Radiotherapy-induced Pathology of the Ear

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KEYWORDS

• Radiotherapy • External ear • External auditory canal
• Soft tissue pathologic condition • Otitis externa • Radiation-induced dermatitis

KEY POINTS

- Acute radiotherapy (RT)-induced soft tissue changes include erythema and dry desquamation, which may be followed by moist desquamation and epithelial ulceration. Acute changes usually resolve 4 to 6 weeks after RT conclusion.
- Chronic RT-induced soft tissue change includes epithelial atrophy, subcutaneous fibrosis, and poor healing capabilities.
- Patients with otitis externa after or during radiation should receive topical antimicrobial steroidal treatment and may benefit from systemic treatment and external ear cleaning.
- Topical steroid therapy has promising early data for treatment of radiation dermatitis, but this has not been studied in the external auditory canal.

BACKGROUND

Radiotherapy (RT) has become a mainstay for definitive or adjuvant therapy for head and neck cancer. Recent technological advances, such as photon intensity modulated radiation therapy (IMRT) and intensity modulated proton therapy (IMPT), have improved targeting from conventional RT. Conformal RT, introduced in the 1990s, provided a novel method for matching high RT doses with irregular tumor shapes and decreased long-term RT-related side effects when compared with conventional RT.[1] IMRT, a subset of conformal RT, uses radiation beams of nonuniform intensity to treat the 3-dimensional tumor shape with higher precision.[2] IMPT has a unique depth-dose that stops proton energy at a set distance, meaning that tissues do not receive radiation upon exit of the beam. Although multiple studies suggest that IMPT may be associated with decreased radiation toxicity and side effects,[3,4] this question will be answered with prospective randomized trials that are currently underway.

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Nondiseased organs in the head and neck, however, still experience collateral radiation toxicity. Berg and Lindgren[5] were the first to explore how radiation changes the external auditory canal (EAC) in 1961, describing an initial epithelial hyperplasia with low-dose RT that transformed into epithelial erosion, ulceration, and suppuration at higher doses. This article focuses on how radiation alters the soft tissue of the external ear, current management strategies to prevent progression, and future directions of treatment.

PATHOGENESIS

RT kills malignant cells by inducing free radicals[6,7] and reactive oxygen species, which cause cellular damage by dismantling DNA and proteins.[6] When skin and subcutaneous tissue are injured, the tissue responds by attempting to heal. Immediate hemostasis, inflammation (days 0–4), proliferation (day 3 to weeks), and remodeling (weeks to years) constitute this multistep, complex process.[6] Although rigorously organized in healthy tissue, postradiation healing is altered because of broad exposure, repeated insult, and cyclic reactivation of the inflammatory cascade. Cytokines attract neutrophils, monocytes, and lymphocytes.[8] Monocytes transform into macrophages as they enter the irradiated soft tissue and stimulate fibroblast migration and maturation. Macrophages, fibroblasts, and epithelial cells secrete transforming growth factor-beta, which activates a fibrotic pathway that persists long after radiation concludes.[8–11] Soft tissue fibrosis ultimately leads to decreased tissue perfusion[12] and lymphovascular drainage, resulting in frail tissue that exhibits poor healing capabilities.[13,14]

Skin and soft tissue are especially radiosensitive, which is indicated by the high frequency of adverse skin reactions (>95%) during radiation therapy.[6,15] Radiation-induced dermatitis is a well-known phenomenon,[16,17] and its severity is classified with the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) criteria, shown in **Table 1**.[18]

NATURE OF THE PROBLEM

The auricle and the EAC make up the external ear; both structures are lined with keratinized stratified squamous epithelium.[19] The auricle is a soft, fibrocartilaginous structure that transitions into the lateral cartilaginous third of the EAC. The EAC is a skin-lined pouch originating at the auricle and ending at the tympanic membrane, which separates the external ear from the middle ear.[20] The auricle and lateral EAC

Table 1
National Cancer Institute Common Terminology Criteria for Adverse Events severity grading for radiation-induced dermatitis

Severity	Physical Findings
Grade 1	Faint erythema with dry desquamation
Grade 2	Moderate erythema and edema with patchy, moist desquamation, mostly confined to skin creases
Grade 3	Confluent, widespread moist desquamation, bleeding is common with trauma
Grade 4	Skin necrosis or full-thickness dermis ulceration, spontaneous bleeding can occur
Grade 5	Death due to dermatitis

Data from Ref.[18]

possess thicker epithelium with pilosebaceous units. The medial two-thirds of the EAC spans the junction between the lateral cartilaginous framework and the tympanic bone to the external surface of the tympanic membrane and is covered by a thin epithelium closely adherent to the underlying periosteum of the bony EAC.

