The Journal of Laryngology & Otology (2009), ***123*** (Suppl. S31), *75–80*.

doi:10.1017/S0022215109005143

Main Article

Superselective, intra-arterial, rapid infusion chemotherapy for external auditory canal carcinoma

Y Ueda, T Kurita, Y Matsuda, S Ito, T Nakashima

Abstract

Previously, the treatment of carcinoma of the external auditory canal has mainly involved surgical resection. In order to enable organ preservation and to obtain cancer-free surgical margins, we introduced the use of superselective, intra-arterial, rapid infusion chemotherapy combined with radiotherapy to treat this condition.

We reviewed our patients' tumour stages, feeding arteries and clinical outcomes. Tumours were staged according to the Pittsburgh staging system. Chemotherapy was administered intra-arterially in the angiography suite via transfemoral catheterisation of the feeding arteries. Four patients underwent superselective, intra-arterial, rapid infusion chemo-radiotherapy. A complete response was obtained in all four patients. The overall toxic side effects were modest.

Superselective, intra-arterial, rapid infusion chemotherapy can be an effective, organ-preserving treatment for external auditory canal carcinoma, with a high cure rate.

Key words: Superselective Intra-arterial Infusion Chemotherapy; Squamous Cell Carcinoma; External Auditory Canal; Curative Effect

Introduction

Carcinoma of the external auditory canal is a rare disease, with an incidence of 1 per 1 000 000 population.[1–3] Owing to the tumour's rarity, it has been difficult to formulate a treatment strategy. With the development of skull base surgery and plastic surgery, surgical resection has become the main treatment for external auditory canal carcinoma.

Between 1981 and 2006, 33 patients were treated for carcinoma of the external auditory canal at Kurume University Hospital. According to Arriaga and colleagues' staging system,[1] this group contained 11 T_1, six T_2, eight T_3 and eight T_4 tumours. Patients' survival rates were calculated by the Kaplan–Meier method. The cause-specific, five-year survival rates were 100, 80, 38 and 50 per cent for stage T_1, T_2, T_3 and T_4 tumours, respectively. Although the five-year survival rate for T_1 plus T_2 patients reached 93 per cent, surgical resection for early cancer severely compromised patients' quality of life, due to the sacrifice of organ function. On the other hand, the five-year survival rate for T_3 plus T_4 cancer was 43 per cent, with a high rate of recurrence due to incomplete tumour resection.

In the treatment of external auditory canal carcinoma, local control of the primary tumour is of great importance, because neck and distant metastases are rare and most treatment failures result from local recurrence. In order to enable organ preservation in this severe disease, and to obtain cancer-free surgical margins, we introduced the use of superselective, intra-arterial, rapid infusion chemotherapy combined with radiotherapy.

Since 2003, we have treated four patients with superselective, intra-arterial, rapid infusion chemotherapy combined with radiotherapy, for carcinoma of the external auditory canal. The aim of this study was to evaluate the efficacy of intra-arterial chemotherapy administered concurrently with radiotherapy, for carcinoma of the external auditory canal.

Patients and methods

The study included four patients with primary squamous cell carcinoma of the external auditory canal (Table I). We retrospectively reviewed the records of all four patients, treated at our hospital for this condition between July 2003 to February 2006. The following information was collected: age, sex, tumour–node–metastasis (TNM) status, therapeutic method (i.e. feeder artery, frequency of intra-arterial chemotherapy and radiation dose), outcome and complications.

Radiography-based TNM staging was performed according to the Pittsburgh staging system. This system is based on improved radiographic methods

From the Department of Otolaryngology-Head and Neck Surgery, Kurume University School of Medicine, Kurume, Japan.

