Management of bilateral locally advanced squamous cell carcinoma of the external auditory canal

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ABSTRACT
Bilateral squamous cell carcinoma (SCC) of the external auditory canal (EAC) is extremely rare. Here, we report the details of the history and management of a 74-year-old patient with bilateral locally advanced SCC of the EAC. The patient underwent subtotal temporal bone resection for primary SCC of the EAC in the right ear. Three years later, a biopsy revealed SCC of the contralateral ear. The patient received proton therapy for the second primary SCC of the EAC and achieved a complete response. Two years after proton therapy, a recurrence was observed in the left ear. Despite systemic chemotherapy for recurrence, the patient died of the disease. Although a second primary SCC in the contralateral ear is extremely rare, clinicians should consider the possibility of bilateral SCC of the EAC and carefully manage each of the ears during the follow-up period.

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Abstract
Bilateral squamous cell carcinoma (SCC) of the external auditory canal (EAC) is extremely rare. Here, we report the details of the history and management of a 74-year-old patient with bilateral locally advanced SCC of the EAC. The patient underwent subtotal temporal bone resection for primary SCC of the EAC in the right ear. Three years later, a biopsy revealed SCC of the contralateral ear. The patient received proton therapy for the second primary SCC of the EAC and achieved a complete response. Two years after proton therapy, a recurrence was observed in the left ear. Despite systemic chemotherapy for recurrence, the patient died of the disease. Although a second primary SCC in the contralateral ear is extremely rare, clinicians should consider the possibility of bilateral SCC of the EAC and carefully manage each of the ears during the follow-up period.

Abbreviations: SCC: Squamous cell carcinoma; EAC: External auditory canal; BAHA: Bone-anchored hearing aid; CDDP: Cisplatin; TPF: Docetaxel, cisplatin, 5-fluorouracil

Introduction
Squamous cell carcinoma (SCC) of the external auditory canal (EAC) arises from the external ear and is rare in head and neck cancers, resulting in less than 0.2% of all head and neck tumors [1,2]. Some factors affecting normal skin to SCC differentiation, such as chronic ear inflammation with otorrhea and a history of exposure to radiation, have been proposed in the literature. Patients with bilateral SCC of the EAC are extremely rare, and only 14 cases have been identified in the English literature, in which most cases were classified as early stage [3].

Surgical resection in en bloc fashion is the mainstay of treatment for SCC of the EAC, even in early [4] and advanced cases [5,6]. Due to the rarity of the disease, it is challenging to treat second primary EAC cancer in patients with primary EAC cancer who underwent an extended surgical resection. Here, we report the details of the history and management of a patient with bilateral locally advanced SCC of the EAC.

Case report
A 74-year-old man with hypertension, atrial fibrillation, and chronic heart failure initially presented with a 1-month history of ear fullness and later developed otalgia on the right side. The patient had been treated for right otitis externa with antibacterial agents and debridement. However, the symptoms had been increasing, and erosion of the skin and necrotic tissue was observed. Biopsies of the right ear were repeated, and they finally revealed SCC. The patient was then referred to our hospital for treatment. Computed tomography and magnetic resonance imaging revealed a tumor with thickening of the soft tissue and destruction of the middle ear and mastoid on the right side (Figure 1). Biopsy revealed well-differentiated SCC at our hospital. There was no facial palsy or lymph node swelling. There were no lymph node- or...
distant metastases on computed tomography, magnetic resonance imaging, or fluorodeoxyglucose positron emission tomography. We diagnosed locally advanced SCC of the EAC as T3N0M0, which was classified using the modified Pittsburgh classification system [2]. In the left ear, the EAC was quite narrow, and swelling was due to granulation tissue. However, no tumor or bone erosion was observed in the left ear. The patient was right-handed and did not have an ear-picking habit. The average hearing levels at three frequencies (500 Hz, 1 kHz, and 2 kHz) were 61.7 dB on the right side and 53.3 dB on the right side (Figure 2(a)). Six months after the first symptom had occurred, primary tumor resection, right selective neck dissection (level I–III), and total parotidectomy were performed at our hospital by the skull base surgery team, as shown in Figure 3. Using the technique of subtotal temporal bone resection, the tumor was removed en bloc, and the defect of the cranial base was covered using a free flap with the omentum. A hypoglossal-facial nerve anastomosis was performed for facial paralysis. The surgical margin was negative based on the resected specimens. The primary tumor invaded the surrounding bones and deep regions of the temporal bone. Thus, postoperative radiotherapy (60 Gy in 30 fractions of 2.0 Gy) was administered to
the tumor bed as adjuvant therapy. The clinical course was good, and no severe surgical complications were observed. Subsequently, the patient visited our hospital regularly every three months and was referred to a previous hospital for the management of persistent inflammation and the use of a hearing aid in the left ear.

