Radiation Necrosis of the Lateral Skull Base and Temporal Bone

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Abstract

Keywords

- ▶ osteoradionecrosis
- ▶ temporal bone cancer
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- ▶ reconstructive surgery

Radiation therapy plays a critical role in the treatment of malignancies involving the head and neck. Although the therapeutic effects of ionizing radiation are achieved, normal tissues are also susceptible to injury and significant long-term sequelae. Osteoradionecrosis of the temporal bone (ORNTB) is among the many complications that can arise after therapy. ORNTB is a debilitating and potentially lethal condition that continues to challenge patients and treating physicians. Herein, we review the pathophysiology, presentation, work-up, and management of ORNTB.

Radiation therapy plays a critical role in the treatment of malignancies involving the head and neck. Although the therapeutic effects of ionizing radiation are achieved secondary to the abnormal repair kinetics in neoplastic cells, normal tissues are also susceptible to injury and significant long-term sequelae.¹ In 1926, Ewing described obliterative endarteritis and subsequent avascular necrosis resulting from radiation-induced injury to underlying bony tissues.² Since that time, osteoradionecrosis (ORN) has become a well-documented complication associated with head and neck radiation therapy. The first reported case of ORN of the temporal bone (ORNTB) was published by Block in 1952 and involved a patient who developed chronic osteomyelitis of the mastoid cavity 15 years after radiation therapy for syringobulbia.³ In the decades following Block's case report, ORNTB has generated increasing interest. Nearly 400 cases are described in the literature, predominantly through the publication of institutional case reports and retrospective case series.^{4–21} Despite increasing awareness, ORNTB

remains a debilitating and potentially lethal condition that continues to challenge patients and treating physicians.

Pathophysiology

Several mechanisms contribute to the development of necrosis following radiation-induced tissue injury. Blood vessels exposed to radiation undergo degenerative changes, involving the smooth muscle and collagen of the vessel walls, resulting in periarthritis and obliterative endarteritis.¹⁰ Subsequent endothelial edema and the formation of small thrombi impede tissue perfusion and lead to aseptic avascular necrosis.^{9,22} Bone metabolism is specifically compromised by diminished osteoblast proliferation in the setting of unchanged or increased osteoclast activity. Eventually, radiation injury decreases the absolute number of osteocytes, producing “empty lacunae” surrounded by spicules of dead bone and fibrous connective tissue.^{1,8,9} Studies suggest that 30 Gy of radiation impairs osteoblastic cell proliferation and 50 Gy kills osteoblastic cells.²³

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Thus, although no definitive data exist to define a minimum radiation dose necessary to produce ORN, exposure to 50 Gy or more is considered a significant risk factor.¹

The temporal bone is exposed to radiation injury during the primary or adjuvant treatment of head and neck malignancies. In a systematic review of 364 patients by Yuhan et al, the most common tumor etiologies were nasopharyngeal carcinoma (NPC) (36.6%), parotid tumors (20.1%), external auditory canal (EAC) pathology (16.3%), primary and metastatic malignancies of the skin (7.6%), and tumors of the brain and central nervous system (6.3%).⁴ Radiotherapy protocols for these malignancies resulted in a mean total radiation dose to the temporal bone of 58.0 Gy (range: 11–160 Gy).⁴ Several factors contribute to the risk of developing ORNTB. Local risk factors include the superficial location of the temporal bone, thin overlying soft tissue, and tenuous vascular supply in the region of the tympanic ring. Furthermore, although a mature bone is relatively radioresistant, the compact architecture of the temporal bone withstands radiation effects less well than more cancellous bone.¹⁰ Additionally, pathogens from the upper respiratory tract have access to the middle ear space through the Eustachian tube, predisposing injured bone to bacterial or fungal infection.^{1,4,10,14,17,20} It is not well understood whether bacteria are the initial cause of ORN or whether they are simply opportunistic pathogens that exacerbate a noninfectious process. However, it is widely accepted that bacterial infection invariably complicates and prolongs the course of ORN.²⁴ Patient comorbidities such as advanced age, diabetes mellitus, hypothyroidism, and immunosuppression impair wound healing and may also cause tissues to be more susceptible to radiation-induced injury.

