Acute hearing loss following fractionated stereotactic radiosurgery for acoustic neuroma

Report of two cases

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Two cases of acute hearing loss are reported following fractionated stereotactic radiosurgery for acoustic neuroma. Both patients had neurofibromatosis type 2 and were treated with a peripheral tumor dose of 21 Gy delivered in three fractions (7 Gy each) with a minimum interfraction interval of 10 hours. One patient who had previously undergone surgical resection of the treated tumor presented with only rudimentary hearing in the treated ear secondary to an abrupt decrease in hearing prior to treatment. That patient reported total loss of hearing before complete delivery of the third fraction. The second patient had moderately impaired hearing prior to treatment; however, within 10 hours after delivery of the final fraction, he lost all hearing. Both patients showed no improvement in response to glucocorticoid therapy. Possible explanations for this phenomenon are presented.

KEY WORDS • acoustic neuroma • hearing loss • linear accelerator • stereotactic radiosurgery

STEREOTACTIC radiosurgery is an accepted treatment for selected small and moderately sized acoustic neuromas. One series in which there was a follow-up period lasting longer than 15 years showed that control of these radiosurgically treated tumors appears durable. The principal advantage of stereotactic radiosurgery for treating acoustic neuromas is the noninvasive nature of the treatment and the modest rate of treatment-related morbidity. Nevertheless, loss of hearing occurring between 3 and 9 months posttreatment is a well-described complication that is produced by subacute or late radiation injury. However, acute hearing loss has not previously been reported.

In this paper we describe two patients with neurofibromatosis type 2 (NF2) who developed hearing loss within 24 hours after undergoing linear accelerator (LINAC)-based radiosurgery. These patients were two of 32 patients (10 with NF2) treated from 1993 to 1997 with fractionated LINAC radiosurgery.

Case Reports

Case 1

History. This 39-year-old woman was informed that she had NF2 at the age of 26 years when bilateral acoustic neuromas and multiple intracranial meningiomas were identified. She underwent microsurgical resection of the acoustic neuroma on the right side in 1983. The following year, the acoustic neuroma on the left side was resected, a procedure that was complicated by complete hearing loss in that ear. In 1991 recurrent acoustic neuromas were noted bilaterally on the patient’s follow-up magnetic resonance (MR) images, and she underwent stereotactic radiosurgery to treat the left-sided tumor at another institution (15 Gy; 20-mm collimator), a procedure that was complicated by a transient partial left-sided facial nerve palsy. That same year, the patient noted an abrupt decrease in hearing in her right ear but declined treatment. In June 1996 a further subjective decrease in hearing on her right side was noted.

Examination. Audiograms showed a mean hearing threshold of 98 dB in the patient’s right ear, with a speech discrimination level of 64% at this level (Class IV hearing on the Gardner–Robertson scale). Serial MR images showed progression of the recurrent right-sided tumor to a maximum transverse diameter of 14 mm.

Radiosurgery. In an effort to save residual hearing on the right side, the patient was treated in a fixed CRW
stereotactic frame (Radionics, Burlington, MA) with LINAC (model 2300; Varian Oncology Systems, Palo Alto, CA) fractionated radiosurgery producing a 6-MV treatment beam performed with the aid of MR imaging localization. A single 15-mm-diameter collimator was used to deliver 21 Gy normalized to the 80th percentile in three fractions (7 Gy each) to the periphery of the recurrent tumor (Fig. 1). The isocenter dose was 23.62 Gy (7.87 Gy/fraction). Interfraction intervals were 14 hours and 10 hours, respectively.

Posttreatment Complication and Course. Immediately following the third fraction the patient reported complete loss of hearing in her right ear. No improvement was noted during 2 weeks of steroid therapy or over the course of the subsequent year.

Case 2

History. Neurofibromatosis type 2 had been diagnosed in this 48-year-old man who presented with NF2. The right-sided acoustic neuroma was treated with LINAC radiosurgery as seen in the pretreatment image (upper) and the treatment plan (lower). The blue area represents the 33% isodose line; the orange area the 66% isodose line; and the red/pink area 100% of the prescribed dose.

