INTRODUCTION
Nasopharyngeal carcinoma (NPC) often affects ethnic Chinese populations. The treatment of choice for NPC remains external beam irradiation to the nasopharynx and nuchal areas.1 In the last century, two-dimensional radiotherapy (2DRT) was adopted to irradiate target regions, but it inevitably damages the adjacent tissues from the skull base to the neck. Irradiated NPC survivors increasingly experienced ear symptoms such as effusion, otitis media with effusion (OME); radiation-induced otitis media (ROM); sensorineural hearing loss; vestibular deficits; and most severely, temporal bone osteoradionecrosis (ORN).2–6 The development of radioimaging diagnostic techniques from computed tomography scan to magnetic resonance imaging, the introduction of chemotherapy to the treatment modality from adjuvant chemotherapy to concurrent chemoradiotherapy, and the invention of radiotherapeutic equipment from two-dimensional radiotherapy (2DRT) to intensity-modulated radiotherapy (IMRT) have increased the survival rate of NPC patients during the past 30 years. The prevalence of cochlear and vestibular deficits has decreased a lot, whereas middle ear complications (i.e., otitis media with effusion and radiation-induced otitis media) do not decline in NPC survivors even in the IMRT era, probably because the medial half of the Eustachian tube receives >95% of the total dose despite 2DRT or IMRT.

Key Words: Intensity-modulated radiotherapy (IMRT), otitis media with effusion (OME), postirradiated sudden deafness (PISD), radiation-induced otitis media (ROM), two-dimensional radiotherapy (2DRT), vestibular-evoked myogenic potential (VEMP).

This article reviews the literature on otological complications in nasopharyngeal carcinoma (NPC) survivors after irradiation during the past three decades. Symptoms of the irradiated ears were assessed from the external ear canal, through the middle ear cavity including the Eustachian tube, and to the inner ear compartments. The development of radioimaging diagnostic techniques, the introduction from adjuvant chemotherapy to concurrent chemoradiotherapy, and the invention of radiotherapeutic equipment to intensity-modulated radiotherapy (IMRT) have increased the survival rate of NPC patients during the past 30 years. The prevalence of cochlear and vestibular deficits has decreased a lot, whereas middle ear complications (i.e., otitis media with effusion and radiation-induced otitis media) do not decline in NPC survivors even in the IMRT era, probably because the medial half of the Eustachian tube receives >95% of the total dose despite 2DRT or IMRT.
pressure, and then the opening pressure was decided (norm, 364 ± 222 mmH2O). Once pressure between the middle ear cavity and the nasopharyngeal region equalized, the tube was closed and closing pressure was decided. Three trials were performed to confirm the reproducibility. Organic obstruction is defined as what occurs when applying middle ear pressure more than +800 mmH2O (limitation of the instrument) fails to open the tube.17 Notably, organic obstruction is not the total occlusion of the tube.

The active opening test applied positive/negative pressure to the middle ear cavity (Fig. 1). Functional impairment is interpreted when the applied positive pressure (+200 mmH2O) does not drop below 100 mmH2O after several swallows, or no pressure equalization after several swallows is noted when negative pressure (−200 mmH2O) was applied.18 For the clearance function test, indigo carmine dye (0.4%, 0.02 mL) was instilled into the middle ear cavity via a perforated eardrum. Clearance time was judged to be delayed when the interval between instillation of the dye into the middle ear cavity and its initial discharge from the pharyngeal orifice of the tube was >15 minutes.17

**Tubal Dysfunction in Nasopharyngeal Carcinoma Patients**

In 1986, a total of 50 fresh NPC patients underwent tubal function testing before radiotherapy. No significant difference in the passive opening pressure was noted between those with and without OME. However, a significant difference in active opening function was identified, indicating that tubal dysfunction in preirradiated NPC patients is mainly caused by functional impairment (50% abnormality) rather than by organic obstruction (15% abnormality) of the tube.17 Furthermore, tumor extension from the Rosenmuller fossa to the parapharyngeal space may cause poor active tubal opening, resulting in the development of OME.18

Tubal function worsened 6 months after irradiation because both functional impairment (75% abnormality) and organic obstruction (60% abnormality) of the tube were identified in NPC patients. Organic obstruction of the tube was noted to be severe with higher dosages of irradiation (up to 80 grays [Gy]), whereas functional impairment was mainly attributed to the inflammatory reaction.17

Nevertheless, the recovery of functional impairment (50% abnormality) was achieved 5 years after irradiation, as evidenced by normal active positive/negative pressure test, although the passive opening test still found that abnormal results indicating organic obstruction (60% abnormality) of the tube persisted. In other words, tubal function in irradiated NPC survivors was found worst at 6 months after irradiation but improved 5 years after irradiation.19

Surprisingly, recovery of tubal function was achieved in NPC survivors 10 years after irradiation. Resolution of the inflammatory reaction plays the most important role in the recovery of functional impairment (10% abnormality remains), and development of a patulous tube cancels previous organic obstruction (5% abnormality remains) of the tube.5 Figure 2 illustrates chronological changes of tubal dysfunction in NPC patients before and 6 months, 5 years, and 10 years after radiotherapy.