Evaluation

In their epidemiological review of ORNTB, Morrissey and Grigg reported an incidence of 8.5% in a cohort of 82 patients who underwent surgery and adjuvant radiotherapy for head and neck malignancies.¹⁴ The average patient follow-up in the study was only 32 months (range: 0–96 months). As a result, given the relatively long latency of this condition, the reported value may be an underestimation of the true incidence. A study by Leonetti et al found that 1.9% of patients treated with parotidectomy and postoperative radiotherapy developed ORNTB; however, the incidence increased to 12.5% when surgical extirpation included mastoidectomy.¹³ Although the incidence of ORNTB following primary radiotherapy is less well defined, recent reviews of NPC patients suggest that the condition is relatively rare.^{11,25}

The latency period between radiation exposure and the development of ORN-related symptoms averages approximately 8 years, but the range varies widely from 6 months to 48 years.^{1,4,10,11,16–19} In their series of 33 patients, Sharon et al found no correlation between radiation dose to the primary site and the time to development of ORN.¹⁷ Ramsden et al suggested that patients younger than 40 years at the time of radiation exposure seemed to present after longer latency periods than patients older than 40 years (8 vs. 6 years).⁶ While subsequent studies have failed to demonstrate

similar age-related correlations, the typical patient presents in the fifth or sixth decade of life. Overall, the literature demonstrates that males and females are equally susceptible to developing ORNTB.^{4,18,19}

Presenting Symptoms

Clinically, the diagnosis of ORN is made when a patient with a history of previous radiation presents with exposed bone that fails to heal over a period of 3 months.^{22,26} The most common presenting symptoms of ORNTB are otorrhea, hearing loss, otalgia, tinnitus, headache, and cranial nerve VII palsy.^{4,9–11,17–19,27} Drainage from the affected ear may be purulent and foul-smelling or sanguinous. The etiology of hearing loss is typically multifactorial with pure tone audiometry demonstrating sensorineural loss resulting from radiation-induced injury to the cochlea, conductive hearing loss secondary to radiation-associated otitis media secondary to Eustachian tube fibrosis, or mixed loss due to the negative impacts of both.^{1,11,17,19}

Examination

The finding of the exposed, necrotic bone in the EAC is sine qua non of ORNTB. The amount of exposed bone can vary from a small area in the posterior canal wall to a large region of necrosis involving the tympanic ring or fistulizing into the mastoid or temporomandibular joint (TMJ).^{11,17} Granulation tissue is often seen adjacent to the necrotic bone. Other common physical examination findings include crusting or debris in the EAC, tympanic membrane perforation, canal stenosis, middle ear effusion, suppurative otitis media, and cholesteatoma.^{1,4,11,17,28} More than half of the patients diagnosed with ORNTB present with concomitant infections involving the affected ear. The most common organism is *Staphylococcus aureus*. Cultures have also demonstrated *Corynebacterium jeikeium*, *Actinomyces* species, *Pseudomonas aeruginosa*, *Streptococcus viridans*, *Klebsiella oxytoca*, *Enterococcus faecalis*, *Escherichia coli*, *Candida albicans*, and *Aspergillus*.^{17,18}

Imaging

In the evaluation of ORNTB, radiological imaging is important for defining the extent of temporal bone involvement and identifying potential complications associated with the condition.²⁷ Computed tomography (CT) is the most commonly employed modality secondary to its ability to delineate osseous structures and the extent of disease. Magnetic resonance imaging (MRI) may be employed to further assess bone marrow changes, soft tissue lesions, or intracranial pathology. In their review of ORNTB patients at MD Anderson Cancer Center, Ahmed et al identified EAC erosions and mastoid effusions in 90% of cases.²⁷ Advanced CT findings were found in 15 to 25% of patients and included loss of mastoid bony septa/coalescence, enhancing soft tissue, air within deep soft tissue spaces, and TMJ involvement. The authors noted that advanced CT findings characterized a more severe disease process and, as such, these patients were

significantly more likely to require surgical management and were also at a higher risk of developing skull base or intracranial abscesses.²⁷

