapy due to its simplicity, but the surgeon should also be guided by cultures, when available. A CT scan with fine cuts (no greater than 0.625 mm slice intervals) is ordered to prepare for surgery. If dentate, the patient is instructed to bite teeth together in the best occlusion possible for the CT scan. If the patient cannot achieve normal intercuspation (due to pathologic fracture, for example), dental impressions (traditional or digital) will be needed so that the dentition can be accurately scanned and integrated into the CT scan. The patient's occlusion can be set during the virtual surgical planning session. To ensure appropriate healing of intraoral wounds/communications, patients are made NPO postoperatively to avoid food contamination within the wound, thus they often require percutaneous endoscopic gastrostomy (PEG) tube placement to allow for adequate nutrition during this phase of treatment. Arrangements for PEG occur within 1 week prior to surgery. Lastly, due to co-morbid conditions (hypertension, diabetes, CHF, etc.), patients are sent to their primary care physician to ensure optimization of their health prior to undergoing surgery.

Virtual surgical planning

Virtual surgical planning (VSP) is done to establish resection margins, set the occlusion (if normal pre-surgical occlusion cannot be achieved) and plan for the fabrication of an initial customized pre-bent reconstruction plate. During VSP, mirroring the contralateral mandible is a mistake. The poor quality of the irradiated soft tissue envelop and overlying skin means that it is best to shorten the length of the ramus, avoid recreation of a mandibular angle, and angulate the plate more medially as viewed in an A-P plane, to help ensure a tension-free closure of the neck *(Figure 1)*.

The goal of the VSP for the first-stage of the PRP is to temporarily replace the condyle and fossa, to achieve a functional joint complex and provide stabilization of the remaining distal mandibular segment. The position of the temporary condylar head is planned along with the pre-bent reconstruction plate via VSP. The temporary condyle should articulate against a stock, ultra-high molecular weight polyethylene (UHMWPE) fossa prosthesis (Zimmer Biomet, Warsaw, IN, USA, off label). The UHMWPE fossa acts as a platform for the prosthetic condylar head articulation, and functions as an ideal "temporary spacer", saving room for a future, custom TMJ fossa prosthesis at Stage 2 surgery. The spacer prevents soft tissue collapse and scar tissue formation in the space once occupied by the condyle, so that little tissue resection is required when the somewhat larger, but similarly shaped TMJ Concepts custom fossa prosthesis (TMJ Concepts, Ventura, CA, USA) is implanted. Typically, the add-on condylar head should be positioned approximately 6 mm below the height of the center of the natural fossa, to accommodate for the measured thickness and the bone recountouring of the eminence that is necessary when placing the stock fossa component *(Figure 1)*.