**Patulous Tube**

Patulous tube was defined as what occurs when the passive opening pressure < 142 mmH2O and the applied positive/negative pressure (±100 mmH2O) cannot be maintained during active opening test.20

A patulous tube is not constantly open; rather, it is insufficiently closed. Closure of a tube is maintained by the elasticity of its cartilage and mucosal lining and extrinsic factors such as peritubal fat (Ostmann’s fatty tissue) and muscles.21 Long-term effects of irradiation may cause atrophy, fibrosis, degeneration, and necrosis in the surrounding tissues, leading to the development of a patulous tube.22,23 The patulous tube still was not identified at 5-year postirradiation; however, 60% of the ears developed patulous tubes 10 years postirradiation.5 Thus, the presence of a patulous tube is related to the interval after irradiation.

Organic obstruction of the tube was once thought to be an irreversible change because irradiation causes permanent tissue damage; however, some long-term NPC survivors were devoid of middle ear complications, implying that both organic obstruction and functional impairment of the tube must resolve. In other words, the development of a patulous tube cancels the organic obstruction of the tube, whereas meticulously local treatment of the ears, nose, and nasopharynx helps diminish the inflammatory process.
EXTERNAL/MIDDLE EAR DYSFUNCTION

**Otitis Media With Effusion**

The pathogenesis of OME has been attributed to either organic obstruction or functional impairment of the tube. Preirradiated NPC patients had less common organic obstruction due to nearly normal passive opening pressure but had impairment in active tubal opening. Prevalence of OME increased once the tumor extended to the parapharyngeal space. Thus, OME in preirradiated NPC patients is associated with tumor extension and functional impairment of the tube.

Deterioration of tubal function persisted after irradiation, and inflammatory reaction was noted in the upper respiratory tract, including the maxillary sinus and nasopharynx. Unlike OME in preirradiated NPC patients, postirradiated OME is due to both organic obstruction and functional impairment of the tube. The former is caused by radiation injury to the peritubal region, especially at radiation dosages up to 80 Gy, and functional impairment is caused by inflammatory process within the radiation field due to radiation-induced tissue reaction (i.e., mucositis, desquamation, or edema) and tissue damage (i.e., atrophy, fibrosis, degeneration, or necrosis) in the radiation-exposed area. Nevertheless, inflammatory reaction may be reversible by halting ongoing destructive processes.

**Grommeted Ear**

Clinicians often insert a ventilation tube (grommet) in cases of OME for the restoration of tubal function, prevention of recurrent OME, and recovery of hearing. Based on this concept, a grommet was thus introduced to treat OME in NPC patients. However, a long-term follow-up study in irradiated NPC survivors with grommet insertion revealed that NPC patients with OME who received grommet insertion increasingly experienced chronic ear discharge.

Although grommets may force the tube opening and drain the middle ear effusion via the tube, infectious foci from sinusitis or nasopharyngitis ascend via the opening tube into the middle ear cavity (Fig. 3), causing superimposed otitis media in postirradiated OME patients. In fact, grommet insertion alone cannot eradicate inflammation outside the middle ear cavity but aggravate it by superinfection. Because both organic obstruction and inflammatory reaction are two major causes of postirradiated OME, controlling these two factors challenges clinicians. First, to preserve the tubal function, 70 Gy is recommended as the maximum dose for NPC. Second, to eradicate the inflammatory response, repeated myringotomies coupled with aspiration rather than grommet insertion are suggested to drain the effusion and relieve the inflammation. Further, all the radiation exposed regions should be meticulously cleansed to eradicate the hidden infectious foci.

**Radiation-Induced Otitis Media With Extratemporal Bone Involvement**

Radiation-induced otitis media with extratemporal bone involvement, briefly ROM, is a chronic inflammation...
of the middle ear that occurs irradiation on the head and neck regions. It differs from conventional chronic otitis media (COM) in the heterogeneity of its pathology. One interesting study analyzed the difference between the ROM and COM ears using the cervical vestibular-evoked myogenic potential (cVEMP) test. To overcome the attenuation of air-conducted sound stimuli caused by middle ear pathology, alternatively tapping evocation or bone-conducted (BC) sound stimuli have been utilized to induce cVEMPs during the 2DRT period. There was no significant difference in the mean air–bone gap between ROM and COM ears. However, unlike COM ears, most ROM ears revealed delayed cVEMPs indicating a retrolabyrinthine or brainstem lesion. Further, most (90%) non-NPC patients with ROM but no neck fibrosis demonstrate delayed or absent cVEMPs. In contrast, all patients with neck fibrosis but no ROM display normal cVEMPs. These observations imply that the effect of neck soft tissue on the cVEMPs is less.