TABLE I

FOUR PATIENTS WITH EXTERNAL AUDITORY CANAL CARCINOMA: SUMMARY

Pt no	Age (yrs) / sex	Stage	RT (Gy)	Feeding artery (no of infusions)	Status	Follow-up (mths)
1	46/F	T_2 N_0 M_0	60	PAA (2)	AAW	50
2	79/F	T_4 N_0 M_0	70	PAA (3)	AAW	30
3	71/M	T_2 N_0 M_0	60	PAA (4)	AAW	19
4	77/M	T_3 N_0 M_0	60	STA (2)	AAW	24

No = number; yrs = years; RT = radiotherapy; mths = months; F = female; M = male; T = tumour; N = node; M = metastasis; PPA = posterior auricular artery; STA = superficial temporal artery; AAW = alive and well.

for assessing temporal bone carcinoma, and is outlined in Table II.

Chemotherapy was administered intra-arterially in the angiography suite via transfemoral catheterisation of the feeding arteries. In principle, patients received a cisplatin infusion (100 mg/patient) for up to one week with simultaneous intravenous administration of sodium thiosulphate, a neutralising agent. Patients received external beam radiation simultaneously with the cisplatin infusion chemotherapy. Radiotherapy was administered at 2.0 Gy per fraction, once daily, five days a week, with a photon beam energy of 6 MV. Two laterally angled, pair-wedged fields were used in all patients.

After two or three intra-arterial infusion chemotherapy sessions, the response to the therapy was evaluated using computed tomography (CT) or magnetic resonance imaging (MRI). Patients who appeared to have a complete response were continuously treated with chemo-radiation therapy for up to four infusions and a total dose of 60 Gy. On the other hand, patients who appeared to have a partial response or no change were treated by surgery, lateral temporal bone resection or subtotal temporal bone resection. The response of the disease to treatment was determined by either CT or MRI, six months after completion of therapy. The criteria for complete response, partial response and no change were based on the standard definitions established by the World Health Organization. We recorded any complications, such as osteoradionecrosis, sensorineural hearing loss and thromboembolic events.

All patients underwent audiological testing before commencing therapy and again 20 months afterwards. Assessment of patients' bone condition was used as an indicator of the stability of their cochlear function. Patients' sensorineural hearing level was calculated as the mean of bone conduction values for 250, 500, 1000, 2000 and 4000 Hz. Significant hearing loss was defined as greater than 15 dB sensorineural hearing loss.

TABLE II

UNIVERSITY OF PITTSBURGH STAGING SYSTEM FOR EXTERNAL AUDITORY CANAL CARCINOMA: TUMOUR STATUS

T_1	Limited to EAC, without bony erosion or evidence of soft tissue involvement
T_2	Limited EAC bony erosion (not full thickness) or limited (<0.5 cm) soft tissue involvement
T_3	Erosion of osseous EAC (full thickness), with limited (<0.5 cm) soft tissue involvement, or Tumour involving the middle ear and/or mastoid, or Presentation with facial paralysis
T_4	Erosion of cochlea, petrous apex, medial wall of middle ear, carotid canal, jugular foramen or dura, or Extensive soft tissue involvement (>0.5 cm)

EAC = external auditory canal.

Results

The four patients comprised two men and two women, with a median age of 68 years (range 46–79 years). All had squamous cell carcinoma. According to the Pittsburgh staging system, two patients had stage T_2 tumour, one had stage T_3 and one had stage T_4. All patients were free of neck or distant metastases. The median follow-up period was 30 months, ranging from 19 to 50 months. The mean dose of radiation was 62.5 Gy (range 60–70 Gy). Cisplatin was delivered via the posterior auricular artery in three patients and via the superficial temporal artery in one. The posterior auricular artery is an important feeding artery. Intra-arterial cisplatin infusions were delivered as follows: two infusions in two patients, three infusions in one patient and four infusions in one patient. All patients were evaluated in order to assess their response. A complete reponse was obtained in all four patients. Following treatment, all patients were well with no signs of recurrence.

Overall, toxic side effects were modest. Osteoradionecrosis of the temporal bone and thromboembolic events were not observed. The median follow-up period for hearing assessment was 27 months, ranging from 22 to 36 month. The average hearing loss in the five frequency areas tested was 5.25 dB (range −17 to 18 dB). A hearing loss of more than 15 dB occurred in only one patient.

