Background: Stereotactic radiotherapy (SRT) may represent a new treatment option for individuals with auditory canal or middle ear cancer.

Methods: Study participants with pathologically proven ear cancer were treated with SRT (35 Gy for 3 fractions or 40 Gy for 5 fractions) as first-line therapy. When local tumor recurrence developed following SRT, subtotal temporal bone resection and postoperative chemoradiotherapy were performed as salvage treatment. Boluses were used for the initial 14 study patients.

Results: Twelve-nine study participants were enrolled and staged with T1 (n = 3), T2 (n = 7), T3 (n = 14), or T4 disease (n = 5). Three-year overall survival rates were 69% for T1/2 disease, 79% for T3 disease, and 0% for T4 disease. Three-year local control rates were 70% for T1/2 disease, 50% for T3 disease, and 20% for T4 disease. Grade 2 or higher dermatitis or soft-tissue necrosis occurred more frequently in study patients treated with boluses (8/14 vs 2/15; P = .02). Salvage treatment was safely performed for 12 recurrent cases.

Conclusions: These results suggest that SRT outcomes are promising for patients with ear cancer (≤T3 disease). The rate of toxicity was acceptable in the study patients treated without boluses. Outcomes of salvage surgery and postoperative radiotherapy following SRT were also encouraging.

Introduction

Because of the rarity of external auditory canal and middle ear cancers, large-scale prospective studies have not been performed, and optimal treatment remains controversial.1,2 Nevertheless, surgery followed by conventional radiotherapy has been recommended.3,5 Subtotal temporal bone resection or total temporal bone resection are often performed.3,4 However, these procedures often cause severe complications. Deafness and facial palsy are generally unavoidable. A need exists for the development of less-invasive treatments, although some hurdles remain for the treatment of ear cancer. For example, reported outcomes of radiotherapy alone or chemoradiotherapy are not satisfactory in patients with advanced-stage ear cancer.5 Local recurrence after radiotherapy may require surgical intervention. Due to the difficulties of en bloc resection and the increased risk of complications, surgeons may be reluctant to approach recurrent ear cancer previously treated with radiotherapy.7,8 Furthermore, postoperative radiotherapy is difficult for patients with a prior history of radiotherapy due to the possible toxicities of reirradiation.

Data regarding the outcomes of radiotherapy for ear cancer are primarily from series of patients who underwent conventional 2- or 3-dimensional radiotherapy.5,6,9-11 However, developments in conformal radiotherapy may provide a new treatment option for ear cancer. Stereotactic radiotherapy (SRT) has the dosimetric advantages of improved target coverage with a steep dose gradient and spares surrounding normal tissues.12,13 Thus, salvage surgery and postoperative radiotherapy can be performed following SRT for intracranial tumors.14,15

Materials and Methods

Study Design and Participants

Initiated in 2008, this prospective study included patients with ear cancer who fulfilled the following inclusion criteria: pathologically proven external auditory canal or middle ear cancer and a Karnofsky Performance Status scale of at least 70. Exclusion crite-
ria were multiple malignant tumors, pregnancy, breastfeeding, previous diagnosis of any psychological disorders, contraindications to iodine or gadolinium, and previous radical surgery or irradiation to the skull or brain. Once enrolled, the participants were classified according to the modified Pittsburgh grading system. Those with T1 to T4 or N1-staged ear cancer were treated with this protocol. Each study patient’s staging classification was determined prior to treatment with SRT based on findings from magnetic resonance imaging, computed tomography (CT), and a physical examination. Study participants were enrolled at a single institution (International University of Health and Welfare Mita Hospital [Tokyo, Japan]). One head and neck surgeon performed all of the physical examinations. Written informed consent was obtained from all patients. This study was approved by our Institutional Research and Ethics committee.

Treatment Strategy and Details
The treatment strategy is described in Fig 1. All study participants underwent SRT as first-line treatment. SRT was carried out at a single institution (Yokohama CyberKnife Center [Yokohama, Japan]). When local recurrence occurred, salvage surgery followed by conventional 3-dimensional radiotherapy was performed at the International University of Health and Welfare Mita Hospital. SRT was performed using CyberKnife (Accuray, Sunnyvale, California). This machine was chosen due to the high conformity in SRT for head and neck tumors.

The study participants were placed in a supine position and a thermoplastic mask was molded to the head and attached to the head support. Axial contrast-enhanced CT with a slice thickness of 2 mm was conducted for treatment planning. The clinical target volume was defined as an abnormal contrast-enhanced lesion seen on CT and magnetic resonance imaging. To create the planning target volume (PTV), 2-mm margins were added to the bone structure side and 5-mm margins to the soft-tissue structure side. Dose distribution was calculated with the ray-tracing algorithm. Boluses with high CT attenuations (250–900 HU) were used for the initial 14 study participants to avoid dose reduction of the skin. Bolus usage was ceased for the latter 15 study participants.

