Treatment Outcomes for Osteoradionecrosis of the Central Skull Base: A Systematic Review

Noah Shaikh[1] Chadi A. Makary[1] Lindsey Ryan[2] Camilo Reyes[2]

[1] Department of Otolaryngology, West Virginia University, Morgantown, West Virginia, United States
[2] Department of Otolaryngology, Augusta University, Augusta, Georgia, United States

Address for correspondence Chadi Makary, MD, Department of Otolaryngology, West Virginia University, PO Box 9200, 4525 HSN, Morgantown, WV 26506-9200, United States (e-mail: chadi.makary@hsc.wvu.edu).

J Neurol Surg B Skull Base 2022;83(suppl S2):e521–e529.

Abstract

Objective Osteoradionecrosis (ORN) of the skull base can have catastrophic consequences if not detected early and managed appropriately. This is a systematic review of the different treatment modalities for skull base ORN and their outcomes.

Study Design This study is a systematic review.

Materials and Methods Two researchers extracted information including patient population, surgical technique, outcomes of interest, and study design. A computerized search of Medline, Embase, and the Cochrane library (January 1990–June 2020) looked for several papers on the subject of skull base ORN.

Results A total of 29 studies had met inclusion criteria, including data from 333 patients. Nasopharyngeal carcinoma was the most common primary tumor (85%). Average age at diagnosis of ORN was 55.9 years (range = 15–80 years) and 72.3% of patients were males. The average time to diagnosis of ORN after radiation therapy was 77 months with an average radiation dose of 76.2 Gy (range = 46–202 Gy). Nighty-eight patients (29.4%) also had chemotherapy as part of their treatment regimen. Although all parts of the central skull base were reported to be involved, the clivus and sphenoid bone were the most commonly reported subsites. Trial of medical treatment had a success rate of 41.1%. About 66% of patients needed surgical treatment, either primarily or after failing medical treatment. Success rate was 77.3%. Overall, the surgical treatment was superior to medical treatment ($p < 0.0001$).

Conclusion ORN is a rare complication of the treatment of skull base tumors. Most cases require surgical treatment, including endoscopic debridement or free flap reconstruction, which has a high success rate.

Level of Evidence Level 3 evidence as a systematic review of case studies, case reports, retrospective, and prospective trials with no blinding or controls.

Keywords
- osteoradionecrosis
- skull base
- reconstruction
- side effects
- rhinology
- evidence-based medicine
- radiation therapy
- systematic review
- outcome

Introduction

Osteoradionecrosis (ORN) was first formally described in 1926 by Ewing.[1] He described the fibrous transformation of radiation-affected tissue as a "radiation osteitis." ORN can present from a spectrum of slow bone erosion to fracture, and the overlying mucosa may develop inflammation and ulceration.[2,3] The current accepted view is that ORN develops from a radiation induced fibroatrophic process involving three phases. This includes the prefibrotic phase, involving chronic inflammation with collagen and endothelial cell degradation; the constitutive organized phase, involving

received
December 20, 2020
accepted after revision
July 11, 2021
published online
August 18, 2021

Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI https://doi.org/10.1055/s-0041-1733973.
ISSN 2193-6331.

increased fibroblast activity; and the fibroatrophic phase, involving the development of poorly vascularized, friable tissue. Reactive oxygen species may also participate in this process by causing local cellular and vascular damage during this inflammatory process.[4]

Most literature on the natural history and treatment of this disease involves mandibular ORN. Rates of ORN after irradiation have been cited between 5 and 15%. It may be insidious in development, with cases presenting more than 30 years after radiation treatment.[5,6] Risk factors suggested for ORN include presence of tumor,[7] extent of radiation field, radiation dose above 60 Gy, brachytherapy, surgical trauma,[8] poor oral hygiene,[9] tooth extractions,[10] and nutritional status.[7] In a study of 80 patients with mandibular ORN, Thorn et al[11] found local malignancy in 10% at time of diagnosis. Moreover, 3 out of 80 patients developed ORN with an accumulated radiation dose of less than 60 Gy, and nearly 75% of patients in their study developed ORN within 3 years of treatment.

Conservative treatments in ORN have demonstrated variable effectiveness between 25 and 44%.[12,13] Patients who receive radiation doses in excess of 60 Gy may be refractory to conservative treatments.[14,15] Multiple authors have demonstrated improvement in ORN with hyperbaric oxygen (HBO) therapy.[12,16–19] However, a few authors[20] have raised concern over the efficacy of this approach. Medication treatment options include pentoxifylline, an anti-inflammatory methylxanthine derivative, which may be combined with the reactive oxygen species scavenger tocopherol.[2] Delanian et al[21] demonstrated the effect of combined pentoxifylline, tocopherol, clodronate, and alternating prednisone and ciprofloxacin in the Pentoxifylline-Tocopherol-Clodronate Combination trial.

Surgical treatments described for ORN include sequestrectomy and fistula closure.[5,22–24] Flap reconstruction has demonstrated promise for ORN.[22,25–27] In spite of these promising studies in the mandibular literature, the treatment effects of debridement and flap reconstruction in ORN affecting the skull base is not well understood.