Diagnosis and Classification

For patients presenting with a constellation of findings consistent with ORN, diagnostic considerations should include other conditions and complications associated with radiotherapy or ORNTB. Cholesteatoma may occur as a result of chronic tympanic membrane perforation or fistula formation directly into the mastoid cavity. Labyrinthitis,^{9,14} cerebrospinal fluid leak,^{12,29,30} cerebellar abscess,²¹ temporal lobe necrosis,¹⁵ sigmoid sinus thrombosis,^{4,14} and internal carotid artery aneurysm^{4,31,32} have also been reported. Finally, in their series of 33 patients, Hao et al reported that tumor recurrence or radiation-associated malignancy was misdiagnosed as ORN in 21% of cases.³³ Therefore, it is critically important that a biopsy be obtained of any suspicious tissue in the EAC to rule out neoplasia.^{1,9,27,33}

Ramsden et al described two patterns of ORNTB based on the extent of disease and presenting symptoms. The localized form is confined to the EAC and tympanic bone and presents with mild otalgia and otorrhea. Physical examination typically demonstrates exposed, necrotic bone isolated to the EAC. In the diffuse form, infection and necrosis are more extensive and are more likely to involve adjacent structures, such as the labyrinth, facial nerve, TMJ, or brain.⁶ Diffuse ORNTB presents with severe otalgia and profuse discharge from the ear.⁹ Examination findings may include mastoid opacification and coalescence, fistulas, or abscess formation (► **Table 1**).¹ Given its simplicity and consistent application in treatment protocols, this classification scheme has been widely used since its introduction in 1975. More recently, Morrissey and Grigg proposed a new system that correlates anatomical progression with increasing disease severity (► **Table 1**).¹⁴ Kammeijer et al employed both classification schemes for their series of 45 patients with ORNTB. They concluded that the two previous schemes demonstrate significant overlap with Ramsden's localized form translating to Morrissey grade I/II and diffuse disease with grade III/IV.¹⁶ They also suggested that the severity of symptoms in

patients with diffuse ORN may be a relevant parameter for distinguishing between appropriate treatment modalities, noting that a subgroup of patients with diffuse disease but fewer symptomatic complaints were treated with conservative measures and that nearly half achieved therapeutic goals (► **Table 1**).¹⁶

Treatment

The evidence supporting optimal management guidelines for ORNTB remains limited to institutionally based algorithms reported in several case series.^{4,16–18} Nevertheless, a general consensus does exist regarding the main tenets for treating this condition. First, given the debilitating complications and significant difficulties in managing ORNTB once established, primary prevention is critical.⁴ Soft tissue reconstruction following ablative oncological procedures should avoid excessive tension over the temporal bone, and, if possible, adjuvant radiotherapy should be deferred in patients with exposed bone or tenuous soft tissue coverage. Patients should also strictly avoid manipulation of EAC skin, especially if it lies within planned radiation fields.⁴ It is also widely accepted that nonsurgical (conservative) therapy is appropriate for localized ORNTB or minor symptoms, whereas patients with diffuse disease or severe symptoms are more likely to require surgical intervention.^{4,9,14,17} Finally, the goal of treatment should be well-defined and is most commonly aimed at control of symptoms rather than complete removal of necrotic bone.^{17,18} A secondary and equally important objective is the prevention of ORN-associated complications.¹¹

Nonsurgical (Conservative) Therapy

There is widespread support in the literature for conservative therapy as the primary modality in the management of localized (Morrissey grade I/II) ORNTB with minor symptoms. Kammeijer et al also advocate for nonsurgical treatment in patients with functional hearing as nearly all surgical options will produce a severe air–bone gap.¹⁶ Treatment regimens should be multifaceted and address all components of the underlying pathology. In-office debridement of squamous debris and bony sequestra should be performed on a regular