Fig. 1. Case 1. Magnetic resonance images obtained in a 39-year-old woman with bilateral acoustic neuromas. The right-sided neuroma (upper) was treated with LINAC radiosurgery according to the treatment plan shown (lower). The blue area represents the 33% isodose line; the orange area the 66% isodose line; and the red/pink area 100% of the prescribed dose.

Fig. 2. Case 2. Magnetic resonance images obtained in a 48-year-old man who presented with NF2. The right-sided acoustic neuroma was treated with LINAC radiosurgery as seen in the pretreatment image (upper) and the treatment plan (lower). The blue area represents the 33% isodose line; the orange area the 66% isodose line; and the red/pink area 100% of the prescribed dose.
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3 × 1.5 cm and the tumor on the right side 1 × 1 × 1 cm. The patient underwent stereotactic radiosurgical treatment (17 Gy) for his left-sided acoustic neuroma in 1993 without complication (single fraction, 3 isocenters, 15, 10, and 10 mm collimators). Serial MR imaging revealed a gradual increase in the size of his untreated right-sided tumor (Fig. 2). Meanwhile, he noted a decrease in right-sided hearing, which was investigated with audiometry. This study revealed a hearing threshold of 40 to 60 dB with a speech discrimination score of 60% at 75 dB (Class III hearing). Repeated MR imaging showed an increase in the size of the right-sided acoustic neuroma to 2 × 1.5 × 1.3 cm.

Radiosurgery. The patient’s right-sided acoustic neuroma was treated with fractionated stereotactic radiosurgery. The procedure had the same treatment parameters as described for Case 1. Two 10-mm isocenters were used to encompass the MR imaging–defined target volume. The isocenter doses were 26.38 Gy and 28.69 Gy.

Posttreatment Complication and Course. Ten hours after the third fraction was delivered, the patient noted complete loss of hearing in his right ear. High-dose corticosteroid therapy was initiated for 2 weeks; however, there was no improvement. At the patient’s 6-month follow-up evaluation, there was no recovery of hearing.

Discussion

Deterioration or loss of hearing during the 1st year after stereotactic radiosurgery is not an uncommon phenomenon, especially in patients with NF2. Hearing loss in such cases is usually thought to be a consequence of radiation injury to the cochlear nerve. In an effort to decrease the incidence of this complication, we recently began using fractionated radiation. However, acute hearing loss in the first 24 hours after treatment is a previously undescribed phenomenon that cannot be explained by the same mechanisms believed to produce late radiation injury.

The late effects of radiosurgery that result in hearing loss appear to depend on the total dose and the size of the radiation fraction. Such complications are believed to be caused by radiation damage to vascular connective stroma or endothelial cells, resulting in disruption of the blood–brain barrier (BBB) or ischemia secondary to vasoocclusion. Alternatively, the late effects of radiation have been ascribed to depletions of targeted cell renewal tissues. Assuming that neural tissue has a limited regenerative capacity, at some dose of radiation this capacity will be exhausted, resulting in neurological injury. Histologically, one finds demyelination, coagulative necrosis, lipophages, and gliosis with late radiation injury. Vascular changes include intimal proliferation, endothelial proliferation, mineralization, and hyalinization. These well-documented alterations in glial, neural, and endothelial tissue occur months after exposure to radiation and cannot account for acute neurological deficits. The patient in Case 1 was treated with a single 15-cm collimator to cover an acoustic neuroma with a maximum diameter of 14 mm. Such treatment, in retrospect, is not as conformational as desired, possibly affecting a segment of the cochlear nerve in the cistern and the internal auditory canal. Others have shown that injury is more likely if a long segment of the cranial nerve is irradiated; however, this observation was made with respect to long-term, delayed complications and not to acute toxicity.