ORN of the central skull base is a rare and serious complication of radiation treatment of head and neck cancer, in particular nasopharyngeal carcinoma. Symptoms of skull base ORN include cerebrospinal fluid (CSF) leak,[23] headache, epistaxis, foul odor,[28] pneumocephalus, central nervous system (CNS) infection, and cranial nerve palsies.[22,23,29] Endoscopic findings include exposed bone, bony sequestra, and internal carotid artery (ICA) exposure.[23,30] MRI findings may include low signal on T1 images, mucosal defect, bone exposure, mucosal atrophy, or granulation tissue, which may extend to the maxillary sinus, clivus, petrous temporal bone, and cervical spine vertebral bodies.[30] Additional radiographic findings include lack of enhancement in the necrotic area, focal tissue necrosis, soft tissue mass, bony cortex disruption, loss of bony trabeculae, soft tissue or bony gas, and absence of bony sclerosis.[22] Biopsy of the affected site may demonstrate chronic inflammation and fibrosis and necrotic bone.[3,31]

The goal of this review is to study the risk factors for development of central skull base ORN, and to explore the treatment modalities and their outcome.

Materials and Methods

Research Questions and Analytic Framework

Our systematic review was designed to investigate risk factors and treatment outcomes for central skull base ORN.

Protocol

Throughout the protocol, we followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) protocols statement.[32]

Eligibility Criteria

Studies with patients of any age who developed central skull base ORN were included. All surgical approaches, urgencies of surgery, or surgical indications were included. We included randomized and nonrandomized control trials, prospective studies, retrospective studies, case series, and case reports. Central skull included anterior and posterior parts of the skull base from the cribriform plate anteriorly to the C1 to C2 posteriorly. Studies on lateral skull base including temporal bone ORN were excluded. The primary outcome of interest was improvement or resolution of skull base ORN. Secondary outcomes of interest were time to development of ORN, need for surgical treatment, surgical treatment complications, and mortality. A table presenting the inclusion and exclusion criteria is included in ►**Supplementary Table S1** (available in the online version).

Data Source and Search Strategy

Two researchers independently conducted an electronic search was performed by using Medline, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). A combination of medical subject headings terms and keywords were searched: "skull base," "skull," "base," and "osteoradionecrosis" using Boolean operators "OR" and "AND." The complete search strategy is included in the appendix. Databases were searched from January 1990 to June 2020. All languages were included, and no search limits were applied. We identified case reports, case series, and prospective and retrospective trials. A table presenting the specific terms used for the search in each database is included in ►**Supplementary Table S2** (available in the online version).

Study Selection and Data Extraction

Studies were screened by title and abstract and full text articles were obtained for potential studies. Data extracted from each study included study ID, study title, year of publication, study design, number of patients, age of patients, tumor histology, tumor subsite, osteoradionecrosis skull base subsite, primary symptoms, primary radiation treatment, radiation dose in Gy, chemotherapy treatment, ORN involvement in tumor bed, time to development of ORN,

surgery as treatment for ORN, endoscopic debridement, flap reconstruction, medical treatments, endovascular treatments, follow-up length, complications of treatment, ORN free survival, and mortality.

Risk of Bias Assessment

The National Institute of Health Quality Assessment Tools systematic assessment of risk of bias in controlled and uncontrolled studies was used. The quality assessment tools for both before-after studies with no control group and case series studies were applied to the included studies. These tools study multiple domains including study objectivity, patient similarity, selection criteria, blinding, classification of interventions, missing data, measurement of outcomes, follow-up adequacy, and result clarity. Studies were assigned an overall score of risk of good, fair, or poor. Tables including all parameters assessed for each study and overall assessments of quality are included in ►**Supplementary Tables S3–S7** (available in the online version). The literature analyzed for the purposes of this study were mostly of poor to fair quality evidence. None of the included studies were randomized, and none had blinded outcome assessment.

Results

Study Selection

A total of 203 studies were identified from literature search. About 101 studies remained after removal of duplicate studies; 72 articles were excluded after viewing title, abstract, or full text for reasons such as not including patients with skull base ORN, no treatment offered for skull base ORN, animal studies, or cadaver studies; and 29 studies were included in the final analysis.[3,22–25,29,31,33–54] The literature search protocol for selection of eligible studies is presented as a PRISMA flow diagram in ►**Supplementary Figs. S1** and **S2** (available in the online version).

Study Characteristics

The 29 studies included a total of 333 patients. There were two prospective studies,[24,33] five retrospective studies,[22,23,25,39,42] six case series,[40,41,46,49,51,55] and 16 case reports.[3,29,31,34,35,37,38,43–45,47,48,50,52–54] The population size in the studies varied from one to 162 patients. All studies were single-center studies. The characteristics of the studies and variables measured are included in ►**Tables 1** and **2**. The complications reported by each study are reported in ►**Table 3**.

Outcomes Assessment

A total of 29 studies had met inclusion criteria. A total of 333 patients were pooled for analysis of prevalence. Nasopharyngeal carcinoma was the most common primary tumor (85%). The average age at occurrence of ORN was 55.9 years (range = 15–80 years). The average time to diagnosis of ORN after radiation therapy was 77 months (range = 1–504). In total, 72.3% of included patients were males. The average dose of radiation therapy was 76.2 Gy (range = 46–202 Gy). Ninety-eight patients (29.4%) received chemotherapy as part of their oncologic treatment.[3,22,23,25,34,37,40,47,48] All parts of the central skull base were involved with ORN, and the clivus and sphenoid bone were the most commonly affected subsites. Average follow-up after ORN treatment was 29 months.