Most often, a second VSP session is done to plan for stage

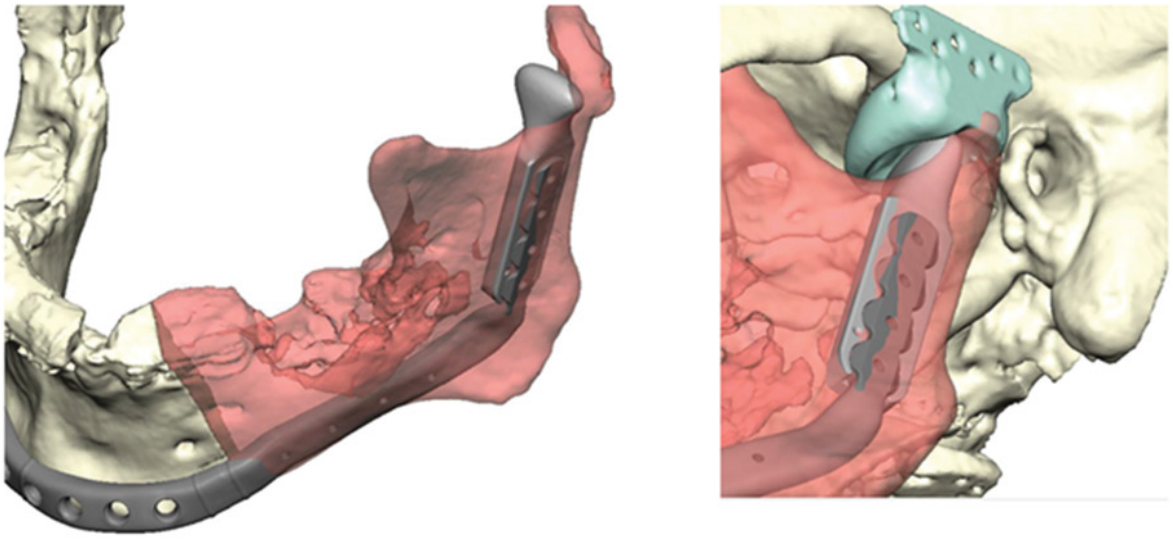

Figure 1. *(1A)Virtual surgical planning showing the placement of the reconstruction plate within the volume of the native mandible; (1B) Virtual surgical plan shows the condylar head placement short of the native fossa to allow for mating with the fossa prosthesis.*

2, removal of the temporary plate/fossa prosthesis and design, fabrication and placement of the custom reconstruction prosthesis. Similar methods are used as above to ensure the occlusion is transferred to the CT scan with high fidelity and once symmetry is satisfied, a medical model is printed to allow for the fabrication of the custom prosthesis.

Stage 1 Surgery (ORNJ resection and intermediate reconstruction, including condyle and fossa): Stage 1 surgery is directed toward resecting the ORN affected mandibular bone. If there is a tooth present at the anterior extent of the planned segment for resection, the case is started by removing that tooth to facilitate the osteotomy. If teeth are present, an arch bar system is placed to stabilize the jaw during fixation of the pre-bent plate and to allow for a short period of maxillomandibular fixation (MMF) after surgery to prevent early mandibular dislocation. The authors prefer the new generation hybrid arch bars because the anchorage is derived from screws in the bone, instead of wires around the teeth. Nerve integrity monitoring (NIM) electrodes are placed to allow neuromonitoring during dissection.

A pre-auricular incision is marked out and the dissection is carried out to expose the TMJ. With the condylar head and neck exposed, an initial condylectomy cut is made. The condylar head is dissected out followed by removal of the articular disc. This surgical site is packed off and attention is turned toward the ipsilateral submandibular region. A standard Risdon incision is marked with the length of the incision depending on the extent of the mandibular resection. Once the mandible is adequately exposed, the bony cut at the anterior extent of the resection can be made. A second osteotomy is made from the sigmoid notch inferior down to a point 2-3 cm anterior to the mandibular angle. Dividing the remaining proximal mandible in this manner eases removal and detachment of the temporalis muscle from the coronoid process.

The bone specimen is sent to Pathology and a representative piece is also sent to Microbiology for culture. With the resected bone removed, the extraoral surgical sites can be draped off and the surgeon can enter the oral cavity to repair any intraoral communications. The poor tissue surrounding the communication must be excised or freshened prior to achieving secure, primary closure with a long-lasting suture material. Following soft tissue closure, the patient can be placed in MMF with bands. Prior to placing the pre-bent reconstruction plate, it is highly recommended to reinforce the underside of the intraoral closure with a piece of supportive, viable tissue that is sutured into place. The authors positive experience is with 2 × 4 cm or 3 × 6 cm cryopreserved umbilical cord membrane, Stravix (Osiris Therapeutics, Inc., Columbia, MD, USA). It is composed of the umbilical amnion and Wharton's Jelly, and retains the extracellular matrix, growth factors, and immuno-privileged endogenous neonatal mesenchymal stem cells, fibroblasts, and epithelial cells of the native tissue. Next, the articular eminence is osteotomized and UHMWPE fossa prosthesis is placed and secured with one screw. With this in place, the pre-bent reconstruction plate with the temporary add-on condyle can be fixated. If the customized fossa aligns well over the condyle prosthesis, then the fossa is secured with a total of 4 screws. If the fossa position needs to be altered because the condylar head is not articulating well against the fossa, it can be done easily by removing the single screw, shifting the fossa prosthesis, and re-stabilizing with 4 screws. After checking for a stable and reproducible occlusion, the wound is closed in typical layered fashion. Another piece of Stravix placed on top of the bone plate but under the tissue closure gives the surgeon more confidence that the wound will not break down. Additional tissue is usually not necessary to achieve primary closure at the submandibular incision, given the previously stated plate design considerations. If incision breakdown occurs, then it is managed with wound healing dressings with the assistance of a wound healing nurse specialist and time. The whole function of this first stage is to achieve closure of the intraoral and extraoral wounds to allow for final prosthesis closure in a healthy stable tissue bed. MMF is maintained with elastics for dentate patients for at least one week to prevent early dislocation of the condylar prosthesis.