Table 1 Classification of osteoradionecrosis of the temporal bone

Ramsden et al, 1975 ⁶	Morrissey and Grigg, 2011 ¹⁴	Kammeijer et al, 2014 ¹⁶
<i>Localized</i> : confined to the EAC and tympanic bone; mild otalgia and otorrhea	<i>Grade I</i> : erosion of the EAC skin without bony involvement	<i>Localized</i> : confined to the EAC and tympanic bone; mild otalgia and otorrhea
	<i>Grade II</i> : erosion of the EAC skin with bony necrosis	
<i>Diffuse</i> : extensive necrosis of the temporal bone with involvement of adjacent structures; severe otalgia and profuse otorrhea	<i>Grade III</i> : involvement of the middle ear space and/or mastoid	<i>Diffuse A</i> : extensive necrosis of the temporal bone with involvement of adjacent structures; little pain and infection and intact hearing <i>Diffuse B</i> : extensive necrosis of the temporal bone with involvement of adjacent structures; severe pain and infection and/or no functional hearing
	<i>Grade IVa</i> : cranial nerve involvement	
	<i>Grade IVb</i> : skull base involvement	

Abbreviation: EAC, external auditory canal.

basis. Several institutions favor aural toilet with acidification or hydrogen peroxide for maintenance therapy,^{10,11,14,16} although Phillips et al discourage the practice as it may lead to maceration of the EAC skin.¹⁸ The infectious component of ORN is universally addressed with topical antimicrobials and, in refractory cases, culture-directed systemic antibiotics.^{4,9–11,16–20,27} Sharon et al advocate the use of gentian violet as it may disrupt biofilms, which have been identified in ORN and may contribute to the chronic, recalcitrant nature of the condition.^{17,24} In a 2015 study of 23 cases, Phillips et al successfully managed 87% of ORNTB patients with nonsurgical treatment. Similarly, in their series of 20 patients, Ahmed et al reported that all 11 patients with mild, localized ORNTB were effectively managed with nonsurgical therapy.²⁷ These outcomes compare favorably with a contemporary systematic review of the ORNTB literature, which found that 89% of all patients with localized disease who were treated conservatively reported adequate resolution of symptoms at their last documented follow-up.⁴

Surgical Management

Surgical management should be considered for patients presenting with diffuse (Morrissey grade III/IV) ORNTB or in cases where localized disease progresses or remains refractory to conservative treatment.^{4,16} Other indications include the inability to tolerate in-office debridement, severe or intractable pain, uncontrolled infection, progression of cranial neuropathies, or the presence of cholesteatoma.^{4,16–18} It should be emphasized that surgery in these patients can be extremely challenging. Studies report that the rates of facial nerve dehiscence, labyrinthine fistulas, great vessel exposure, and dural dehiscence are higher in previously irradiated temporal bones, thus increasing the risk of intraoperative complications.^{17,34} It may also be very difficult to intraoperatively determine if all diseased bone has been completely removed, resulting in inadequate resection.⁹ Therefore, indications for ablative surgery and the potential benefits gained from symptomatic relief should be carefully weighed against the inherent procedural risks.¹⁷

Yuhan et al reported that 221 of the 364 ORNTB patients described in the literature underwent a surgical procedure, with the most common being lateral temporal bone resection (40.9%), mastoidectomy (33.9%), and subtotal petrosectomy (12.8%).⁴ Kammeijer et al advocate the use of subtotal petrosectomy, citing a success rate of 90.9% when the procedure adhered to the following three steps: (1) removal of necrotic bone and all mastoid air cells and mucosa, (2) prevention of new infection (closure of the EAC and Eustachian tube), and (3) promotion of revascularization (vascularized flap obliteration).¹⁶ In the same study, two out of the three patients treated with canal wall down (CWD) mastoidectomy required revision surgery and prolonged timeframes to fully epithelialize. This led the authors to conclude that CWD mastoidectomy was a suboptimal technique with unpredictable results.¹⁶ Similar outcomes were recorded in an earlier case series published by Guida et al.⁹