The prescribed dose covered 95% of the PTV. Depending on tumor volume and risk-organ doses, 37.5 Gy in 3 fractions or 40.0 Gy in 5 fractions was delivered on consecutive days. The maximum doses to risk organs were limited to 21 to 25 Gy for 5 fractions and 15 to 18 Gy for 3 fractions. The 5-fraction regimen was applied to large tumors (size > 30 cc) or tumors close to the internal carotid artery. When local tumor recurrence developed following SRT, subtotal resection of the temporal bone and postoperative 3-dimensional chemoradiotherapy (60 Gy/30 fractions) were performed using 4 or 10 MV photons generated by a conventional linear accelerator. Intravenous cisplatin 80 mg/m² was administered twice on a 3-week interval. Radical neck dissection was performed for lymph-node metastases.

End Points
We evaluated rates of nonhematological toxicities, local tumor control, and overall survival (OS) as end points. Toxicities were recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4. Grade 3 or higher toxicity was considered unacceptable. All toxicities were evaluated by an otolaryngologist. The OS and local control rates were calculated by the Kaplan-Meier method. The cumulative incidence of local control failure was calculated by accounting for death as a competing risk. All local control failures were pathologically confirmed. The log-rank test and the Gray test were used in the univariate analyses. These analyses were implemented in the R package survival (Therneau, Rochester, Minnesota) or package cmprsk (Gray, Cambridge, Massachusetts). All analyses were performed in R version 3.0.0 (Hornik, Wien, Austria) for Windows (Microsoft, Redmond, Washington).

Results
Between 2008 and 2011, a total of 29 patients with ear cancer were enrolled. Details of the study participants and treatment prior to SRT are summarized in Table 1. Three study participants had T1 tumors. One study patient had a Karnofsky Performance Status score of 70 and 22 study participants had scores of 100. Histology was squamous cell carcinoma in all study participants. The median observation period was 40 months.

Overall Survival
The three-year OS rates were 69% for T1/2 (95% confidence interval [CI], 31–89), 79% for T3 (95% CI, 47–93), and 0% for T4 disease (95 CI, 0–52; \( P = 0.0003 \); Fig 2).
In 3 study participants with T1 tumors, recurrence was not present at 3 years, and their hearing had been preserved. Operability was also a significant prognostic factor for median OS (44.0 vs 23.5 months; \( P = .01 \)). No statistically significant differences were observed with respect to age (< 65 vs ≥ 65 years), PTV (< 25 vs ≥ 25 cc), bolus usage, fractionation schedule, or sex.

**Local Control**

Three-year local control rates were 70% (95% CI, 41–94) for T1/2, 50% for T3 (95 CI%, 27–79), and 20% for T4 disease (95 CI%, 2–95; Fig 3). Patterns of recurrence were local failure in 9 study participants and mixture of local failure and lymph-node metastases in 5 study participants. No marginal recurrence was observed. All lymph-node metastases developed in the ipsilateral internal jugular nodes, which are usually not irradiated in conventional radiotherapy for ear cancer. In univariate analyses, no statistically significant differences were observed with respect to PTV (< 25 vs ≥ 25 cc), fractionation schedule, operability, or sex. Similar local control rates were obtained after ceasing bolus usage (\( P = .99 \)).

**Toxicity**

Toxicities after SRT are summarized in Table 2. Grade 3 vertigo was observed as an early toxicity. These symptoms ceased a few weeks following SRT. For late toxicities, grade 2 vertigo and grade 2 facial nerve disorder were observed (1 patient each). Grade 2 or higher dermatitis or soft-tissue necrosis occurred in 8 of the initial 14 study participants treated with boluses; among them, 1 patient had grade 3 dermatitis, which developed around the bolus. Therefore, use of boluses was stopped. After boluses were stopped, no grade 2 or higher skin toxicity was observed. Asymptomatic auditory canal cartilage exposure was evaluated as grade 2 soft-tissue necrosis because intraear washing was regularly performed. Necrosis of at least grade 3 occurred in 1 patient. Dermatitis or soft-tissue necrosis of at least grade 2 occurred more frequently in study participants treated with boluses (8/14 vs 2/15; \( P = .02 \)). No other statistically significant risk factors were identified.