Healing phase: Within one post-operative day, an Infectious Disease consultation is obtained and a PICC line is placed. The patient is started on a 6-week course of home-based IV antibiotics based on the culture report. Nutrition is delivered by PEG tube feeds and the patient is only allowed water by mouth. Oral hygiene is important, and many surgeons recommend chlorhexidine rinses, in addition to brushing, during this time. Additional HBO dives are arranged, usually 10 or more. During post-operative visits, examinations should include careful surveys of all incisions and the intraoral communication repair. Once complete healing of the intraoral wound is apparent, the PEG tube is discontinued and the patient may begin a soft diet. As the patient progresses with post-operative healing, a new maxillofacial CT scan is obtained to begin the planning for fabrication of a TMJ Concepts custom extended-ramus mandibular prosthesis and fossa component. The patient is now ready for Stage 2 surgery.

Stage 2 Surgery (Placement of the custom extended-ramus TMJ prosthesis): Stage 2 surgery is directed toward explanting the intermediate hardware and fossa component after complete intraoral closure is obtained and replacing it with a TMJ Concepts custom extended-ramus mandibular prosthesis and fossa. Arch bars are placed at the start of the procedure to facilitate MMF. The pre-auricular and submandibular incisions are re-opened and the dissection is carried out to expose the existing hardware. Once the plate with connected condylar head is removed, the fossa component stock can be removed and replaced with the TMJ Concepts custom fossa component. With the fossa in place, the extended condylar component can be placed and fixated to the mandible. The occlusion is checked to ensure it is stable and reproducible. The patient is placed into MMF with elastics and all incisions are closed in layered fashion.

One reason for designing a staged surgical protocol is the fact that the population that suffers from ORNJ is often burdened with severe medical co-morbidities. Stage I accomplishes the first goal of resection of the affected bone and closure of the intraoral wound. This is accomplished with a custom reconstruction plate and temporary fossa/eminence prosthesis. If medical conditions dictate, the reconstruction process can stop there and the patient will be left whole and

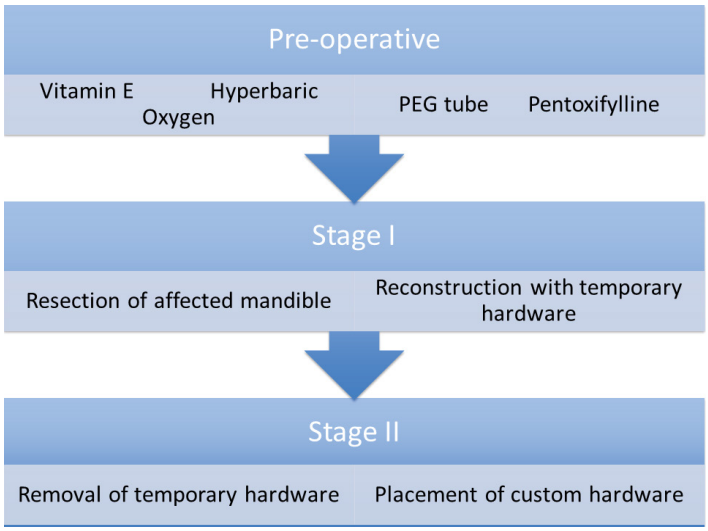

Figure 2. *SPR protocol is designed with 3 stopping points: 1. Stage II with full custom prosthetic reconstruction; 2. Stage I, for medical reasons or other challenges with custom temporary reconstruction plate; 3. "Free-swinging" is a reversal of stage I in setting of plate exposure or infection.*