In the published ORNTB literature, mastoidectomy and lateral temporal bone resection were the most commonly

Fig. 1 Defect following a standard lateral temporal bone resection.

performed procedures for patients treated with primary radiation for NPC.⁴ Chen et al compared the outcomes of these two techniques in a cohort of 77 patients. After a 2-year follow-up, patients who underwent lateral temporal bone resection with pedicled temporalis muscle flap and EAC closure had a significantly lower percentage of purulent otorrhea (5%) or persistent ORN (0%) than patients treated with CWD mastoidectomy (40 and 35%, respectively).¹⁹ In their series of 14 patients who underwent radical mastoidectomies for ORNTB, Xu et al found that less than half (6 out of 14) achieved complete resolution of symptoms.¹¹

Overall, the systematic literature review by Yuhan et al supports the institutional results described previously, with 30 (93.8%) of 32 subtotal petrosectomies, 90 (90.9%) of 99 lateral temporal bone resections, 49 (59.76%) of 82 of mastoidectomies successfully achieving treatment goals.⁴ The most commonly reported postoperative complications were chronic, purulent otorrhea, and wound dehiscence.^{4,16,19,20,30,35} ▶ **Fig. 1** depicts an example of the bony defect after lateral temporal bone resection.

Postablative Reconstructive Surgery

Collective surgical experience for ORNTB demonstrates the importance of reconstructing the ablative defect with vascularized tissue.^{11,17,19,20,35,36} The combined effects of radiation-induced injury and chronic infection serve to compound the unique challenges faced by the reconstructive surgeon in the lateral skull base (LSB). Ablative surgeries for ORNTB

Fig. 2 Temporal bone resection with reconstruction by superficial temporalis vascularized pedicled graft (in place) and overlay free fat grafts (left of image) about to be placed in the defect. The external auditory canal has been sealed.

typically produce defects of substantial volume and three-dimensional complexity in addition to the potential for exposure of dura and great vessels.³⁷ In general, the goals of reconstruction are to promote healing of the underlying tissues, facilitate epithelial coverage, prevent future infection, eliminate dead space, restore bony contour, and separate intracranial and extracranial spaces.^{37,38}

Reconstruction with Local and Regional Flaps

The temporalis muscle provides a local flap that is well-suited for LSB defects secondary to its close proximity and ability to provide an adequate volume of vascularized muscle with minimal donor-site morbidity.³⁷ **Fig. 2** demonstrates temporalis flap reconstruction combined with free adipose transfer after temporal bone resection. In a series of 40 patients who underwent lateral temporal bone resection followed by pedicled temporalis muscle flap obliteration and EAC closure, Chen et al reported no cases of persistent ORN and only two patients who required minor revision surgery for wound dehiscence.¹⁹ Kammeijer et al described similar success in three patients reconstructed with pedicled temporalis muscle flaps following subtotal petrosectomy.¹⁶ Other studies, however, express concerns regarding the viability of this flap in the setting of prior radiation and ORN. In a single-surgeon series of 47 cases, Kadakia et al reported a significant increase in wound breakdown for patients who underwent local flap reconstruction when compared with techniques that employed regional flaps or free tissue transfer.²⁰

Regional flaps offer reconstructive options with larger soft tissue volumes that are outside previous radiation fields. Although several regional options exist, the pectoralis major myocutaneous flap and supraclavicular flap benefit from historical and increasing contemporary popularity, respectively. An historic workhorse in head and neck reconstruction, the pectoralis major myocutaneous flap benefits from a straightforward harvest technique and provides a substantial amount of soft tissue supported by a robust, reliable vascular pedicle. The primary disadvantages stem from the flap's

excessive tissue bulk and limited reach, which may predispose to wound dehiscence. Technical modifications have overcome these drawbacks to some degree by lengthening of the skin paddle and incorporation of superior rectus fascia into the flap.³⁷ The supraclavicular flap is a fasciocutaneous flap that provides an ample amount of pliable soft tissue and has an arch of rotation sufficient to reach LSB defects without prohibitive tension. It also provides superior color and texture match when compared with other regional and free flap options.³⁷ Kadakia et al reported the successful use of both pectoralis major and supraclavicular flaps for primary and revision reconstruction in their series of ORNTB patients.²⁰