Case reports

Case one. In June 2003, a 46-year-old woman was referred to our hospital after presenting with a one-year history of otorrhoea. The tumour was located on the posteroinferior wall of the left external auditory canal. A CT showed the tumour to involve the left external auditory canal with bony erosion, but not to invade the soft tissue (Figure 1). A MRI showed that the mass measured 10 × 5 × 5 mm and was enhanced by gadolinium administration. A biopsy specimen suggested a diagnosis of squamous cell carcinoma. The patient was diagnosed with a T_2 N_0 M_0 external auditory canal squamous cell carcinoma.

We selected intra-arterial infusion chemotherapy combined with radiotherapy, because the patient was eager for therapy which would preserve her

https://doi.org/10.1017/S0022215109005143 Published online by Cambridge University Press

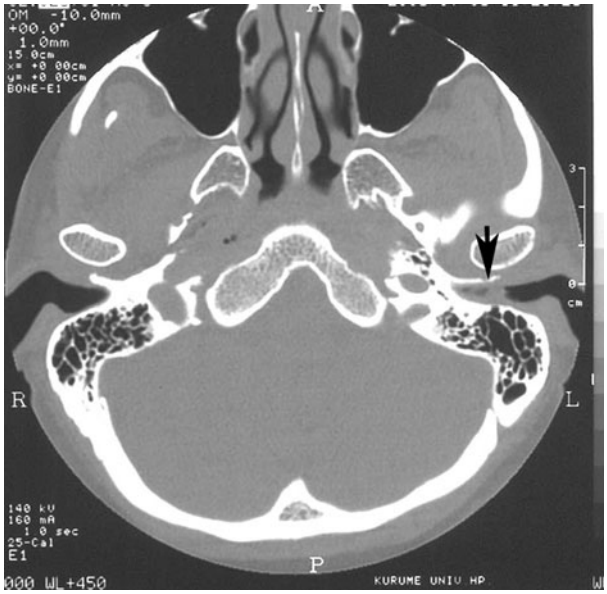

FIG. 1

Axial computed tomography scan for case one. The tumour (arrow) involved the left external auditory canal. Bony erosion was present.

hearing function. Cisplatin was delivered via the posterior auricular artery (Figure 2), and radiotherapy (60 Gy) was performed.

After this treatment, the tumour disappeared. The follow-up examination revealed no local recurrence or distant metastasis.

Case two. In March 2005, a 79-year-old woman was referred to our hospital with a one-year history of otorrhoea and otalgia. Her left external auditory canal was filled with tumour. A CT showed that the tumour had destroyed the bony wall of the external auditory canal and was invading into the tympanic cavity and mastoid. In addition, it had eroded into the basilar skull, including the posterior and middle fossae (Figure 3). A MRI demonstrated the presence of dural invasion, and the tumour was well enhanced by gadolinium administration (Figure 4). The histological diagnosis from a biopsy specimen was squamous cell carcinoma. The patient was diagnosed with stage T_4 N_0 M_0 external auditory canal squamous cell carcinoma.

Because of the patient's advanced age and the fact that her tumour was not deemed to be resectable, she underwent intra-arterial infusion chemotherapy combined with radiotherapy. Cisplatin was delivered through the posterior auricular artery three times (Figure 5), and radiotherapy (70 Gy) was performed.

After the treatment, the tumour disappeared. The follow-up examination revealed no local recurrence or distant metastasis.