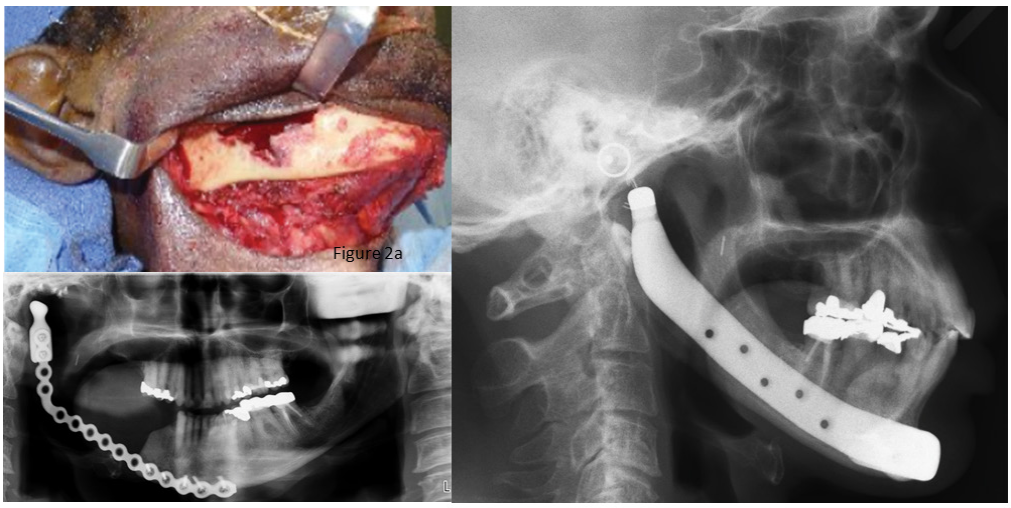

Figure 3. *The full SPR protocol. Stage I consists of the resection and temporary reconstruction plate. Stage II is the removal of the temporary reconstruction plate and placement of the final customized, extended fossa/eminence and condylar/body/symphyseal units. Occasionally, due to medical problems or patient intolerance the reconstruction protocol is ended at stage I. Though it is desired to proceed to stage II when possible due to concerns about long term durability of the temporary reconstruction plate.*

functional. However, it is preferable to proceed to the final customized prosthesis for long-term strength and stability in Stage II. Occasionally, there will be cases where the temporary reconstruction in Stage I has to be reversed due to plate exposure/infection or other. In this case, the patient is left swinging, a state that has also proven to be functional and stable. The possible end points of the SPR are depicted in *(Figure 2)* and illustrated in *(Figure 3)* as below:

- Two-stage prosthetic reconstruction with custom prosthesis.
- One-stage intermediate reconstruction with pre-bent plate, add-on condylar prosthesis, and stock Biomet TMJ fossa *(Figure 3)*.
- "Free Swinging" mandible with no reconstruction.

Clinical Experience

Materials and methods

This study followed the Declaration of Helsinki and was in accordance with US and Italian Laws. Appropriate Institutional Review Board approval was granted for this retrospective study. The procedures were approved by the Institutional Review Boards of University of California San Francisco, San Francisco, CA (13-12140 T) and the University of Milano Bicocca, Milano, IT (IRB02–2010 Doc. 5-2010). All patients were given a thorough explanation regarding the surgical procedures and signed a written consent form.

Patient sample

Sixteen adult patients (13 males, 3 females mean age 68.5) who had a history of oral squamous cell carcinoma (SCCA) or adenoid cystic carcinoma (ACC) and who subsequently developed ORNJ from radiation therapy and had undergone mandibular ORNJ surgery from November 2005 to May 2018 *(Tables 2 and 3)*, were examined during an annual or semi-annual clinical follow-up appointment. ORNJ was initially staged for each patient following the Notani Classification [12] in *(Table 4)*. All patients had at least 10 occluding teeth (natural or prosthetic).