Reconstruction with Free Tissue Transfer

Although locoregional flaps have been successfully utilized in reconstructing postablative ORNTB defects, the tenuous viability of irradiated soft tissues, chronic infection, and complex nature of these wounds may necessitate the use of vascularized tissue from remote locations.^{20,38} The choice of free flap should be dictated by the volume of the defect as well as the structures resected.³⁷ Historically, the rectus abdominus free flap served as the workhorse for LSB reconstruction. Although it continues to be utilized effectively,^{16,20,38} the donor-site morbidity associated with the rectus flap has led many reconstructive surgeons to favor the anterolateral thigh flap or latissimus dorsi flap for larger LSB defects.^{16,37} The radial forearm free flap provides a less bulky, pliable alternative for smaller surgical defects. Success rates for free flap reconstruction of LSB defects are consistently favorable with flap failures occurring in less than 5% of the time.^{35,38,39} Furthermore, although complications may occur in 11 to 68% of patients with LSB defects, most are related to minor healing issues that resolve with local wound care.^{16,37,39} Kadakia et al endorse the use of free flaps for reconstructing LSB defects in ORNTB patients. In a series of 23 free flaps employed for this purpose, they reported only one incidence of delayed flap loss and another of wound breakdown requiring revision surgery. The group also noted that regional and free tissue reconstruction experienced wound breakdown at significantly lower rates than local flaps, suggesting that the former are the preferred modality for postablative ORNTB defects.²⁰

Hyperbaric Oxygen Therapy

Hyperbaric oxygen (HBO) therapy exerts its physiological effects on irradiated, hypoxic tissue by increasing arterial oxygen tension, which, in turn, promotes angiogenesis and facilitates wound healing by stimulating collagen and fibroblast proliferation.^{4,17,40} HBO may also play an adjunctive role in eradicating chronic infection through the bactericidal effects of free radical production and enhancing the phagocytic abilities of human leukocytes.^{40,41} Although HBO therapy has become a standard component in the therapeutic regimens for ORN of the mandible,²⁶ its role in the treatment of ORNTB is not well-defined. Comprehensive review of the ORNTB literature demonstrates the use of HBO in conjunction with surgery approximately 11% of the time. Unfortunately, meaningful

evaluation of the data is hampered by a lack of standardized treatment protocols, small patient cohorts, and concurrent use with a wide variety of surgical modalities.⁴ The efficacy of HBO in this patient population is also inconsistent. A combination of small case series and individual case reports documents the successful treatment of ORNTB with HBO therapy either alone or in conjunction with surgery.^{40–42} However, several studies document little to no benefit from the use of HBO. Necrosis failed to resolve in all six patients treated with HBO by Sharon et al.¹⁷ Kadakia et al observed similar findings in all 36 patients who underwent HBO therapy in addition to ablative surgery.²⁰ Thus, while HBO therapy may be considered as an adjunctive therapeutic modality in the treatment of ORN, these inconsistencies and a lack of sufficient evidence recommend against its widespread use.

Conclusion

ORNTB is a challenging and debilitating condition that may develop years after exposure to radiation. Despite increasing awareness of the condition, definitive understanding of the underlying pathophysiology and optimal therapeutic guidelines remain elusive. In general, localized disease is effectively managed with nonsurgical treatment, whereas severe, diffuse, or recalcitrant ORNTB requires surgical intervention. Reconstruction of postablative defects is equally demanding and requires careful, individualized selection of the surgical option that provides the greatest chance of success. There is insufficient data to recommend the widespread, standardized use of HBO therapy in the treatment of ORNTB.

Disclosures

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Conflicts of Interest

None declared.

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