RT-induced soft tissue changes happen acutely (≤30 days of initial exposure) and chronically. Common acute changes include erythema, which sets in hours after radiation, and both dry and moist epithelial desquamation, which occur 3 to 4 weeks after initial RT exposure.[21–23] Erythema and dry epithelial desquamation are shown in **Fig. 1**. Initial erythema is similar to a sunburn and consists of hyperemia and inflammation.[16] With moist desquamation, patients begin to experience otorrhea, similar to **Fig. 2**.[23] Secondary epithelial ulceration can be seen 6 weeks into RT[22]; when this happens, the patient may experience significant otalgia and worsening serous otorrhea.[21,24] Most acute soft tissue reactions resolve spontaneously 4 to 6 weeks after the conclusion of RT.[25] **Table 2** shows the different ways acute external ear toxicity severity has been classified by the NCI CTCAE.[18,26]

With disruption of the protective squamous barrier and a proinflammatory environment, otitis externa can develop with worsening edema and purulent otorrhea. Desquamation combined with edema can result in keratinous debris accumulating in the external ear canal, in turn further obstructing evacuation of debris from the canal and sound propagation.[23] Robinson[23] described 4 cases of RT-induced otitis externa in the 1990s, with growth of *Staphylococcus aureus*, coagulase negative *Staphylococcus*, *Diphtheroids*, and *Pseudomonas aeruginosa* isolated from the EAC. Complete resolution of the radiation-induced otitis externa took from 1 to 18 months.[23] More recent data show that chronic otitis externa occurs in 1% to 3% of patients who receive high-dose RT (55–70 Gy) and in 0% of patients who underwent medium-dose RT (40–55 Gy).[27]

Chronic effects of radiation include atrophy of the epidermis, dermis, and pilosebaceous units as shown in **Fig. 3**, resulting in a thinner epithelium, which is inherently more vulnerable to injury and poor wound healing.[6,13,28] After conclusion of RT, atrophy begins after 12 weeks, and subcutaneous fibrosis begins after 6 to 12 months and continues to progress over time.[22,24] Rates of late auricular skin and cartilage necrosis

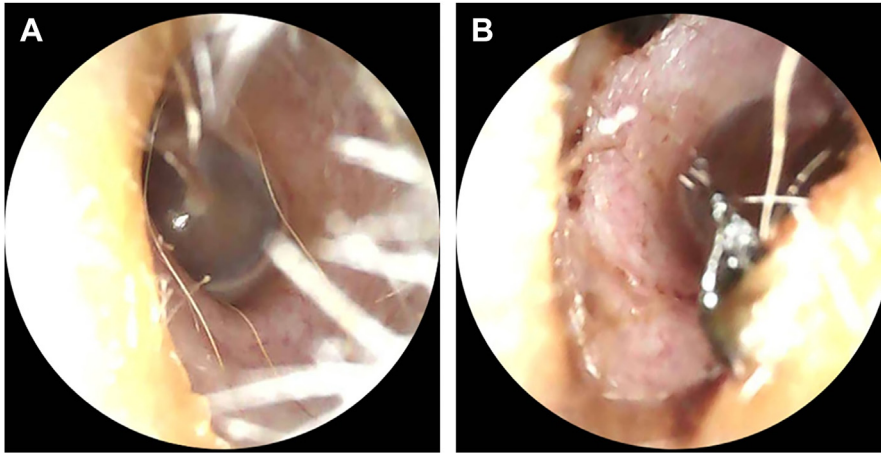

Fig. 1. A 59-year-old woman with salivary duct carcinoma of the right parotid gland who has received 29 Gy proton RT (total planned 63 Gy). (*A*) Nonradiated left EAC. (*B*) Irradiated right ear with faint erythema and dry desquamation, similar to grade 1 external ear toxicity.

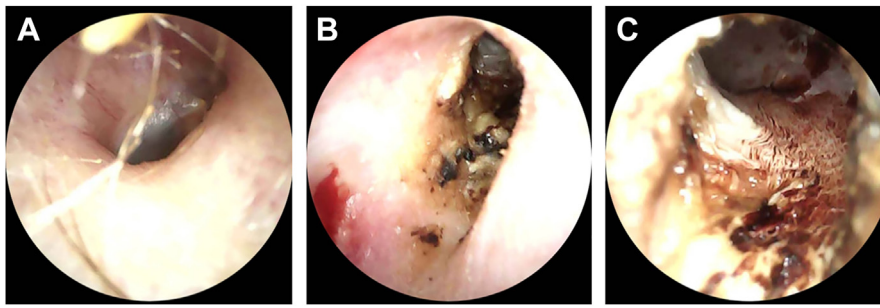

Fig. 2. An 84-year-old man with squamous cell carcinoma of the left parotid gland who has received 40 Gy proton RT (total planned 60 Gy). (*A*) Nonradiated right EAC. (*B*) Irradiated left lateral EAC with bleeding and moist desquamation, which extends medially to the bony EAC as shown in (*C*), similar to grade 3 acute radiation dermatitis and external ear toxicity.

have been historically reported in up to 13% of patients undergoing conventional irradiation of the pinna for superficial cutaneous carcinomas,[25,29,30] but these complications have not been seen with IMRT and IMPT. Canal cholesteatoma[28] and EAC stenosis[27] have also been reported with chronic soft tissue changes. Radiation-induced EAC stenosis has been seen in 8.7% of patients who receive high-dose RT (55–75 Gy) and is higher risk in patients who underwent surgery adjacent to the EAC, such as parotidectomy.[27] Canal cholesteatoma and acquired stenosis will be discussed in detail in separate articles.