Table 2. *Prosthetic Reconstruction (PR) group: Patient characteristics.*

Gender	Age at Stage 1	ORN Stage	Stage 1 Surgery	Date of stage 1 surgery	Stage 2 Surgery	Time between Stage 1 and Stage II	MIO (mm) prior to Stage 1	MIO (mm) after Stage 1	MIO (mm) after Stage 2	VAS prior to Stage 1	VAS after Stage 1	VAS after Stage 2	Case type (follow-up length as of May 2019)
M	56	Stage 3	Resection including condyle, reconstruction plate	Nov. 2005 (outside facility)	Custom TMJ-extended ramus prosthesis	42 months	10	12	29	9	4	0	Stage 2 completed (follow-up 23 months, died)
M	69	Stage 3	Resection sparing condyle, reconstruction plate	Oct. 2012	Custom TMJ-extended ramus prosthesis, pectoralis flap	8 months	22	34	46	9	3	0	Stage 2 completed (follow-up 71 months)
F	86	Stage 3	Resection sparing condyle, reconstruction plate	Aug. 2013	Plate and condyle removed 14 months later (infection)	37 months	22	29		1	0		Swing only (follow-up 29 months, died)
M	73	Stage 3	Resection including condyle, reconstruction plate	Dec. 2014	Not planned due to medical history	-	18	34		5	1		Stage 1 only (follow-up 53 months)
M	71	Stage 3	Resection including condyle, no plate	Mar. 2015 (outside facility)	Custom TMJ-extended ramus prosthesis	7 months	12	24	44	8	1	0	Stage 2 completed (follow-up 43 months)
M	53	Stage 3	Resection including condyle, reconstruction plate	Apr. 2015	Custom TMJ-extended ramus prosthesis	13 months	14	21	25	8	2	1	Stage 2 completed (follow-up 8 months, died)
M	64	Stage 3	Resection including condyle, reconstruction plate	42125	Plate removed 1 week later (infection)	-	19	34		9	0		Swing only (follow-up 6 months, moved from area)
M	78	Stage 3	Resection including condyle, reconstruction plate	Nov. 2015	Plate removed 4 months later (infection)	-	18	47		2	0		Swing only (follow-up 38 months)
M	74	Stage 3	Resection sparing condyle, reconstruction plate	Apr. 2016	Not planned due to medical history	-	15	34		9	1		Stage 1 only (follow-up 31 months, died)
M	61	Stage 3	Resection including condyle, reconstruction plate	Dec. 2016	Custom TMJ-extended ramus prosthesis	8 months	22	28	40	10	1	0	Stage 2 completed (follow-up 22 months)
M	67	Stage 3	Resection including condyle, reconstruction plate	Jan. 2017	Custom TMJ-extended ramus prosthesis	13 months	24	32	35	8	2	0	Stage 2 completed (follow-up 15 months)
M	70	Stage 3	Resection including condyle, reconstruction plate	43221	Stage 2 surgery planned	-	21	37		10	2	-	Stage 1 only (follow-up 12 months)

The Prosthetic Reconstruction group (n=12) has 6 patients who completed Stage 2 surgery, 3 patients who completed Stage 1 surgery only, and 3 patients who underwent Stage 1 surgery but had the reconstruction plate removed and are therefore “swinging” on one temporomandibular joint.

Table 3. *Free Fibula Flap (FFF) group: Patient characteristics.*

Gender	Age at Stage 1	ORN Stage	Stage 1 Surgery	Date of stage 1 surgery	MIO (mm) prior to Stage I	MIO (mm) after Stage 1	VAS prior to Stage 1	VAS after Stage 1	Stage 2 Surgery
M	54	3	Resection sparing condyle, fibula free flap reconstruction	April 2014	22	25	3	1	-
F	84	3	Resection including condyle, fibula free flap reconstruction	November 2015	20	26	5	0	-
M	62	3	Resection of condyle, fibula free flap reconstruction	January 2014	21	23	2	0	-
F	55	3	Resection sparing condyle, fibula free flap reconstruction	July 2016	22	25	2	0	-
The Free Fibula Flap group (n=4). All patients underwent radiation therapy to the primary tumor and developed Stage 3 osteoradionecrosis.									