Treatment Outcome

Outcome of medical treatment was compared with that of surgical treatment. Treatment success was defined as resolution or improvement of ORN as defined in each of the studies included. However, 275 patients had trial of medical treatment with a success rate of 41.1%, whereas 220 patients had surgical treatment, either primarily or after failing medical treatment. Success rate was 77.3%. Overall, the surgical treatment was superior to medical treatment ($p < 0.0001$).

Patients included in the analysis were then divided into three groups of treatment approaches: those who had medical treatment first, those who had surgical treatment first, and those who needed surgical treatment due to failure of medical treatment (those are patients who had medical treatment first). These data are summarized in flow chart (x).

Medical Treatment First

There were 275 patients who had medical treatment first. Overall success rate for this group was 41.1% (113 patients out of 275 patients). There were four treatment protocols in the medical treatment group. A total of 87 patients had a course of antibiotic alone. Only five patients had resolution of their symptoms (5.7% success rate). When HBO was added to the course of antibiotics (22 patients), success rate was still low at 9%. Only three patients had a course of HBO treatment alone, with only one patient had success (33.3%). The use of pentoxifylline and tocopherol (PENTO) in addition to antibiotics was only reported in one large study.[22] It was used in 163 patients with a success rate of 64.4% (105 patients). Treatment with PENTO and antibiotics was significantly superior to antibiotics alone or antibiotics with HBO ($p < 0.0001$ for both; ►**Table 4**).

Surgical Treatment First

There were 58 patients in our pooled data who were treated with surgical intervention as a first line treatment. The overall success rate was 87.9%. The main two surgical approaches used were either endoscopic debridement ± nasoseptal flap (NSF) (16 patients with 100% success rate) or debridement with free flap reconstruction (29 patients with 79.3% success rate). Other surgical treatments included debridement with local flap reconstruction (eight patients with 50% success rate), cervical spine fusion which was performed for stabilization (three patients with 100% success rate). Two patients had open craniotomies with CSF leak repair.

Surgical Treatment after Failed Medical Treatment

A total of 162 patients were included in this group. These are the patients that failed medical treatment. Endoscopic debridement ± NSF, temporoparietal fascia flap (TPFF), or pericranial flap (PCF) and debridement with free flap were

Table 1 Characteristics of included studies

Study	Year	Design	Size	Mean age (range)	Sex (M:F)	Tumor type
Habib et al[25]	2020	Retrospective	31	61.1	18:13	Mixed
Daoudi et al[23]	2020	Retrospective	7	53.7 (31–74)	4:3	Mixed
Ungar[49]	2020	Case series	7	37.8 (15–70)	3:4	Mixed
Vieira et al[50]	2020	Case report	1	56	1:0	Chordoma
Liu[24]	2019	Prospective	59	53 (36–79)	44:15	NPC
Chapchay[34]	2019	Case report	1	64	1:0	NPC
Hallak et al[37]	2019	Case report	1	65	1:0	NPC
Vlantis[51]	2018	Case series	4	45 (38–53)	3:1	NPC
Huang[22]	2018	Retrospective	162	58.2 (43–72)	125:37	NPC
London[44]	2018	Case report	1	ND	0:1	Chordoma
Choi[55]	2017	Case series	4	61 (45–74)	3:1	NPC
Risso et al[48]	2016	Case report	1	36	1:0	NPC
Adel and Chang[3]	2016	Case report	1	65	1:0	NPC
Tan[31]	2015	Case report	1	56	0:1	NPC
Brand[29]	2015	Case report	1	37	1:0	NPC
Hu[38]	2013	Case report	1	35	0:1	Astrocytoma
Raza[47]	2013	Case report	1	52	1:0	SCC larynx
Wang[53]	2011	Case report	1	80	1:0	SCC maxilla
King et al[41]	2010	Case series	9	53 (37–65)	6:3	NPC
Kakarala et al[40]	2010	Case series	1	57	1:0	Metastatic liver cancer
Liang et al[42]	2009	Retrospective case control	10	55.3 (43–69)	7:3	NPC
Huang et al[39]	2006	Retrospective	15	43 (32–67)	10:5	NPC
Wang[52]	2006	Case report	1	45	1:0	NPC
Mut[45]	2005	Case report	1	45	1:0	OPSCC
Liu[43]	2004	Case report	1	59	1:0	NPC
Chen et al[35]	2004	Case report	1	55	1:0	NPC
Chang[33]	2000	Prospective	6	53.5 (44–64)	3:3	NPC
Wu and Lee[54]	1999	Case report	1	59	1:0	NPC
Ness[46]	1996	Case series	2	63.5 (61–66)	1:1	Mixed

Abbreviations: ND, not discussed; OPSCC, oropharyngeal squamous cell carcinoma; NPC, nasopharyngeal carcinoma.
Note: Mixed indicates that multiple tumor types were included in the study.

the most commonly used surgeries with success rates of 57.3 and 94.3%, respectively. In this group, treatment with debridement and free flap reconstruction was significantly superior to endoscopic debridement alone or with combination of a local flap (NSF, TPFF, or PCF; $p < 0.0001$; ►**Table 4**).

Endoscopic Debridement ± Local Flap versus Debridement with Free Flap Reconstruction

We then compared the two most common surgical treatments used: endoscopic debridement ± local flap (NSF, TPFF, or PCF) [3,22–25,29,31,33,35,37–40,48,50] versus debridement with free flap reconstruction.[22,25,29,34,40,44,46,49–51,55] We found that a total of 105 patients were undergone endoscopic debridement with success rate of 63.8%, whereas the success rate of free flap was 92.9% (total of 99 patients; $p < 0.0001$; ►**Table 4**).