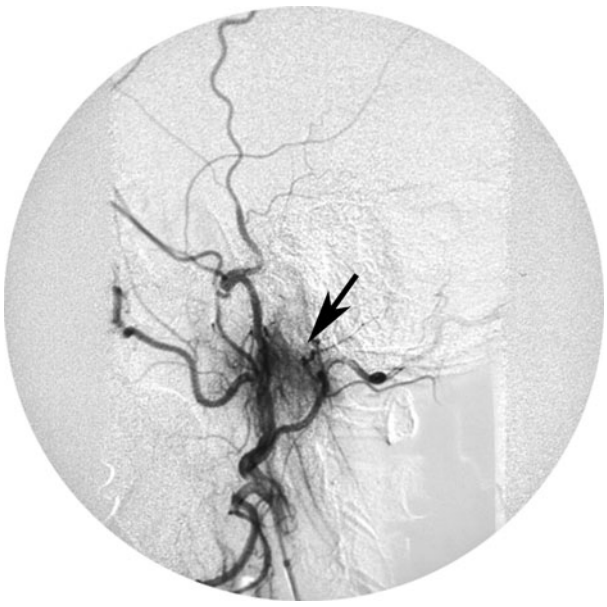

FIG. 2

Angiographic scan for case one. A rapid infusion of cisplatin was delivered twice through the posterior auricular artery. Arrow indicates the posterior auricular artery (the feeding artery).

Discussion

Treatment principles for external auditory canal carcinoma

Surgery plays a central role in the treatment of squamous cell carcinoma arising from the external auditory canal, and most patients are considered to benefit from a combination of surgery and radiation therapy. The role of chemotherapy remains uncertain. Because distant metastases are not commonly reported and local control of the primary tumour is

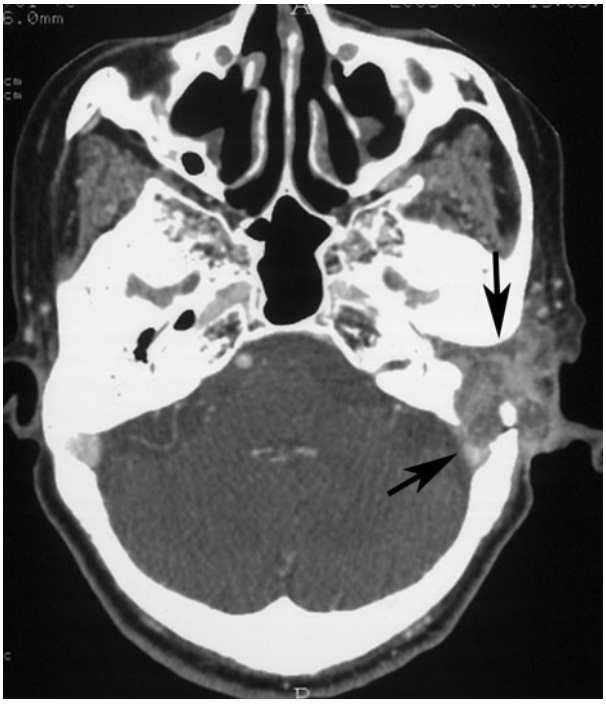

FIG. 3

Axial computed tomography scan for case two. The tumour (arrows) had destroyed the bony wall of the external auditory canal and eroded into the basilar skull, including the posterior and middle fossae.

https://doi.org/10.1017/S0022215109005143 Published online by Cambridge University Press

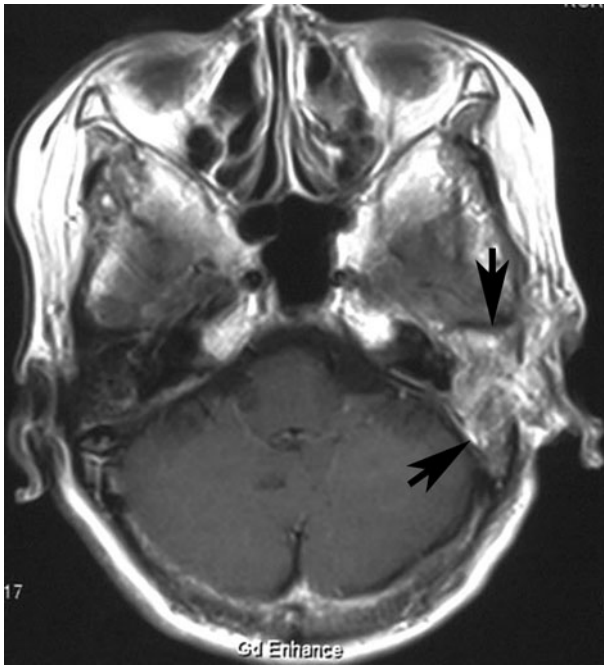

FIG. 4

Axial magnetic resonance imaging scan with gadolinium enhancement, for case two. The tumour (arrows) was well enhanced by gadolinium administration, and was invading the dura.