Table 4. *Classification of ORNJ (The Notani classification).*

Notani classification of osteoradionecrosis of the jaw (ORNJ)	
I	Confined to the alveolar bone
II	Limited to the alveolar bone and/or mandible above the level of the inferior alveolar canal
III	Involving the mandible below the level of the inferior alveolar canal and/or skin fistula and/or pathologic fracture

All patients in the study presented with the following initial findings:

- Adult patients with history of head & neck cancer, for which radiation therapy was included in the treatment of the malignancy.
- Presentation of Stage III ORN of the mandible involving the unilateral mandibular body or angle.
- Intraoral bone exposure.

Patients who underwent FFF reconstruction (N=4) had an absence of a comorbid condition contraindicating a larger two-site surgery, did not have peripheral vascular disease limiting the ability to harvest a free flap, and accepted the need for a second surgical site. FFF reconstruction was accomplished in the standard manner that has been previously described in detail [13]. Patients who underwent all or a portion of the prosthetic mandibular reconstruction protocol (N=12) were those who either had a comorbid condition contraindicating FFF surgery or refused to undergo FFF surgery due to the need for a second surgical site. A significant contraindication for FFF surgery is the presence of diffuse atherosclerotic plaque throughout the arterial vasculature of the lower extremities, and this played a role in the majority of patients in the SPR cohort.

Surgical results were compared between the two patient groups, the SPR group (stage 1 and stage 2) and the FFF group. The FFF group was used as the control, to represent conventional treatment. Parameters examined included pain score, maximum opening, and complications resulting in protocol failure. The reached statistical power for inter-group differences of described study design was calculated using GPower software (version 3.1.9.4) and reached 19%.

Criteria of success

We analyzed postoperative surgical complications, maximal incisal mouth opening (MIO), Pain Visual Analog Scale (VAS) at the different end points for the SPR and FFF groups. All patient data were assessed qualitatively for clinical conditions and quantitatively for MIO and VAS scale. Paired and unpaired t-test was used to compare the initial, Stage 1 and Stage 2 surgery (as applicable) MIO and VAS scores, and to assess inter-group differences. A two-sided p-value <0.05 was considered statistically significant.

Results

A total of 16 cases of mandibular ORN resections were included in the study. Twelve patients (11 men and 1 woman mean age of 62) were enrolled in the SPR protocol and were treated by the same surgical team. Of the 12 cases in the PR group, 6 patients completed Stage 2 surgery, 3 patients underwent surgery up to Stage 1 only (one is planned for Stage 2 at the time of manuscript preparation), and 3 patients had Stage 1 surgery reversed due to infection and were left swinging with a hemimandible after the hardware was removed. In total, 9 patients completed Stage 1 surgery with 6 patients going on to complete Stage 2 surgery. All the cases, at the time of manuscript publication, had achieved both intraoral and extraoral closure of all wounds and are functional with either elimination of or a significant reduction in pain levels as compared to initial presentation. The median follow-up period for patients in the SPR group is 26 months (range 6-71 months) following the last surgery undertaken. The follow-up period was terminated by death for 4 patients in the SPR group. The median number of months between Stage 1 and Stage 2 surgery for the 6 patients who completed the full PR protocol is 10.5 months (range 7-42 months).

Among the 16 cases in the SPR group, 3 patients underwent Stage 1 resections that spared the condyle because the surgical team felt that the condyle was distant from the center of the irradiated field. Of the 3 patients, one had Stage 1 surgery reversed due to persistent infection, with surgery consisting of removal of the pre-bent plate as well as the condyle, which had developed ORNJ. Another patient had the condyle removed when he underwent full Stage 2 surgery. In this case, the condyle (not a Biomet UHMWPE fossa) acted as a “space maintainer” for the custom TMJ Concepts

fossa and condyle. It was noted that during the 8 months between Stage 1 and 2 surgeries, the condylar bone quality was deteriorating per CT scan findings, the result of the late effect of radiation therapy, which is why it was planned for removal during Stage 2 surgery. The third patient with a spared condyle was not planned for Stage 2 surgery due to significant medical history. The small condylar segment was attached to the pre-bent reconstruction plate during Stage I surgery and the patient was functional and nearly pain-free until he died 31 months later.