**Salvage Surgery and Postoperative Radiotherapy**

As salvage treatment, subtotal temporal bone resection and reconstruction were carried out for 3 study participants with T1/2 disease, 7 study participants with T3 disease, and 2 study participants with T4 disease (Table 3). Among them, 3 study participants (T3 = 1,
T4 = 2) had been evaluated as inoperable prior to SRT. Among study participants with recurrent T3 disease, 5 study participants survived more than 3 years after salvage treatment. Of the 4 study participants with T4 tumors, intrathecal dissemination was observed in 2 at the recurrence sites. En bloc resection was performed in 9 of the 12 study participants (see Table 3). At surgery, dissemination to the dura was observed in 2 study participants (T3 = 1, T4 = 1). Neck dissection was also performed in 5 study participants who developed lymph-node metastases (T1/2 = 1, T3 = 4).

As complications of salvage surgery, grade 1 cerebrospinal fluid leak was observed in 1 patient. Grade 3 abscess, grade 2 vertigo, and grade 3 necrosis of the skin flap also occurred (n = 1 for all). Because of these events, 2 study participants required hospital admission for 71 and 110 days, respectively. The median hospitalization period of the 12 study participants was 27 days. Postoperative chemoradiotherapy was delivered to 7 study participants (T3 = 5, T4 = 2; see Table 3). The median follow-up period after salvage irradiation was 40 months (range, 4–60 months). Grade 2 contralateral side otitis media occurred 5 years after reirradiation. No grade 2 or higher brain necrosis or soft-tissue necrosis was observed.

### Discussion

In our study, tumor stage was a prognostic factor of OS.5,6 The reported 5-year survival rates for ear cancer vary, ranging from 21% to 86%.4,6 Prognosis of early-stage ear cancer is generally satisfactory; thus, organ preservation should be considered as the treatment for early stage ear cancer. By contrast, further improvement in rates of OS and local control also remains an issue to be resolved for advanced-stage ear cancer in addition to avoiding surgery. The present study was designed to achieve these outcomes using SRT.

T1/2-staged disease is confined to the auditory canal and receives full benefit from definitive therapy. The 5-year OS rates after temporal bone resection have ranged from 28% to 100%.4 Zhang et al18 performed definitive surgery to conserve the facial nerve for early-stage ear cancer; however, positive surgical margins were observed in 54% of patients, and the recurrence rate was 46%. In patients with early-stage ear cancer, it may be difficult to conserve the facial nerve at surgery. By contrast, conventional radiotherapy achieved sufficient outcomes. Hashi et al10 treated 8 patients with T1 disease with radiotherapy, and the disease control rate was 100%. Pemberton et al11 also treated 27 patients with early-stage ear cancer; the 5-year cancer-specific survival rate was 85%. SRT also achieved comparable rates of local control and OS in the present study.

Although a comparison of the treatment strategies is difficult, owing to the heterogeneity of staging classification and the types of treatment used, radiotherapy, including SRT, may be preferable to surgery for early-stage ear cancer.

The prognosis of T3 disease was nearly equivalent to that of early-stage ear cancer in our study. Testa et al19 reported that the 5-year survival rate for patients who

### Table 2. — Toxicity Rates of Stereotactic Radiotherapy

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Stage</th>
<th>T1/2 (n = 10)</th>
<th>T3 (n = 14)</th>
<th>T4 (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Ear pain</td>
<td>Grade 0</td>
<td>8</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Grade 1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Radiation dermatitis</td>
<td>Grade 0</td>
<td>9</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Grade 1</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>External ear inflammation</td>
<td>Grade 0</td>
<td>10</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Grade 1</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Late Ear pain</td>
<td>Grade 0</td>
<td>8</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Grade 1</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Radiation-related dermatitis</td>
<td>Grade 0</td>
<td>10</td>
<td>10</td>
<td>4</td>
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<td></td>
<td>Grade 1</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Soft-tissue necrosis</td>
<td>Grade 0</td>
<td>7</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Grade 1</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>Grade 2</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

### Table 3. — Rates of Local Recurrence and Salvage Treatment

<table>
<thead>
<tr>
<th>Stage</th>
<th>T1/2 (n = 10)</th>
<th>T3 (n = 14)</th>
<th>T4 (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence</td>
<td>3</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Salvage surgery</td>
<td>3</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>En bloc resection</td>
<td>3</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Postoperative radiotherapy</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>
underwent radiotherapy was 29%, but that rate was 63% for patients treated with a combination of surgery and radiotherapy. Austin et al also reported that combination therapy involving surgery and radiotherapy provided a higher 5-year survival rate than either surgery or radiotherapy alone. Thus, combination therapy has been considered optimal for the treatment of T3 tumors. The 3-year OS rates after surgery in combination with postoperative conventional radiotherapy for T3 disease has ranged from 21% to 86%.