Endovascular Treatment of the Internal Carotid Artery

Only six studies[22–24,35,43,53,55] discussed management of the ICA. Twenty-six patients required endovascular treatment for the ICA, either stenting or embolization (7.8%). Some of those were done due to severe epistaxis/ICA blowout, and some were performed preemptively due to the ORN being close or abutting the ICA.

Table 2 Surgical outcomes

Study	Year	ORN cause	Rx dose Gy (range)	Chemo Tx	Time to ORN after Rx	Medical Tx	Endovascular Tx
Habib et al[25]	2020	Sx + RT ± CT	60	27/31 adjuvant 7/31 neoadjuvant	52 (1–305)	15/31	ND
Daoudi et al[23]	2020	(Sx or CT) + RT	108 (70–202)	4/7	84 (12–300)	7/7 abx, PENTOCLO	4/7
Ungar[49]	2020	RT	ND	ND	84 (24–384)	ND	ND
Vieira et al[50]	2020	Sx + proton RT	75 Gy	0/1	12	1/1	ND
Liu[24]	2019	RT	ND	0/59	96 (6–504)	0/7	4/59
Chapchay[34]	2019	RT + CT	70.4	1/1	2	1/1	ND
Hallak et al[37]	2019	RT + CT	70	1/1	4	1/1 abx	ND
Vlantis[51]	2018	RT	ND	ND	ND	4/4	ND
Huang[22]	2018	RT ± CT	78.6 (68–94)	68/162	81.6 (54–158)	162/162 nasal irrigation, PENTO, abx	14/162
London[44]	2018	Sx + proton RT	ND	0/1	ND	18/162 HBO	ND
Choi[55]	2017	RT ± CT	111.6 (68.4–126)	2/2	56 (8–120)	ND	1/1
Risso et al[48]	2016	RT + CT	93	1/1	42	1/1 abx	ND
Adel and Chang[3]	2016	RT	384	0/1	384	ND	ND
Tan[31]	2015	RT	ND	0/1	300	ND	ND
Brand[29]	2015	RT	ND	0/1	60	1/1 abx	ND
Hu[38]	2013	Sx + RT + CT	60	1/1	14	ND	ND
Raza[47]	2013	RT + CT	ND	1/1	22	ND	ND
Wang[53]	2011	Sx + RT	ND	0/1	121	ND	1/1
King et al[41]	2010	RT + CT	ND	8/9	44.6 (6–156)	9/9 abx, HBO	ND
Kakarala et al[40]	2010	Proton RT + CT	ND	1/1	6	1/1 abx, HBO	ND
Liang et al[42]	2009	RT	101.5 (70–197)	0/10	ND	ND	ND
Huang et al[39]	2006	RT	70	0/15	(36–180)	6/15, nasal irrigation, abx, HBO	ND
Wang[52]	2006	RT	70.2	0/1	18	1/1 abx	ND
Mut[45]	2005	RT	60	0/1	60	1/1 steroids	ND
Liu[43]	2004	RT	72	0/1	18	1/1 HBO	1/1
Chen et al[35]	2004	RT	81.8	0/1	4	ND	1/1
Chang[33]	2000	RT	76.5 (64.8–119.8)	0/1	116 (21–183)	2/6 abx	ND
Wu and Lee[54]	1999	RT	118	0/1	12	ND	ND
Ness[46]	1996	Sx + RT	58 (46–70)	0/2	2, 12	2/2 ABT, HBO	ND

Abbreviations: abx, antibiotics; CT, chemotherapy; HBO, hyperbaric oxygen; ND, not discussed; PENTO, pentoxifylline, tocopherol; PENTOCLO, pentoxifylline, tocopherol, clodronate; RT, radiation therapy; Sx, surgery; Tx, treatment.