Three patients in the SPR group underwent reversal from Stage 1 surgery (pre-bent plate with condylar prosthesis and UHMWPE fossa removed), due to acute or chronic surgical site infection. Reversal surgery was carried out a median of 4 months (range 1 week-14 months) after Stage 1 surgery. All 3 patients achieved good function and had very low pain levels post-operatively. None of the patients elected or felt it necessary to reattempt further reconstruction.

A total of 4 patients (2 men, 2 women) underwent FFF reconstruction. The median age in the FFF group was 58.5 (range 54-84). Similar to the SPR group, at the time of manuscript publication, all 4 patients in the FFF group were functional and achieved a significant improvement in comfort. The median follow-up period for patients in the FFF group is 34 months (range 45-18 months) following the last surgery undertaken. The FFF patients group had one-time surgery.

Among the patients in the SPR protocol who completed Stage 1 surgery without removal of hardware (n=9), the VAS significantly decreased and the MIO significantly increased, comparing pre-operative and post-operative measures (8.45 ± 1.51 vs. 1.89 ± 1.05, $p<0.000$ and 17.56 ± 5.00 vs. 28.44 ± 8.10, $p<0.000$, VAS and MIO, respectively).

Among the SPR protocol patients that completed Stage 2 surgery (n=6), the VAS and MIO were similarly affected (8.7 ± 0.82 vs. 0.17 ± 0.41, $p<0.000$ and 17.3 ± 6.02 vs. 36.5 ± 8.37, $p=0.003$ VAS and MIO, respectively). When comparing the pain and functional end-points of the Stage 1 and Stage 2 surgery sub-groups of SPR group, VAS significantly differed but there was no statistically significant difference in MIO (1.89 ± 1.05 vs. 0.17 ± 0.41, $p=0.002$ and 28.44 ± 8.10 vs.36.5 ± 8.37, $p=0.085$ VAS and MIO, respectively).

Among the FFF group (n=4), the VAS significantly decreased and MIO significantly increased (3.0 ± 1.41 vs. 0.25 ± 0.5, $p=0.035$ and 21.25 ± 0.96 vs. 24.75 ± 1.26, $p=0.027$).

Comparing stage 1 SPR patients and FFF patients, there was a significant difference in pain, but not in function (1.89 ± 1.05 vs 0.25 ± 0.5, $p<0.01$ and 28.44 ± 8.10 vs 24.75 ± 1.26 $p>0.20$). Comparing Stage 2 SPR patients and FFF patients, there was a significant difference in function, but not a significant difference in pain (24.75 ± 1.26 vs 36.5 ± 8.37, $p=0.026$ and 0.25 ± 0.5 vs 0.17 ± 0.41, $p=0.779$).

Discussion

The incidence of ORNJ has been reported to range from 5%-25%. Intensity-modulated radiotherapy (IMRT) is theorized to reduce the incidence of ORNJ due to improved sparing of non-involved tissues. Although some authors have reported a decrease in ORNJ cases with IMRT, Maesschalck's group found similar rates of ORNJ in patients with oropharyngeal carcinoma who received either conventional radiotherapy or IMRT (11% versus 10%) [14-18]. Normal bone responds slowly to radiation damage, nevertheless, the severity of fibrotic changes does increase with time, dose and dose per fraction of radiation [19].