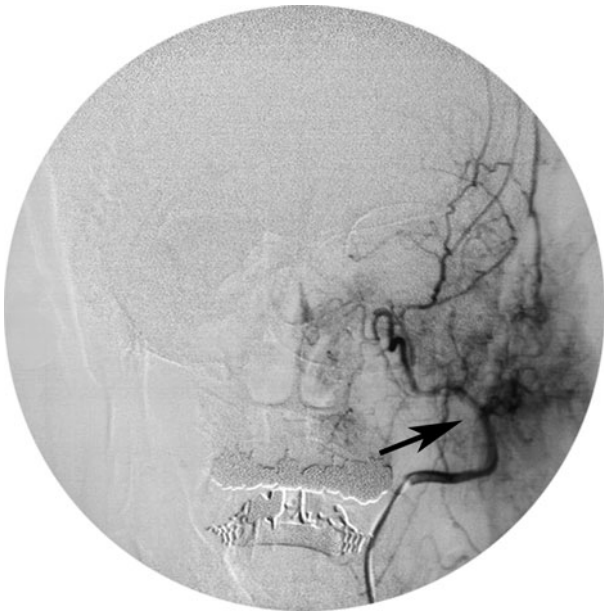

FIG. 5

Angiographic scan for case two. Rapid infusion of cisplatin was delivered three times through the posterior auricular artery. Arrow indicates the posterior auricular artery (the feeding artery).

important, systemic chemotherapy is not routinely used. It is widely accepted that radiotherapy or radiotherapy combined with surgery is a reasonable treatment for patients with T_1 disease.[4–7] On the other hand, the prognosis of patients with T_2 or more advanced disease treated by radiotherapy alone is poor, and radiotherapy combined with surgery is recommended as the standard treatment for these patients.[4,7–10] Surgical resection for external auditory canal SCC is often followed by local recurrence, due to frequent invasion of the adjacent temporal bone.[6] Most investigators agree that a wide *en bloc* resection of the tumour, with clear surgical margins, is the optimal treatment.[3,4,11] Nevertheless, a pathologically positive margin was mainly observed in patients with stage III and IV tumours.[11] Some investigators have found the five-year disease-free survival rate to be significantly higher in patients with a negative surgical margin than in patients with a positive surgical margin.[3,11,12] Several investigators have indicated incomplete resection to be the major cause of recurrence, and have found post-operative radiotherapy not to be beneficial.[3,13] Patients with advanced cancer who undergo an incomplete tumour resection should be treated with neoadjuvant therapy. Therefore, some investigators have recommended pre-operative radiotherapy.[3] Nakagawa *et al.*[3] stated that a complete *en bloc* resection with tumour-free surgical margins plus pre-operative chemoradiotherapy effectively improved the estimated survival of patients with advanced SCC of the temporal bone. Comparing concurrent chemo-radiotherapy with radiotherapy alone, several investigators have found that chemo-radiotherapy improved local control, while often resulting in tumour absence at the surgical margin.[14,15]

Intra-arterial infusion chemotherapy combined with radiotherapy

No previous reports have indicated that intra-arterial infusion chemotherapy combined with radiotherapy is equally effective for the treatment of external auditory canal carcinoma, compared with surgical resection. However, Robbins *et al.*[16] developed a delivery system for administration of high dose cisplatin to patients with head and neck cancer. Intra-arterial chemotherapy has a theoretical advantage over standard intravenous chemotherapy because of the higher concentration of chemotherapeutic agent delivered directly to the tumour bed, and the lower concentration delivered to other organs.