Table 3 Surgical outcomes

Study	Year	Surgical Tx	Complications	Follow-up Mean (range)	ORN improved (months improved)
Habib et al[25]	2020	31/31 FF: 23; LF: 8	6/31 cellulitis, CSF leak, frontal mucocele	16.3	24/31; 84
Daoudi et al[23]	2020	5/7 ESx + LF: 5	3/7 sepsis, stent thrombosis, ICA rupture	24 (7–42)	4/7; 24
Ungar[49]	2020	7/7 FF: 7	0/7 major complications	48 (12–144)	4/7; 48
Vieira et al[50]	2020	1/1 ESx + LF + FF:1	1/1 local flap failure, CSF leak, pneumocephalus	24	1/1; 24
Liu[24]	2019	59/59 ESx: 59	25/59 stroke, hemorrhage	27 (1–108)	31/59
Chapchay[34]	2019	1/1 FF: 1	0/1	48	1/1; 48
Hallak et al[37]	2019	1/1 ESx: 1	1/1; abscess + ICA compression	4	1/1
Vlantis[51]	2018	4/4 FF: 4	3/4 complete unilateral choanal stenosis	18 (5–35)	4/4
Huang[22]	2018	58/162 LF: 16; FF: 42; ESx: 12/58	8/58 CSF leak, hematoma donor flap site, aspiration pneumonia	36 (2–68)	58/58; 36
London[44]	2018	1/1 FF: 1	1/1 CSF leak	6	1/1; 6
Choi[55]	2017	4/4 FF: 4	0/4 no flap failure or infection	3	4/4; 4
Risso et al[48]	2016	1/1 ESx + LF: 1	1/1 CSF leak, pneumocephalus, flap dehiscence, pneumonia	1	1/1; 1
Adel and Chang[3]	2016	1/1 ESx + LF: 1	ND	12	1/1; 12
Tan[31]	2015	1/1 ESx: 1	ND	12	1/1; 12
Brand[29]	2015	1/1 ESx + free flap: 1	ND	3	1/1; 3
Hu[38]	2013	1/1 LF: 1	1/1 CSF leak	4	1/1; 4
Raza[47]	2013	1/1 Spinal fusion	ND	12	0/1; 12
Wang[53]	2011	1/1 ND	1/1 hemorrhage	6	ND
King et al[41]	2010	3/9 Spinal fusion	1/9 meningitis	42 (15–58)	7/9; 42
Kakarala et al[40]	2010	1/1 FF: 1; ESx: 1	ND	22	1/1; 22
Liang et al[42]	2009	ND	10/10 cavernous thrombosis, meningitis, cerebral abscess	88 ± 36 for whole group	ND
Huang et al[39]	2006	9/15 ESx: 9	Surgical Tx: 2/9 temporal lobe necrosis, cerebral edema medical Tx: 3/6 epistaxis, pneumonia	24 (6–84)	Surgical: 7/9 Medical: 0/6
Wang[52]	2006	1/1 craniotomy	1/1 CSF leak	6	1/1; 6
Mut[45]	2005	1/1 spinal fusion	1/1 brainstem compression	3	1/1; 3
Liu[43]	2004	1/1 debridement	ND	6	1/1; 6
Chen et al[35]	2004	1/1 ESx: 1	1/1 ICA rupture	3	1/1; 3
Chang[33]	2000	6/6 ESx: 6	ND	15 (5–26)	6/6; 15
Wu and Lee[54]	1999	1/1 fascial graft	ND	6	ND
Ness[46]	1996	2/2 FF: 2	1/2 pneumocephalus, encephalomalacia	12, ND	2/2; 13

Abbreviations: ORN, osteoradionecrosis; Tx, treatment; CSF, cerebrospinal fluid; ICA, internal carotid artery; LF, local flap; FF, free flap; ESx, endoscopic debridement; ND, not discussed.

Discussion

Skull base ORN is a rare condition with devastating complications,[22,23,28] and fortunately, the treatment options are expanding with advances in endoscopic surgery and microvascular reconstruction.

Development of Skull Base Osteoradionecrosis

Our study demonstrates a natural history of the skull base ORN similar to that of mandibular ORN. The average radiation dose received prior to development of skull base ORN was 76.2 Gy, with most patients receiving greater than 60 Gy. The mandibular ORN literature has similarly demonstrated

Table 4 Table of Fisher's test treatment comparison arms

Comparison arm	Fisher's exact test treatment success OR (95% CI)	*p*-Value
Surgery vs. medicine	4.9 (3.2–7.4)	<0.0001
PENTO + Abx vs Abx[b]	29.3 (11.2–97.9)	<0.0001
PENTO vs. Abx + HBO[b]	17.9 (4.1–62.8)	<0.0001
Secondary free flap vs. endoscopic debridement ± local flap[a]	12.1 (4–49.8)	<0.0001
Total free flap vs. endoscopic debridement ± local flap[a]	7.4 (3–20.8)	<0.0001

Abbreviations: abx, antibiotics; ORN, osteoradionecrosis; CI, confidence interval; HBO, hyperbaric oxygen; OR, odds ratio; PENTO, pentoxifylline-tocopherol.

[a]Statistical comparison of primary surgery with free flap versus endoscopic debridement ± local flap reconstruction was not performed due to a lack of observed failures in the endoscopic debridement group.

[b]Surgical treatment was more successful than medical treatment alone. PENTO + abx was more successful than abx alone or abx + HBO alone. Free flap was more successful than endoscopic debridement ± local flap reconstruction in both the medical failure group and when considering all patients who had received surgery for ORN.

radiation doses above 60 Gy to be associated with increased risk for ORN.[8,11] Most patients in our study developed ORN secondary to radiation treatment for skull base tumors. However, one patient developed ORN after radiation treatment for laryngeal cancer, resulting in destruction of the atlantooccipital joint and neck stiffness.[47] We have demonstrated an average onset of skull base ORN of 77 months, although the onset can occur within one month[25] to 42 years.[24] The mandibular ORN literature has similarly demonstrated development from 3 months to 45 years after radiation treatment, with a mean time of 22 to 47 months.[56,57]

Complications of Skull Base Osteoradionecrosis

Complications from skull base ORN include cranial nerve palsies, CSF leak,[23] severe pain, epistaxis,[28] pneumocephalus, and central nervous system (CNS) infection.[22] Additionally, temporal lobe necrosis may occur in up to 13% of patients.[22] In the largest trial to date of skull base ORN, Huang et al[22] identified an overall rate of secondary complications of ORN at 36%. Due to proximity of the skull base to critical vasculature, severe epistaxis may occur as a result of carotid artery complications, which frequently require endovascular treatment.[23,24,48] However, 7.8% of patients in our study required endovascular treatment for carotid artery complications.