Restated, ROM extends its inflammation from the middle ear to the extratemporal bone region. Thus, neither grommet insertion nor tympanoplasty is beneficial to irradiated ears, possibly because both managements limited inside the middle ear cavity, which failed to eradicate inflammation outside the middle ear cavity.

Osteoradionecrosis of the External Ear Canal
A case series of 33 ORN of the temporal bone comprised 14 cases irradiated in the 1990s (2DRT era) and 15 cases irradiated in the 2000s (IMRT era), indicating an extremely rare prevalence. The external ear canal can be affected with ulceration, epithelial thickening with stenosis, fibrosis, and atrophy of cerumen glands mimicking ROM or malignancy. Diagnosis of ORN is based on identifying necrotic bone, usually visible within the external ear canal in patients with previous irradiation. Further, ORN frequently presents with foul odorous and crusted tissue sticking to bare bone accompanied by superimposed infection of the affected region, which may provide another clue for diagnosis.

Hao et al. reported that radiation itself causes hypoxia, hypocellularity, and hypovascularity, which impaired normal collagen synthesis and cell production, leading to tissue breakdown and eventual necrosis. Additionally, superimposed infection is common within radiation damaged bone, and bacterial biofilms have been shown to be present as well. Hence, management of ORN is aimed at relief of symptoms by meticulously local cleansing and antibiotics treatment. Those with progressive and extensive ORN should be managed by ablative surgery and local reconstruction.

COCHLEAR DYSFUNCTION
There are four causal factors related to cochlear dysfunction in irradiated NPC survivals, namely 1) sequel of otitis media, 2) chemotherapeutic ototoxicity, 3) radiation damage, and 4) intracranial relapse, resulting in progressive or sudden sensorineural hearing loss.

Sequela of Otitis Media
A comparison of the hearing levels between grommeted and nongrommeted ears revealed that the air-conducted but not the bone-conducted hearing level had significantly greater deterioration in grommeted ears. The reason is probably that a chronic discharging ear is often observed in a grommeted ear of an irradiated NPC survivor. Inflammatory foci from the nose, sinuses, and nasopharynx that ascend via the tube into the middle ear cavity may cause suppurative otitis media (Fig. 3). Temporal bone study in COM ears has demonstrated that the round window membrane is infiltrated by inflammatory cells, and the round window niche is frequently obliterated by thick fibrous granulation tissue. Thus, the round window membrane is a likely pathway for toxin or pathogens from the middle ear invading into the cochlea, leading to sensorineural/mixed hearing loss. Moreover, the usage of otic drops (containing aminoglycosides) to combat the suppurative otitis media may produce otic ototoxicity and subsequently aggravate the hearing deterioration.

Chemotherapeutic Ototoxicity
In addition to otic ototoxicity, cisplatin-based chemotherapy warrants concern for delayed onset sensorineural hearing loss. Wei et al. reported that NPC patients who had received concurrent chemoradiotherapy experienced greater sensorineural hearing loss than those treated with radiotherapy alone. Temporal bone study in patients treated with cisplatin demonstrated damage to the inner and outer hair cells and degeneration of the spiral ganglion. However, the vestibular endorgans appeared normal, indicating that the cochlear partition is more susceptible than the vestibular partition to cisplatin toxicity.

A characteristic audiographic feature of chemotherapeutic ototoxicity is progressive onset, which is bilateral involvement alongside symmetric, high-tone (4,000
and 8,000 Hz) sensorineural hearing loss. This should be differentiated from the sudden onset, unilateral involvement, and global sensorineural hearing loss, termed postirradiated sudden deafness (PISD).

Radiation Damage: Postirradiated Sudden Deafness

Postirradiated sudden deafness is the sudden deafness that occurs several years following irradiation, with a mean interval from the completeness of radiotherapy to the occurrence of PISD of 10 ± 6 years.44 Because radiation induces advanced atherosclerosis, obliteratorative endarteritis, and thrombosis,2 damage to the vasoconductive tissue that impairs perfusion to the inner ear is responsible for the pathogenesis of PISD.