Intra-arterial infusion is an especially relevant delivery system for cisplatin, because this agent's tumour cell killing effect is known to be dose-dependent.[17] Intra-arterial, high dose, cisplatin chemotherapy combined with concurrent radiation therapy showed high complete response rates and good local control rates in patients with paranasal sinus, pharyngeal and laryngeal cancer.[18–21] Furthermore, intra-arterial infusion chemotherapy combined with radiotherapy has been effectively used in the treatment of maxillary sinus carcinoma, and it has been proven as an effective organ preservation treatment with a high cure rate.[21–23]

It is our opinion that intra-arterial infusion chemotherapy combined with radiotherapy is also effective for the treatment of external auditory canal carcinoma. The following three points are thought to support this belief. (1) Anatomically speaking, it is difficult to remove external auditory canal carcinoma by *en bloc* resection with tumour-free surgical

https://doi.org/10.1017/S0022215109005143 Published online by Cambridge University Press

margins, because the external auditory canal is enclosed by a bony wall and important organs are located close by. (2) Functionally speaking, wide surgical resection severely compromises the patient's quality of life, due to sacrifice of organ function. (3) Regarding the availability of a feeding artery, the external auditory canal is supplied by branches of the external carotid artery.

In our study, cisplatin was delivered via the post-auricular artery in three patients (75 per cent); this artery was identified as an important feeding artery of external auditory canal carcinoma. A complete response was obtained in all four patients; these results indicate that intra-arterial infusion chemotherapy may be an effective organ preservation treatment with a high cure rate. In addition, these results suggest this treatment modality to be an effective therapy for advanced external auditory canal carcinoma.

Complications

Osteoradionecrosis. Osteoradionecrosis of the temporal bone is a major and not infrequent complication of radiotherapy; its reported incidence ranges from 5 to 30 per cent.[24–27] In a series reported by Nadol and Schuknecht,[27] of 27 patients with carcinoma of the ear treated with a combination of surgery and post-operative radiation therapy, osteoradionecrosis developed in eight (30 per cent). These authors reported that osteoradionecrosis occurred in 42 per cent of cases (eight of 19) treated with surgery leaving an open cavity plus post-operative radiotherapy of average 5840 rad. On the other hand, they reported no osteoradionecrosis in eight patients treated by surgery with cavity obliteration plus post-operative radiotherapy of average 5700 rad. As a result, Nadol and Schuknecht concluded that cavity obliteration significantly decreased the incidence of osteoradionecrosis. The latent period between radiotherapy and the onset of osteoradionecrosis has been reported to range from eight months to 13 years.[26,27] Further investigations of osteoradionecrosis in such cases should therefore be conducted.

Sensorineural hearing loss. The effects of radiation on the auditory apparatus have long been a topic of interest. In such circumstances, hearing loss is due to the direct effect of ionising radiation on postmitotic cells and/or altered vascular physiology which interferes with oxygen supply to the cochlea.[28] The latent period between radiotherapy and the onset of sensorineural hearing loss has been reported to range from six month to four years.[29–32] In some studies, mainly those involving nasopharyngeal carcinoma and parotid tumours, the incidence of sensorineural hearing loss following radiotherapy ranged from approximately 30 to 50 per cent.[29,33] In the current study, the average hearing loss over five frequencies was 5.25 dB, and significant hearing loss occurred in only one patient; no deafness was found to occur.

Thromboembolic events. We did not observe any thromboembolic events in our series. However, we recognise that catheter-related thromboembolic events remain a potential complication associated with intra-arterial infusion chemotherapy.

Conclusions

With the development of skull base surgery and plastic surgery, the survival rate for external auditory canal carcinoma has improved. However, surgical treatment for this tumour can often cause facial paresis, cosmetic damage (due to deformation of the auricle) and hearing loss. Considering such quality of life issues, a less aggressive treatment is therefore desirable for patients with external auditory canal cancer. Our results indicate that superselective intra-arterial infusion chemotherapy may be a safe and effective organ preservation treatment, with a high cure rate.