A consensus definition or classification for ORNJ remains controversial [20,21], however, the accepted risk factors for developing ORNJ include; radiation to the head and neck (particularly at doses above 60 Gy), dental extractions after irradiation, poor dentition, chronic infection and any other types of surgical injury to the irradiated bone [22]. The only protective state is edentulism [23,24]. Advanced ORNJ causes severe pain as well as reduction in quality of life [25-27]. Just as there is a lack of a unifying classification, there is also a lack of consensus on how to treat ORNJ. Regardless, in this manuscript, we propose that surgical goals include; enhancement of the compromised tissue, resection of the necrotic/infected bone, provide hard tissue continuity, optimize function, reduce or eliminate discomfort, and closure of both intra-oral and extra-oral communications/fistulas.

Reconstruction of a defect resulting from the resection of mandibular ORNJ is not analogous to reconstructing a defect resulting from tumor ablation or trauma. Patients with mandibular ORNJ present with chronically exposed, infected bone in a bed of densely fibrotic, hypoxic, hypovascular and hypocellular tissue. Although the free flap carries with it a blood supply, the compromised host tissues are much less amenable to short and long-term flap integration compared to flap placement and integration in a non-irradiated, non-infected host site. FFF complication rates approach 20-40% in ORNJ reconstructions and includes fistulas, exposure of hardware and infection [28,29] in comparison to microvascular reconstructions in non-irradiated patients.

In the proposed SPR we advocate disarticulation because in advanced ORNJ with a pathologic fracture in the posterior body region, the affected bone often also extends to include much of the ramus and condyle. This is a clear indication for disarticulation of the condyle, for experience dictates that a reconstruction plate secured to an inadequate condylar segment, with compromised or dead bone is frequently doomed to failure, *(Figure 4)* whether or not it is supporting a segment of vascularized fibula. Thus, the SPR takes advantage of recent advances in techniques and materials that have been developed for TMJ total joint reconstruction. Current technologies allow for the design of a customized total joint prosthesis that extends all the way from the fossa/condyle/ramus unit to the symphyseal region.

Finally, it is notable that the final prosthesis is not placed for at least six weeks, until it is clear that all of the soft tissue is healthy. Both stage I and stage II reconstructions are equally able to function as a complete temporomandibular joint unit for the long-term. Each stopping point is designed to more accurately capture the pre-morbid state of the TMJ anatomical form and function than a FFF. We report above improved functional outcomes in the 2nd stage SPR group compared to FFF group, which is a possible reflection of the prosthetic TMJ unit being more functional than the end of a fibula in the joint space. The observation that there is no difference in the amount of pain relief in the SPR vs. the FFF

groups is logical because the majority of the pain is suffered on occurrence of the pathological fracture. Resection of the dead bone and fracture site resolves the pain in both groups.

It is our experience that all three categories of patients; “free-swinging”, stage 1 temporary or stage 2 final reconstructions all achieve acceptable function, symmetry and quality of life. Alleviation of the pain and associated dysfunction is the important part and is achieved in all three categories upon resection of the pathologic fracture and necrotic/infected bone. The preferable and most stable situation for the long-term is to bring patients through to the final second stage custom prosthesis step, but we have found that when necessary stage 1 is viable as is allowing the patient to function with no reconstruction at all. The most common reasons for stopping at stage 1 were inability for the patient to undergo a second surgery due to medical comorbidities. The most common reason for having to reverse stage 1 surgery and remain “free-swinging” was persistent extraoral plate exposure and unwillingness to undergo further surgery other than plate removal.

Conclusion

D This retrospective study illustrates that the Staged prosthetic reconstruction protocol is an alternative for patients with advanced ORNJ of the posterior mandible who cannot or will not undergo traditional FFF reconstruction. This treatment approach represents comprehensive management for a medically complex patient population, while preserving an esthetic and functional outcome and reducing complications and morbidities commonly encountered in free flap surgery. The nature of the staged approach allows for multiple definitive endpoints for patients with advanced ORN. Through a multi-center study, outcomes should be studied with more patients to determine the success and patient satisfaction with the technique long term as current study setting was able to detect inter-group differences of more than 19% only. Larger samples are also needed to achieve higher statistical power-40, 50 and 69 patients per group to achieve 70%, 80% and 90% statistical power respectively. Similarly, the improvement of patient`s life quality should be studied, as presented publication focuses only on indicator of pain and function.

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