Treatment of Skull Base Osteoradionecrosis

Due to an overall low prevalence of disease, few studies have been able to investigate the effects of treatment with a larger patient sample. Our review shows that a majority of the patients pooled underwent a medical treatment as first line treatment (82.6%). The success rate of that was 41.1%. It does seem that the addition of PENTO to the antibiotic regimen is superior to antibiotics alone or antibiotics with HBO. Limiting the treatment to just antibiotic ± HBO shows very low success rate (5.7 and 9%, respectively).

When comparing different surgical treatment, it appears that debridement with free flap reconstruction was superior. However, not all patients required free flap reconstruction. It is rather reserved for patients with more severe presentation.

Because of the heterogeneity of the data in the studies included, it is difficult to make any conclusions regarding the indicators for disease severity that may make one treatment more successful. However, we suggest classifying the disease severity into mild, moderate, and severe based on the clinical and imaging findings that we gathered from the studies included. Mild disease is usually characterized by foul odor, mild blood tinged nasal drainage, and partial thickness bony erosion as seen on imaging (CT and/or MRI scans). Patients with moderate disease may have, in addition to the above symptoms, low flow CSF leak, and their quality of life is significantly affected. Imaging in these patients may show full thickness bony erosion with or without dural exposure. Severe disease is usually characterized by altered mental status, high flow CSF leak, meningitis, severe epistaxis, and/or neurologic deficits. Imaging in these patients may show large dural exposure, large area of bony erosion, ICA exposure, tension pneumocephalus, and intracranial abscess.

Guiding treatment based on disease severity is best using clinical judgement. Based on the studies included, patients with mild disease could benefit from trial of culture directed antibiotics and PENTO. Endoscopic debridement is usually highly successful for these patients. Patients with more advanced disease (moderate or severe) will likely fail medical treatment alone and may benefit from surgical treatment. The choice of endoscopic debridement with local flap, versus debridement with free flap reconstruction may need to be individualized. The more advanced the disease is, the more likely patients will need free flap reconstruction.

There are some clinical signs that may need additional care. These are ICA exposure or pseudoaneurysm, severe recurrent epistaxis, or cervical spine instability. If ICA is at risk, balloon occlusion test and early surgical intervention with coverage of the artery may also be beneficial. Occipitocervical spine fusion will be needed when cervical spine instability is present.

Complications of Surgical Treatment of Osteoradionecrosis

Surgical complications include flap failure, CSF leak, frontal sinus fistula, mucocele, meningitis, and sepsis.[23,25,41] Due to several patients developing carotid artery complications, endovascular treatment may also cause significant morbidity, with several patients in studies dying from in-stent thrombosis and ICA rupture.[23] Huang et al[22] identified a surgical complication rate of 14% in 58 patients undergoing

free flap placement for skull base ORN. No patient in their study developed flap necrosis. Other studies, however, have demonstrated a considerably higher complication rate. Habib et al[25] assessed 31 patients and found an overall short-term complication rate of 12.9% with 6.5% of patients developing long-term complications after either primary closure or free flap coverage.

The mean follow-up time for patients in our study was 29 months (range = 1–144), which may not be a sufficient time to adequately assess treatment outcomes. Further studies would benefit from a longer period of patient surveillance.

Conclusion

Our study has demonstrated a high rate of surgical treatment success for skull base ORN. We recommend surgical therapy in cases of high risk of ICA or CNS complications and in cases where secondary complications are present. No studies to date have performed a comparative analysis of different treatment options for skull base ORN. Further higher level studies assessing treatment outcomes with appropriate medical therapy and surgery and adequate follow-up would be of benefit.

Authors' Contributions

C.A.M., L.R., and C.R. involved in the conception and design of study. C.A.M., L.R., and N.S. supported in the acquisition of data. C.A.M., L.R., N.S., and C.R. dedicated to analysis and interpretation of data. C.A.M. and L.R. helped in drafting of article. C.A.M., L.R., N.S., and C.R. critically revised the article.

Note

This study is a systematic review of literature and does not require institutional review board approval.

Conflict of Interest

None declared.