Three years after surgery on the right ear, otorrhea continued, and granulation tissue was found in the left ear. His hearing level gradually worsened during the follow-up period (Figure 2(b)). Biopsies were repeated from the granulation tissue, and invasive SCC was finally diagnosed in the left EAC. Magnetic resonance imaging revealed an invading tumor in the left ear, and the tumor was classified as T3N0M0 (Figure 4). Due to severe postoperative complications, including hearing loss and facial paralysis bilaterally, we decided not to perform surgical resection for the second primary cancer. As an alternative treatment, proton therapy (70 GyE in 35 fractions of 2.0 GyE) was used in the second primary SCC of the EAC of the left ear. During the treatment, only Grade 1 dermatitis was found using Common Terminology Criteria for Adverse Events v4.0, and no severe complications, such as mucositis, nausea, or pancytopenia, were observed. The second primary cancer shrank and was diagnosed as a complete response (Figure 5(a)). The hearing level did not improve 6 months after proton therapy for the second primary SCC of the EAC in the left ear (Figure 2(c)).

Two years after proton therapy for the left ear, otorrhea and swelling of the skin occurred again, and granulation tissue was found yet again (Figure 5(b)). A biopsy revealed SCC recurrence in the left ear, and there were no lymph node- or distant metastases. The patient underwent systemic chemotherapy, including carboplatin plus 5-fluorouracil, nivolumab, and paclitaxel, for recurrence in the left ear. Despite systemic
chemotherapy for recurrence for 2 years, the patient died of the disease.

Discussion

Bilateral SCC of the EAC is extremely rare and presents diagnostic and therapeutic difficulties [3]. Common symptoms of SCC of the EAC are otorrhea, otalgia, hearing loss, and bleeding, and its diagnosis is often delayed due to concealment by primarily benign symptoms [7]. Risk factors for SCC include fair skin, solar ultraviolet light exposure, immunosuppression, and chronic inflammation of the otitis externa and otitis media [7]. It has been reported that for most patients, EAC SCC occurs on the same side as their handedness, and mechanical stimulations to the EAC, such as ear picking, may plausibly cause SCC in the EAC [8]. In the contralateral ear, the patient started to use an air conduction hearing aid after surgery, and suffered from chronic inflammation for a long time. The use of external devices, such as air conduction hearing aids, is a predisposing factor for the development of acute otitis externa [9]. Although this patient had been treated in the contralateral ear and received several biopsies, it was not easy to diagnose second primary SCC of the EAC due to chronic inflammation, resulting in a delayed diagnosis at the T3 stage. Although second primary SCC in the contralateral ear is extremely rare, clinicians should consider the possibility of bilateral SCC of the EAC and carefully manage each ear during the follow-up period.

In patients who underwent temporal bone resection for EAC cancer, commonly used air conduction hearing aids were not effective due to ear canal stenosis or closure. Bone conduction is an efficient pathway for sound transmission that can be harnessed to provide hearing amplification. Bone conduction hearing aids or bone-anchored hearing aids (BAHAs) may be indicated when ear canal pathology precludes the use of a conventional air conduction hearing aid [10]. Moreover, cartilage conduction hearing aids have also been developed, and adult patients with ear canal stenosis or closure are the best candidates for cartilage conduction hearing aids, regardless of their hearing thresholds [11]. This patient continued using an air conduction hearing aid in the contralateral ear and then presented with chronic inflammation of the otitis.
externa. Using alternatives to air-conducted hearing aids, such as bone conduction hearing aids, BAHAs, and cartilage conduction hearing aids, might be helpful in improving the hearing threshold in the surgical ear and in controlling chronic inflammation in the contralateral ear.