PREVENTION

Patients who have their external ear in the radiation field need to be instructed to keep their ears as dry as possible to avoid infection.[23] Before the start of RT, patients should have their ears cleaned and inspected to promote proper ventilation of the EAC. With atrophy of the epithelium, patients should be counseled to avoid blindly placing objects into the EAC, as self-inflicted trauma combined with poor healing can result in worsening pathologic condition.[31] Monthly application of mineral oil has been

Table 2
National Cancer Institute Common Terminology Criteria for Adverse Events severity grading comparison for external ear in 1999, and otitis externa in 2017

Severity	1999 NCI CTCAE External Ear	2017 NCI CTCAE Otitis Externa
Grade 1	External otitis with erythema or dry desquamation	Localized intervention indicated
Grade 2	External otitis with moist desquamation	Oral intervention indicated
Grade 3	External otitis with discharge	IV antibiotic, antifungal, or antiviral medication indicated; invasive intervention indicated
Grade 4	Necrosis of the canal soft tissue or bone	Life-threatening consequences; urgent intervention indicated
Grade 5	N/A	Death

Abbreviation: N/A, not applicable.
Criteria from Ref.[26] and data from Ref.[18]

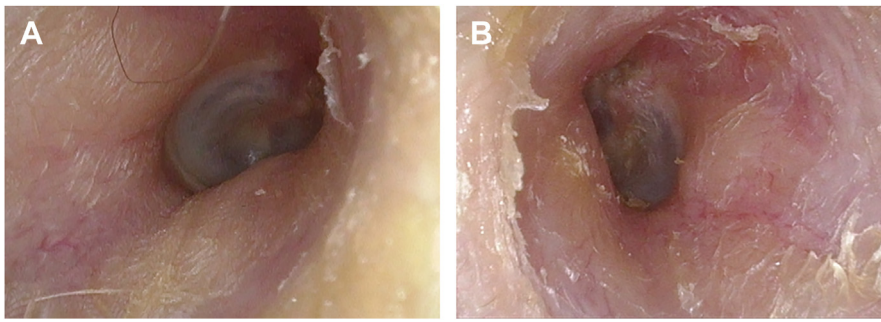

Fig. 3. A 72-year-old man with a history of left nasopharyngeal carcinoma status post definitive chemoradiation (70 Gy). (*A*) Nonradiated right EAC for comparison. (*B*) Irradiated left EAC with thinned epidermis and dry sloughing consistent with chronic radiation change.

suggested as a lubricating agent for the EAC to prevent injury, late epithelial necrosis, and ulceration for patients who have completed radiation.[21,32]

THERAPEUTICS

Management of acute radiation-induced soft tissue EAC disease is not well protocolized and has not been recently studied. Robinson[23] treated 4 cases of RT-induced otitis externa with frequent aural toilet and cleaning, placement of ribbon gauze, and 1% aqueous solution of Gentian Violet in the 1990s. Robinson[23] suggested that excessive topical and oral antibiotics use can prolong RT-induced otitis externa owing to growth of opportunistic organisms, but specific regimens for RT-induced otitis externa have not been described since. Current otitis externa treatment guidelines state that systemic antimicrobial therapy may be beneficial in addition to topical antimicrobial therapy.[33] Leonetti and colleagues[32] stated that topical antibiotic and steroidal drops should be prescribed in cases of skin ulceration to prevent infection and progression to temporal bone osteoradionecrosis. Topical corticosteroids have been used to treat chondritis and external EAC irritation.[25]

Radiation dermatitis, however, has been thoroughly studied. Grade 1 dermatitis (faint erythema and dry desquamation) is managed with routine hygiene and routine daily application of hydrophilic moisturizers.[34] Treatment of grade 2 or 3 dermatitis (moist desquamation) focuses on preventing secondary infection and protecting sloughing skin with dressings. Grade 4 dermatitis is particularly rare; the patient may require discontinuation of radiation and specialized wound care.[34] Patients with symptomatic discomfort and pruritis are treated with topical corticosteroids,[34] and daily application during RT has been shown to decrease rates of wet desquamation.[35,36] A randomized controlled trial[37] was conducted for radiation dermatitis treatment comparing topical steroid with hydrophilic ointment application. When grade 1 dermatitis was observed, the patient experienced pruritis, or when 30 Gy total radiation dose was reached, the intervention arm applied topical difluprednate versus petrolatum to the irradiated skin. The number of patients who suffered from grade 2 radiation dermatitis was similar between the 2 groups, but the number of patients who progressed to grade 3 dermatitis was significantly lower in the topical steroid group.