In our study, the OS rate was satisfactory, and 50% of our study participants avoided surgery. Although 50% of study participants experienced local recurrence, these patients could undergo radical salvage treatment, including subtotal temporal bone resection and postoperative radiotherapy. SRT reduces tumor bulk and allows salvage surgery, even if pathological complete response cannot be obtained; hence, our treatment protocol may improve patient prognosis and quality of life among those with T3 disease.

By contrast, the prognosis for T4 tumors remained poor in the present study. Many investigators have also reported similar, unfavorable outcomes. Xie et al reported a 2-year OS rate of 22% in 39 patients with T4 tumors undergoing temporal bone resection and postoperative radiotherapy. Leong et al performed subtotal resection and postoperative chemoradiotherapy in 23 patients with T4N0M0 disease. Among them, 14 died of ear cancer within 22 months of surgery. Koto et al reported a 3-year OS rate of 44% with carbon-ion radiotherapy in 13 patients with T4 tumors. These outcomes are attributed to the tumor location and anatomical features. T4 tumors erode the deep parts of the auditory canal, including the cochlea, petrous apex, carotid canal, dura, and facial nerve. The foramina, fissures, and channels for the nerves and vessels are thought to provide the routes for tumor dissemination.

In our study, dissemination to the dura was observed in 3 of the 4 patients with T4 tumors. T4 disease may spread beyond the definitively irradiated volume of SRT. Therefore, patients with T4 tumors are not good candidates for SRT, which is in contrast to those with T1/2 or T3 disease.

Grade 2 or higher dermatitis occurred more frequently in study participants treated with boluses in our study. Dermatitis was observed in areas around the bolus, suggesting that its usage is associated with these toxicities. The boluses had high CT values, and the PTV was in contact with air-density areas. In such cases, the dose around the bolus was overestimated or underestimated in the treatment planning system due to electron scattering. Although dosimetry of actual skin doses is difficult, ceasing bolus usage may decrease actual doses by 5% to 10%. With respect to soft-tissue necrosis, we may have overdiagnosed the toxicities in our study compared with the results from previous studies. Grade 3/4 necrosis or dermatitis was previously reported to develop in 6% to 15% of patients. However, 3 out of 4 of these studies were retrospective, and the toxicities were evaluated by radiation oncologists. By contrast, ours was an exploratory, prospective study design, and toxicities were evaluated by an otolaryngologist. Without bolus usage, grade 3 necrosis occurred in 1 of our 15 study participants, suggesting that SRT had acceptable rates of toxicity and did not require bolus treatment.

Conventional radiotherapy may complicate the care of patients who require salvage surgery. Surgical complication rates in patients with a prior history of radiotherapy are generally higher than those with untreated disease. In our study, surgical complications of grade 2 or higher were observed in 2 study patients, and the median admission period was acceptable, suggesting that salvage surgery had acceptable rates of toxicity. In addition, after careful follow-up, no grade 3 or higher radiation-associated late toxicities (eg, soft tissue necrosis, brain necrosis) occurred. With use of SRT, the irradiated volume was limited, and the irradiated tissues were excised and reconstructed with normal tissues. In our protocol, doses to the cranial nerves and brain stem were restricted within the tolerance level. These results indicated that SRT for ear cancer provides a sufficiently steep dose gradient to deliver re-irradiation after surgery.

**Future Directions**

Results of the current protocol appear promising, but further improvement in local control is desirable, especially because the local control rate for T3 tumors should be increased from 50% of the present study. A large tumor may contain many hypoxic cells resistant to radiation. Thus, the phenomenon of reoxygenation and redistribution should be utilized in radiotherapy against these large tumors. Fractionation has radiobiological advantages because reoxygenation of hypoxic tumor cells and the redistribution of the cell cycle to a more sensitive phase can be expected. Therefore, further increase in the fraction number may improve rates of local control. In addition, use of radiosensitizers may enhance radiation effects and improve prognosis of individuals with advanced cancer. Conventional cytotoxic chemotherapy agents like cisplatin and fluorouracil are considered to have a radiosensitizing effect. An oral formation of tegafur/gimeracil/oteracil has also been shown to enhance the radiation effect. Conventional hypoxic cell sensitizers may also be effective when combined with high-dose radiotherapy. Thus, the increase the fraction number and use of these radiosensitizers should be considered for inclusion in a new protocol to improve local efficacy rates.
Conclusions
To the best of our knowledge, this is the first study that demonstrates the efficacy of stereotactic radiotherapy for ear cancer. The results of this protocol for individuals with T3 disease or higher are promising. In study participants treated without a bolus, toxicities were acceptable and tolerable. Salvage surgery and postoperative radiotherapy after stereotactic radiotherapy are also feasible, and these results are encouraging.

References