Although the mechanism is poorly understood, hypotheses that explain the origins of acute radiation injury may provide a basis for understanding the rapid hearing loss observed in the two patients reported. Radiosurgery might cause acute edema within the acoustic neuroma by disrupting the BBB, which through compression could result in decreased blood flow within the cochlear artery. The stria vascularis, the site where the cochlear potential is generated, has a rich blood supply, suggesting that a disturbance in circulation can lead to cochlear dysfunction. Studies in rat brains in which immunohistochemically labeled albumin has been used have shown that extravasation of albumin occurs within 24 hours after irradiation with 20 to 40 Gy and increases during the first 72 hours. In addition, the extent of albumin extravasation appears to be related to the dose of radiation (≤ 80 Gy). Electron microscopy studies have shown ultrastructural evidence for increased BBB permeability in the monkey brain as early as 6 hours after doses of 27 Gy, whereas the perivascular spaces are distended with protein-rich edema for up to 6 days. This edema may be significant enough to compress the arterial supply of the cochlear nerve. The cochlear receptor cells and spiral ganglia have been shown in animal models (rat and cat) to be exquisitely sensitive to even mild hypoxia. Studies have shown that the human fetus, whose blood carries less oxygen, actually has hypoxia-induced sensory-hair cell loss that resolves at birth with improved oxygenation. Such sensitivity to hypoxia could possibly predispose cochlear cells to injury in the event that tumor edema compromised the blood supply. However, no MR images, which might document acute edema, were obtained in these two patients immediately posttreatment, and MR images obtained at 6 months demonstrated no evidence of edema. Furthermore, no published gamma knife series has documented acute edema.

An alternative hypothesis for acute hearing loss invokes the generation of free radical ions. In guinea pig and rabbit models, superoxide anion radicals are released within minutes of radiation treatment or acoustic trauma. The release of these radicals results in a dramatic decrease in blood flow to the cochlea, perhaps inducing vasospasm in the stria vascularis lasting up to 6 hours. Other studies indicate that the free radicals produced by radiation inactivate sodium- and potassium-activated adenosine triphosphate, the enzyme responsible for the generation of the membrane potential between cytoplasm and the extracellular medium, dramatically reducing the activity of this enzyme to zero in a dose-dependent fashion. Disruption of this enzymatic function has been proposed as a major source of damage following myocardial ischemia, and it appears reasonable that radiation-induced free radicals could significantly reduce blood flow and produce similar effects within the neurological system.

In other animal models, free radicals increase calcium ion influx across cell membranes, presumably leading to changes in acoustic transduction and, possibly, causing cell death. This phenomenon is similar to models in which...
high doses of glutamate and elevated intracellular calcium mediate neural toxicity. Previously, others proposed that cellular oxidative damage caused by calcium influx results in an ototoxic effect.\(^3\)\(^4\) In the guinea pig, an increase in intracellular calcium, which follows acoustic trauma, can be blocked by calcium channel blockers (nifedipine) or enzymes that degrade free radicals (superoxide dismutase).\(^5\)\(^6\) If this model were applicable to the radiosurgical treatment of acoustic neuroma, calcium channel blockers might reduce toxicity if administered before radiosurgery.

Both patients who suffered acute hearing loss had NF2, a disease that is associated with an increased risk of hearing loss with all surgical procedures (compared with patients who harbor solitary acoustic neuromas).\(^7\)\(^8\) Furthermore, because NF2 neuromas tend to surround the cochlear nerve as opposed to displacing the nerve (as do unilateral acoustic neuromas), the involved nerve may traverse the central region of the isocenter and, thereby, receive a higher dose of radiation. Such a situation may increase the susceptibility of patients with NF2 to the acute effects of radiation hypothesized earlier. However, given the apparent rarity of acute hearing loss after radiosurgery, it is unclear whether the complication rate differs between patients with NF2 and those with sporadic acoustic neuromas.

Despite these two cases, hearing preservation rates are higher and the incidence of cranial neuropathy after radiosurgery is comparable to if not lower than those achieved by the best reported series of microsurgery.\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\)\(^17\)\(^18\)\(^19\)\(^20\)\(^21\)\(^22\)\(^23\)\(^24\)\(^25\)\(^26\)\(^27\)\(^28\)\(^29\)\(^30\)\(^31\)\(^32\)\(^33\)\(^34\) Therefore, because the incidence of cranial neuropathy fell from 17% at doses of 18 to 20 Gy to 1% at doses of 10 to 15 Gy, lower LINAC doses may reduce the incidence of acute complications. Although uncommon, acute hearing loss is an important risk and both the patient and the treating physician need to be aware of this risk. Additional work is necessary to elucidate the exact mechanism responsible for this complication.

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References

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