For late RT-induced complications, randomized controlled trials for patients with breast cancer have demonstrated prevention[38] and even regression[39] of subcutaneous fibrosis with prolonged treatment with pentoxifylline and vitamin E. The dosing

recommendations have not been well-defined, but Delanian and colleagues[39] used 800 mg daily of pentoxifylline in combination with 1000 Units per day of vitamin E. Magnusson and colleagues[38] used an incremental dosing increase of pentoxifylline (400 mg daily for 2 weeks, 400 mg twice daily for 2 weeks, and then 400 mg 3 times daily) in combination with 100 mg vitamin E 3 times daily. The most common side effect related to this regimen was nausea, which was attributed to the pentoxifylline. Pentoxifylline and vitamin E have been studied for osteoradionecrosis of the temporal bone and EAC,[40] but not for RT-induced soft tissue EAC disease. Hyperbaric oxygen therapy (HBO) has been used for both osteoradionecrosis of the mandible[41] and of the temporal bone,[42,43] but its effects on EAC RT-induced soft tissue disease are unclear. HBO works by prompting angiogenesis and alteration in fibrous tissue, effectively restoring the organized proliferation and healing of epithelium.[44]

Traditional hearing aids can be troublesome for irradiated patients because of possible EAC irritation, which is posited as a risk for otitis and osteoradionecrosis.[45] Nader and Gidley[46] determined that hearing aid fitting should be done with special care to avoid models that will exert EAC pressure. Patients with head and neck cancer requiring amplification owing to sensorineural hearing loss are typically fitted with behind-the-ear devices with an open-fit dome.[46] Osseointegrated hearing aids are an option for patients with significant otorrhea and soft tissue changes precluding the use of conventional hearing aids.[21,47] The concern of decreased rates of osseointegration, however, is pertinent; implant survival rate is quoted between 83% and 100%.[46]

DISCUSSION

There is a paucity of literature addressing the treatment of RT-induced soft tissue disease of the external ear and the subsequent progression to temporal bone osteoradionecrosis. There is good evidence, however, to support management strategies of RT-induced dermatitis that can be applied to the external ear.[36,37] The varying levels of severity of RT-induced dermatitis (erythema, dry desquamation, or moist desquamation) can be applied to otoscopic examination to determine if topical corticosteroid treatment may be beneficial. However, the EAC is more challenging to visualize for a nonspecialist, and otolaryngologists do not routinely see patients during RT unless their symptoms warrant specialized evaluation.

Routine otologic examination for patients whose radiation field includes the temporal bone may be useful to identify grade 1 dermatitis of the EAC, as these patients may benefit from topical steroid therapy. The current otitis externa guidelines recommend that patients with otitis externa and a history of RT may benefit from systemic treatment in addition to topical antimicrobial agents.[33] Increased attention to external ear soft tissue disease after radiation may decrease the risk of progression to osteoradionecrosis, but interventions that have been applied in the field of radiation oncology for dermatitis and emerging interventions warrant further study.

SUMMARY

Acute RT-induced external ear soft tissue changes typically start early during the radiation course with erythema and dry desquamation and may progress to moist desquamation and epidermal ulceration. Chronic RT-induced changes include epithelial atrophy and subcutaneous fibrosis. After RT, patients should avoid EAC trauma. Interventions for EAC soft tissue pathologic condition include topical steroid treatment for erythema and dry desquamation and topical antibiotic therapy for suppurative otitis externa; topical corticosteroid treatment may prevent worsening of RT-induced soft

tissue disease. Interventions for soft tissue radionecrosis involving the EAC warrant further investigation.

CLINICS CARE POINTS

- Acute radiotherapy-induced soft tissue changes include erythema and dry desquamation first, which may be followed by moist desquamation and epithelial ulceration.
- Chronic radiotherapy-induced soft tissue changes include epithelial atrophy, subcutaneous fibrosis, and overall poor wound-healing capabilities.
- Patients with otitis externa after or during radiation should receive topical antimicrobial steroidal treatment and may benefit from systemic treatment.
- Topical steroid therapy is promising for radiation dermatitis management but has not been studied in the external auditory canal.
- Hearing aid fitting and selection for irradiated patients should aim for minimal irritation and applied pressure to the external auditory canal.

DISCLOSURE

The authors testify no financial relationships to disclose or conflicts of interest pertaining to this work.

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