References

1 Arriaga M, Curtin H, Takahashi H, Hirsch BE, Kamerer DB. Staging proposal for external auditory meatus carcinoma based on preoperative clinical examination and computed tomography findings. *Ann Otol Rhinol Laryngol* 1990;**99**:714–21
2 Arena S, Keen M. Carcinoma of the middle ear and temporal bone. *Am J Otolaryngol* 1988;**9**:351–6
3 Nakagawa T, Kumamoto Y, Natori Y, Shiratsuchi H, Toh K, Kakazu Y *et al*. Squamous cell carcinoma of the external auditory canal and middle ear: an operation combined with preoperative chemoradiotherapy and a free surgical margin. *Otol Neurotol* 2006;**27**:242–9
4 Ogawa K, Nakamura K, Hatano K, Uno T, Fuwa N, Itami J *et al*. Treatment and prognosis of squamous cell carcinoma of the external auditory canal and middle ear: a multi-institutional retrospective review of 87 patients. *Int J Radiat Oncol Biol Phys* 2007;**68**:1326–34
5 Pemberton LS, Swindell R, Sykes AJ. Primary radical radiotherapy for squamous cell carcinoma of the middle ear and external auditory canal – a historical series. *Clin Oncol* 2006;**18**:390–4
6 Wang CC. Radiation therapy in management of carcinoma of the external auditory canal, middle ear, or mastoid. *Radiology* 1975;**116**:713–15
7 Hashi N, Shirato H, Omatsu T, Kagei K, Nishioka T, Hashimoto S *et al*. The role of radiotherapy in treating squamous cell carcinoma of the external auditory canal, especially in early stages of disease. *Radiother Oncol* 2000;**56**:221–5
8 Austin JR, Stewart KL, Fawzi N. Squamous cell carcinoma of the external auditory canal. Therapeutic prognosis based on a proposed staging system. *Arch Otolaryngol Head Neck Surg* 1994;**120**:1228–32
9 Stell PM, McCormick MS. Carcinoma of the external auditory meatus and middle ear. Prognostic factors and a suggested staging system. *J Laryngol Otol* 1985;**99**:847–50
10 Korzeniowski S, Pszon J. The results of radiotherapy of cancer of the middle ear. *Int J Radiat Oncol Biol Phys* 1990;**18**:631–63
11 Yin M, Ishikawa K, Honda K, Arakawa T, Harabuchi Y, Nagabashi T *et al*. Analysis of 95 cases of squamous cell carcinoma of the external and middle ear. *Auris Nasus Larynx* 2006;**33**:251–7
12 Nyrop M, Grontved A. Cancer of the external auditory canal. *Arch Otolaryngol Head Neck Surg* 2002;**128**:834–7
13 Goodwin WJ, Jesse R. Malignant neoplasms of the EAC and temporal bone. *Arch Otolaryngol Head Neck Surg* 1980;**106**:675–9
14 Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous cell carcinoma: three meta analyses of updated individual data. MACH-NC Collaborative Group/

https://doi.org/10.1017/S0022215109005143 Published online by Cambridge University Press