References

1 Eiving J. Radiation osteitis. Acta Radiol 1926;6(1–6):399–412
2 Rice N, Polyzois I, Ekanayake K, Omer O, Stassen LF. The management of osteoradionecrosis of the jaws–a review. Surgeon 2015; 13(02):101–109
3 Adel M, Chang KP. Using a nasoseptal flap for the reconstruction of osteoradionecrosis in nasopharyngeal carcinoma: a case report. J Otolaryngol Head Neck Surg 2016;45:27
4 Delanian S, Lefaix JL. The radiation-induced fibroatrophic process: therapeutic perspective via the antioxidant pathway. Radiother Oncol 2004;73(02):119–131
5 Ang E, Black C, Irish J, et al. Reconstructive options in the treatment of osteoradionecrosis of the craniomaxillofacial skeleton. Br J Plast Surg 2003;56(02):92–99
6 Epstein J, van der Meij E, McKenzie M, Wong F, Lepawsky M, Stevenson-Moore P. Postradiation osteonecrosis of the mandible: a long-term follow-up study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997;83(06):657–662
7 Teng MS, Futran ND. Osteoradionecrosis of the mandible. Curr Opin Otolaryngol Head Neck Surg 2005;13(04):217–221
8 Schwartz HC, Kagan AR. Osteoradionecrosis of the mandible: scientific basis for clinical staging. Am J Clin Oncol 2002;25 (02):168–171
9 Murray CG, Daly TE, Zimmerman SO. The relationship between dental disease and radiation necrosis of the mandible. Oral Surg Oral Med Oral Pathol 1980;49(02):99–104
10 Reuther T, Schuster T, Mende U, Kübler A. Osteoradionecrosis of the jaws as a side effect of radiotherapy of head and neck tumour patients–a report of a thirty year retrospective review. Int J Oral Maxillofac Surg 2003;32(03):289–295
11 Thorn JJ, Hansen HS, Specht L, Bastholt L. Osteoradionecrosis of the jaws: clinical characteristics and relation to the field of irradiation. J Oral Maxillofac Surg 2000;58(10):1088–1093, discussion 1093–1095
12 Marx RE. A new concept in the treatment of osteoradionecrosis. J Oral Maxillofac Surg 1983;41(06):351–357
13 Støre G, Boysen M. Mandibular osteoradionecrosis: clinical behaviour and diagnostic aspects. Clin Otolaryngol Allied Sci 2000; 25(05):378–384
14 Oh HK, Chambers MS, Martin JW, Lim HJ, Park HJ. Osteoradionecrosis of the mandible: treatment outcomes and factors influencing the progress of osteoradionecrosis. J Oral Maxillofac Surg 2009;67(07):1378–1386
15 Beumer J, Harrison R, Sanders B, Kurrasch M. Osteoradionecrosis: predisposing factors and outcomes of therapy. Head Neck Surg 1984;6(04):819–827
16 Hart GB, Mainous EG. The treatment of radiation necrosis with hyperbaric oxygen (OHP). Cancer 1976;37(06):2580–2585
17 Mainous EG, Hart GB. Osteoradionecrosis of the mandible. Treatment with hyperbaric oxygen. Arch Otolaryngol 1975;101(03): 173–177
18 Davis JC, Dunn JM, Gates GA, Heimbach RD. Hyperbaric oxygen. A new adjunct in the management of radiation necrosis. Arch Otolaryngol 1979;105(02):58–61
19 Kraut RA. Prophylactic hyperbaric oxygen to avoid osteoradionecrosis when extractions follow radiation therapy. Clin Prev Dent 1985;7(05):17–20
20 Maier A, Gaggl A, Klemen H, et al. Review of severe osteoradionecrosis treated by surgery alone or surgery with postoperative hyperbaric oxygenation. Br J Oral Maxillofac Surg 2000;38(03): 173–176
21 Delanian S, Chatel C, Porcher R, Depondt J, Lefaix JL. Complete restoration of refractory mandibular osteoradionecrosis by prolonged treatment with a pentoxifylline-tocopherol-clodronate combination (PENTOCLO): a phase II trial. Int J Radiat Oncol Biol Phys 2011;80(03):832–839
22 Huang WB, Wong STS, Chan JYW. Role of surgery in the treatment of osteoradionecrosis and its complications after radiotherapy for nasopharyngeal carcinoma. Head Neck 2018;40(02):369–376
23 Daoudi H, Labeyrie MA, Guillerm S, et al. Multimodal strategy for the management of sphenoid osteoradionecrosis: preliminary results. Laryngoscope Investig Otolaryngol 2020;5(01):19–23
24 Liu J, Ning X, Sun X, Lu H, Gu Y, Wang D. Endoscopic sequestrectomy for skull base osteoradionecrosis in nasopharyngeal carcinoma patients: a 10-year experience. Int J Clin Oncol 2019;24 (03):248–255
25 Habib A, Hanasono MM, DeMonte F, et al. Surgical management of skull base osteoradionecrosis in the cancer population - treatment outcomes and predictors of recurrence: a case series. Oper Neurosurg (Hagerstown) 2020;19(04):364–374
26 Hirsch DL, Bell RB, Dierks EJ, Potter JK, Potter BE. Analysis of microvascular free flaps for reconstruction of advanced mandibular osteoradionecrosis: a retrospective cohort study. J Oral Maxillofac Surg 2008;66(12):2545–2556
27 Gal TJ, Yueh B, Futran ND. Influence of prior hyperbaric oxygen therapy in complications following microvascular reconstruction for advanced osteoradionecrosis. Arch Otolaryngol Head Neck Surg 2003;129(01):72–76

28 Huang XM, Zheng YQ, Mai HQ, et al. [Diagnosis and treatment on osteoradionecrosis of skull base after radiotherapy for nasopharyngeal carcinoma]. Zhonghua Er Bi Yan Hou Ke Za Zhi 2004;39 (09):558–561

29 Brand Y, Lim E, Waran V, Prepageran N. Endoscopic transpterygoidal repair of a large cranial defect with cerebrospinal fluid leak in a patient with extensive osteoradionecrosis of the skull base: case report and technical note. J Laryngol Otol 2015;129 (12):1243–1247

30 Han P, Wang X, Liang F, et al. Osteoradionecrosis of the skull base in nasopharyngeal carcinoma: incidence and risk factors. Int J Radiat Oncol Biol Phys 2018;102(03):552–555

31 Tan SH, Ganesan D, Rusydi WZ, Chandran H, Prepageran N, Waran V. Combined endoscopic transnasal and transoral approach for extensive upper cervical osteoradionecrosis. Eur Spine J 2015;24 (12):2776–2780

32 Pestana IA, Coan B, Erdmann D, Marcus J, Levin LS, Zenn MR. Early experience with fluorescent angiography in free-tissue transfer reconstruction. Plast Reconstr Surg 2009;123(04):1239–1244