Compared to 2DRT, both radiation dosages to the cochlea and radiation damage to the tissues surrounding the inner ear are lessened by IMRT.10,45,46 Using the 2DRT, estimated radiation dose of 50 Gy was delivered to the cochlea, which was more than 35 Gy to the cochlea by IMRT.12 Consequently, irradiated NPC survivors treated by IMRT (0.2%) have a significantly lower prevalence of PISD than those treated by 2DRT (2%).47 Nevertheless, mean radiation dosage to the nasopharynx did not significantly differ between 2DRT and IMRT, indicating that radiation effect on the tissue depends on the amount of radiation absorbed rather than on the quantity of radiation delivered.

The mechanism of PISD is considered an aseptic inflammation of the endothelium of the blood vessel. The collagen and smooth muscles in the blood vessels degenerate and swell; this process may narrow or close the lumen of vessel and reduce blood supply, causing advanced atherosclerosis, obliteratorative endarteritis, and thrombosis.2,44

Intracranial Relapse

For irradiated NPC survivors with sensorineural hearing loss of acute onset, differentiation between PISD and tumor relapse often challenged the clinicians.48 The mean interval between completion of radiotherapy and onset of acute hearing loss is > 10 years for PISD. In contrast, acute hearing loss that occurs < 5 years after irradiation may indicate tumor relapse.49 Further, newly developed multiple cranial nerve deficits provide another clue to differentiate intracranial tumor relapse from PISD.

VESTIBULAR DYSFUNCTION

Vertigo rarely manifests as an initial symptom of NPC either before or early after irradiation; however, vertigo presents as a later complication in irradiated NPC survivors, with a mean interval of 10 years after completion of radiotherapy.11

Postirradiated Vertigo

Postirradiated vertigo in NPC survivors is mostly caused by peripheral labyrinthine origin (70%), followed by central vestibular origin (30%).12 Sequela of ROM plays a major causal role for the peripheral labyrinthine origin, which is correlated with radiation dosage but not with radiation interval. The ROM can be aggravated by bacterial superinfection, which subsequently induces the toxin or pathogens entering the inner ear, resulting in labyrinthitis.

In contrast, three pathogeneses are proposed for central vestibular origin, namely 1) vascular insufficiency, 2) radiation necrosis, and 3) tumor relapse. Of these, vascular insufficiency plays the dominant role in inducing audiovestibular loss.3 Next, radiation necrosis is concerned which originates from endothelial injury, and is followed by thickening of vascular wall, ischemic change, and finally coagulation necrosis.50 Radiation necrosis may occur from several months to years after irradiation by 2DRT. Nevertheless, radiation necrosis is rarely seen in NPC patients treated by IMRT.

For those with peripheral vertigo, controlling ROM by local cleansing of the inflamed regions is suggested to lessen the middle ear inflammation, thereby preventing later onset vertigo. In contrast, enhancing perfusion of the inner ear by plasma expander is recommended for NPC survivors with central vertigo.44,47,51

Postirradiated Oscillopsia

Oscillopsia is a symptom of jumbling eye movements, manifested as blurred vision when walking or running, and is caused by poor stabilization of the retinal image during head movements.92 In irradiated NPC survivors, oscillopsia occurs primarily from loss of vestibulo-ocular reflex due to bilateral ROM, or ocular oscillations caused by radiation necrosis.53,54 Because radiation damage to the inner ear or brain is dose-dependent and high dosage of irradiation relates to the oscillopsia, postirradiated oscillopsia was occasionally encountered at the clinic during the 2DRT era but not during the IMRT era.

Abnormal Cervical VEMP

The majority (61%) of irradiated NPC survivors showed delayed cVEMPs during the 2DRT era, which was different from normal cVEMPs in COM ears55,56 and likely due to sequela of ROM or radiation-induced brainstem damage. However, the prevalence of delayed cVEMPs using IMRT (31%) appeared significantly lower than that using 2DRT (61%),9 which further confirmed that IMRT is better than 2DRT due to decreased radiation on the temporal bone and brainstem.

The previous irradiation method utilized 2DRT to target structures yet inevitably damages adjacent tissues, with otological complications as the most notable adverse effects.58 Alternatively, to overcome adverse effects and improve patient quality of life, IMRT is well recognized as superior in escalation of dose coverage to the skull base and cervical nodes, thereby increasing the survival rate.59

CONCLUSION

The use of IMRT coupled with better imaging and chemotherapy tumor control rate in NPC has
significantly increased up to >80% for overall 5-year survival rate. Although radiation dose is reduced to 50% of total dose for the inner ear, it does not decrease the prevalence of middle ear complications in NPC survivors, probably because the medial half of the tube receives >95% of total dose. Even the lateral half of the tube also receives 90% of the total dose, despite 2DRT or IMRT. Thus, reduction of the dosage applied to the Eustachian tube becomes a task for decreasing the complications of irradiated ears in the future.

**BIBLIOGRAPHY**