Surgical resection is an important treatment strategy that enables better survival outcomes in locally advanced carcinoma patients [5,6]. In previous reports of bilateral SCC in EAC, most cases of primary SCC of the EAC diagnosed in the early stage received radiotherapy and/or surgery, such as sleeve resection and lateral temporal bone resection. In this patient, we performed subtotal temporal bone resection and postoperative radiation for primary SCC of the right ear. No tumor recurrence was observed in the right ear. Generally, patients who undergo subtotal temporal bone resection often suffer from postoperative neurological dysfunction, such as hearing loss and facial paralysis. When the patient was diagnosed with second primary SCC of the EAC in the left ear, the tumor stage was T3, which invaded the surrounding temporal bone. Treatment for second primary SCC has become more complicated owing to the significantly lower quality of life due to neurological dysfunction of the ears and the face after the second extended surgery. Therefore, we decided not to perform extended surgical resection and chose an alternative treatment for the second primary SCC of the EAC.

Concomitant chemoradiotherapy with modified docetaxel, cisplatin (CDDP), and 5-fluorouracil (TPF) regimens or CDDP regimens is commonly used for locally advanced EAC cancer [12]. Chemoradiotherapy using a TPF regimen is an effective alternative for surgical treatment and achieved a 5-year survival rate of 56% for 34 patients with unresectable advanced SCC of the temporal bone [13]. However, this study demonstrated that Grade 3 acute non-hematotoxicity occurred in 30% of patients with EAC cancer, such as mucositis, vomiting, and anorexia, and 70% of patients experienced moderate or complete hearing impairment on the ipsilateral side as late toxicity [13]. Thus, concomitant chemoradiotherapy with TPF regimens or CDDP regimens is often not suitable for elderly patients or patients with poor general condition. In contrast, proton therapy is a relatively new treatment strategy, and a recent report showed the effectiveness of proton therapy for skull base malignancies. A systematic review showed that intensity-modulated proton therapy in head and neck cancer had a lower normal tissue dose while maintaining similar or better target coverage than intensity-modulated photon therapy, which is conventional radiation therapy [14]. Simone et al. reported that protons allowed significant sparing of important organs and should be considered for locally advanced head and neck SCC to decrease normal tissue toxicity while still providing optimal tumor coverage compared to various radiotherapies [15]. In our patient, only Grade 1 dermatitis was found, with no severe complications. Although tumor recurrence was found in the second primary SCC of the left ear, the patient achieved complete tumor response for 2 years after proton therapy. In the clinical setting, appropriate treatment should be selected for bilateral SCC of the EAC based on tumor stage, age, comorbidity, and quality of life.

Despite the efficacy of proton therapy as a treatment option in head and neck cancer, there is concern about severe late complications of proton therapy such as craniospinal dissemination, osteoradionecrosis of the maxilla and skull base, and brain necrosis [16]. Some studies demonstrated that temporal lobe necrosis rates ranged from 12% to 17% in patients with head and neck cancer receiving proton therapy to the skull base during an approximately 3-year follow-up period [17,18]. Our patient did not experience severe neurological dysfunction on the left side after proton therapy. Clinical studies or reports concerning patients with SCC of EAC treated with proton therapy are scarce, and further investigations and treatment results are necessary.

Conclusions

Although second primary SCC in the contralateral ear is extremely rare, clinicians should consider the possibility of bilateral SCC of the EAC and carefully manage each ear during the follow-up period.

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Ethical statement

This manuscript was written in accordance with the Code of Ethics of the World Medical Association (Helsinki Declaration). We confirmed a patient’s anonymity. We have obtained informed consent from the participant presented in the study.
**Disclosure statement**

The authors have no financial conflicts of interest to declare.

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