33 Chang KP, Tsang NM, Chen CY, Su JL, Hao SP. Endoscopic management of skull base osteoradionecrosis. Laryngoscope 2000;110 (07):1162–1165

34 Chapchay K, Weinberger J, Eliashar R, Adler N. Anterior skull base reconstruction following ablative surgery for osteoradionecrosis: case report and review of literature. Ann Otol Rhinol Laryngol 2019;128(12):1134–1140

35 Chen HC, Lin CJ, Jen YM, et al. Ruptured internal carotid pseudoaneurysm in a nasopharyngeal carcinoma patient with skull base osteoradionecrosis. Otolaryngol Head Neck Surg 2004;130 (03):388–390

36 Choi WY, Sung KW, Kim YS, et al. Reconstruction for skull base defect using fat-containing perifascial areolar tissue. Ann Plast Surg 2017;78(06):673–679

37 Hallak B, Morrison M, Kohler R, Bouayed S. Deep radiation-induced ulcer following nasopharyngeal carcinoma: surgical management. BMJ Case Rep 2019;12(11):e230700

38 Hu Z, Godoy BL, Zadeh G. Spontaneous cerebrospinal fluid rhinorrhea secondary to anterior fossa osteoradionecrosis. J Clin Neurosci 2013;20(09):1314–1315

39 Huang XM, Zheng YQ, Zhang XM, et al. Diagnosis and management of skull base osteoradionecrosis after radiotherapy for nasopharyngeal carcinoma. Laryngoscope 2006;116(09):1626–1631

40 Kakarala K, Richmon JD, Durand ML, Borges LF, Deschler DG. Reconstruction of a nasopharyngeal defect from cervical spine osteoradionecrosis. Skull Base 2010;20(04):289–292

41 King AD, Griffith JF, Abrigo JM, et al. Osteoradionecrosis of the upper cervical spine: MR imaging following radiotherapy for nasopharyngeal carcinoma. Eur J Radiol 2010;73(03):629–635

42 Liang KL, Jiang RS, Lin JC, et al. Central nervous system infection in patients with postirradiated nasopharyngeal carcinoma: a case-controlled study. Am J Rhinol Allergy 2009;23(04):417–421

43 Liu SH, Chang JT, Ng SH, Chan SC, Yen TC. False positive fluorine-18 fluorodeoxy-D-glucose positron emission tomography finding caused by osteoradionecrosis in a nasopharyngeal carcinoma patient. Br J Radiol 2004;77(915):257–260

44 London NR Jr, Ishii M, Gallia G, Boahene KDO. Technique for reconstruction of large clival defects through an endoscopic-assisted tunneled retropharyngeal approach. Int Forum Allergy Rhinol 2018;8(12):1454–1458

45 Mut M, Schiff D, Miller B, Shaffrey M, Larner J, Shaffrey C. Osteoradionecrosis mimicking metastatic epidural spinal cord compression. Neurology 2005;64(02):396–397

46 Ness JA, Chang HS, Grabowski CM, Marentette LJ. Osteoradionecrosis of the anterior cranium. Skull Base Surg 1996;6(04): 259–266

47 Raza A, Islam M, Lakshmanan P. Secondary atlanto-odontoid osteoarthritis with osteoradionecrosis of upper cervical spine mimicking metastasis. BMJ Case Rep. 2013http://dx.doi.org/10.1136/bcr-2013-009319

48 Risso A, Zoia C, Gianformaggio C, et al. Tension pneumoc ephalus secondary to osteoradionecrosis of the clivus. Rep Pract Oncol Radiother 2016;21(01):71–75

49 Ungar OJ, Abergel A, Safadi A, Zaretzki A, Yanko-Arzi R, Fliss DM. Anterior median skull base reconstruction using a vascularized free flap: rationale, patient selection and outcome. J Neurol Surg B Skull Base 2020;81(01):30–36

50 Vieira S, Nabil A, Maza G, et al. Salvage free tissue transfer for clival osteoradionecrosis after repeat proton beam therapy. World Neurosurg 2020;138:485–490

51 Vlantis AC, Wong EWY, Chiu TW, Chan JYK. Vastus lateralis muscle free flap for skull base osteoradionecrosis in nasopharyngeal carcinoma. J Neurol Surg B Skull Base 2018;79(04): 349–352

52 Wang HC, Hwang JC, Peng JP, Hsieh CH, Liliang PC. Tension pneumocephalus–a rare complication of radiotherapy: a case report. J Emerg Med 2006;31(04):387–389

53 Wang JJ, Wang Y, Chang PH, Lee TJ, Wang DH. Nontraumatic and postirradiated intracavernous carotid hemorrhage: an unusual case of epistaxis and review of the literature. Am J Otolaryngol 2011;32(02):162–164

54 Wu CT, Lee ST. Delayed spontaneous tension pneumocephalus caused by radionecrosis of the skull base. Br J Neurosurg 1999;13 (02):214–216

55 Choi NY, Kim HJ, Baek CH. Surgical management of extensive osteoradionecrosis in nasopharyngeal carcinoma patients with the maxillary swing approach and free muscular flaps. Clin Otolaryngol 2017;42(05):1100–1104

56 Lambade PN, Lambade D, Goel M. Osteoradionecrosis of the mandible: a review. Oral Maxillofac Surg 2013;17(04):243–249

57 Costa DA, Costa TP, Netto EC, et al. New perspectives on the conservative management of osteoradionecrosis of the mandible: a literature review. Head Neck 2016;38(11):1708–1716