Meta-analysis of Chemotherapy on Head and Neck cancer. *Lancet* 2000;**355**:949–55
15 Al-Sarrf M, Marts K, Herskovic A, Leichman L, Brindle JS, Vaitkevicius VK *et al*. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. *J Clin Oncol* 1997; **15**:277–84
16 Robbins KT, Staniolo AM, Kerber C, Seagren S, Berson A, Howell SB. Rapid superselective high dose cisplatin infusion for advanced head and neck malignancies. *Head Neck* 1992;**14**:364–71
17 Los G, Blommaert A, Barton R, Heath DD, den Engelse L, Hanchett C *et al*. Selective intra-arterial infusion of high dose cisplatin in patients with advanced head and neck cancer results in high tumor platinum concentrations and cisplatin-DNA adduct formation. *Cancer Chemother Pharmacol* 1995;**37**:150–4
18 Robbins KT, Vicario D, Seagren S, Weisman R, Pellitteri P, Kerber C *et al*. A targeted superdose cisplatin chemoradiation protocol for advanced head and neck cancer. *Am J Surg* 1994;**168**:419–21
19 Robbins KT, Fontanesi J, Wong FS, Vicario D, Seagren S, Kumar P *et al*. A novel organ preservation protocol for advanced carcinoma of the larynx and pharynx. *Arch Otolaryngol Head Neck Surg* 1996;**122**:853–7
20 Robbins KT, Kumar P, Wong FS, Hartsell WF, Flick P, Parmer R *et al*. Targeted chemoradiation for advanced head and neck cancer. *Head Neck* 2000;**22**:687–93
21 Samant S, Robbins KT, Vang M, Wan J, Robertson J. Intra-arterial cisplatin and concomitant radiation therapy followed by surgery for advanced paranasal sinus cancer. *Arch Otolaryngol Head Neck Surg* 2004;**130**:948–55
22 Fujishiro Y, Nakao K, Watanabe K, Ebihara Y, Nakamura N, Mori H *et al*. A new aspect of tri-modal therapy with superselective intra-arterial chemotherapy in maxillary sinus carcinoma. *Acta Otolaryngol Suppl* 2007;**559**:151–6
23 Shiga K, Yokoyama J, Hashimoto S, Saijo S, Tateda M, Ogawa T *et al*. Combined therapy after superselective arterial cisplatin infusion to treat maxillary squamous cell carcinoma. *Otolaryngol Head Neck Surg* 2007;**136**:1003–9
24 Wang PC, Tu TY, Liu KD. Cystic brain necrosis and temporal bone osteoradionecrosis after radiotherapy and surgery in a patient with ear carcinoma. *J Chin Med Assoc* 2004;**67**:487–91
25 Wang CC, Doppke MS. Osteoradionecrosis of the temporal bone – consideration of nominal standard dose. *Int J Radiat Oncol Biol Phys* 1976;**1**:881–3
26 Pemberton LS, Swindell R, Sykes AJ. Primary radical radiotherapy for squamous cell carcinoma of the middle ear and external auditory canal. *Clin Oncol* 2006; **18**:390–4
27 Nadol JB, Schuknecht HF. Obliteration of the mastoid in the treatment of tumors on the temporal bone. *Ann Otol Rhinol Laryngol* 1984;**93**:6–12
28 Moretti JA. Sensori-neural hearing loss following radiation therapy to the nasopharynx. *Laryngoscope* 1976;**86**: 598–602
29 Grau C, Moller K, Overgaard M, Overgaard J, Elbrond O. Auditory brain stem responses in patients after radiation therapy for nasopharyngeal carcinoma. *Cancer* 1992;**70**: 2396–401
30 Pan CC, Eisbruch A, Lee JS, Snorrason RM, Haken RKT, Kileny PR. Prospective study of inner ear radiation dose and hearing loss in head-neck cancer patients. *Int J Radiat Oncol Biol Phys* 2005;**61**:1393–402
31 Kun LE, Thompson JW, Gould HJ, Stocks RMS. Hearing loss as a late complication of radiotherapy in children with brain tumors. *Ann Otol Rhinol Laryngol* 2005;**114**: 328–31
32 Ho WK, Wei WI, Kwong DL. Long-term sensorineural hearing deficit following radiotherapy in patients suffering from nasopharyngeal carcinoma: A prospective study. *Head Neck* 1999;**21**:547–53
33 Schot LJ, Hilgers FJM, Keus RB, Schouwenburg PF, Dreschler WA. Late effects of radiotherapy on hearing. *Eur Arch Otorhinolaryngol* 1992;**249**:305–8

Address for correspondence:
Dr Yoshihisa Ueda,
Department of Otolaryngology-Head and Neck Surgery,
Kurume University School of Medicine,
67 Asahi-machi,
Kurume 830-0011, Japan.

Fax: +81 942 37 1200
E-mail: yued@med.kurume-u.ac.jp

Dr Y Ueda takes responsibility for the integrity of the content of the paper.
Competing interests: None declared