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CLINICAL INVESTIGATION **Head and Neck**

TREATMENT AND PROGNOSIS OF SQUAMOUS CELL CARCINOMA OF THE EXTERNAL AUDITORY CANAL AND MIDDLE EAR: A MULTI-INSTITUTIONAL RETROSPECTIVE REVIEW OF 87 PATIENTS

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Purpose: To examine the relative roles of surgery, radiotherapy, and chemotherapy in the management of patients with squamous cell carcinomas of the external auditory canal and middle ear.

Methods and Materials: The records of 87 patients with histologically confirmed squamous cell carcinoma who were treated between 1984 and 2005 were reviewed. Fifty-three patients (61%) were treated with surgery and radiotherapy (S + RT group) and the remaining 34 patients with radiotherapy alone (RT group). Chemotherapy was administered in 34 patients (39%).

Results: The 5-year actuarial overall and disease-free survival (DFS) rates for all patients were 55% and 54%, respectively. On univariate analysis, T stage (Stell's classification), treatment modality, and Karnofsky performance status had significant impact on DFS. On multivariate analysis, T stage and treatment modality were significant prognostic factors. Chemotherapy did not influence DFS. The 5-year DFS rate in T1, T2, and T3 patients was 83%, 45%, and 0 in the RT group ($p < 0.0001$) and 75%, 75%, and 46% in the S + RT group ($p = 0.13$), respectively. The 5-year DFS rate in patients with negative surgical margins, those with positive margins, and those with macroscopic residual disease was 83%, 55%, and 38%, respectively ($p = 0.007$).

Conclusions: Radical radiotherapy is the treatment of choice for early-stage (T1) diseases, whereas surgery (negative surgical margins if possible) with radiotherapy is recommended as the standard care for advanced (T2–3) disease. Further clarification on the role of chemotherapy is necessary.

Radiation therapy, Surgical resection, Chemotherapy, External auditory canal, Middle ear.

INTRODUCTION

The occurrence of squamous cell carcinoma of the external auditory canal and middle ear is rare, with a reported prevalence of 1 per 1 million persons (1, 2). Because of the rarity of the tumors, it has been difficult for a single institution to analyze data and formulate an optimal evaluation and treatment strategy. The reliability of the radiologic evaluation of disease extent, the surgical procedures, and the efficacy of radiotherapy are still matters of controversy. In addition, the lack of a universally accepted staging system poses a critical problem when attempting to compare treatment strategies and outcomes among multiple institutions (1, 3).

Several reports have indicated that the assessment of a tumor's extension is an important prognostic factor for squamous cell carcinoma of the external auditory canal and middle ear (1, 4–11). However, the studies were based on a small number of patients, and various treatment modalities were used (9, 12, 13). Therefore, the relative roles of surgery, radiotherapy, and chemotherapy in the management of patients with such lesions have remained controversial. Although several reports have indicated the efficacy of radio-

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Table 1. Stell's and Arriaga's staging systems for external auditory canal and middle ear

Stell's classification (10)	
T1	Tumor limited to site of origin *i.e.,* with no facial nerve paralysis and no bone destruction on radiography
T2	Tumor extending beyond the site of origin indicated by facial paralysis or radiologic evidence of bone destruction, but no extension beyond the organ of origin
T3	Clinical or radiologic evidence of extension to surrounding structures (dura, base of the skull, parotid gland, temporomandibular joint, etc)
TX	Patient with insufficient data for classification, including patients previously treated elsewhere
Arriaga's classification (1)	
T1	Tumor limited to the external auditory canal without bony erosion or evidence of soft tissue extension
T2	Tumor with limited external auditory canal bony erosion (not full thickness) or radiographic finding consistent with limited (<0.5 cm) soft-tissue involvement
T3	Tumor eroding the osseous external auditory canal (full thickness) with limited (<0.5 cm) soft-tissue involvement, or tumor involving middle ear and/or mastoid, or patients presenting with facial paralysis
T4	Tumor eroding the cochlea, petrous apex, medial wall of middle ear, carotid canal, jugular foramen or dura, or with extensive (>0.5 cm) soft-tissue involvement

therapy for these tumors (12, 14), there is little information available regarding the relationship between the extent of a tumor and the outcomes of radical radiotherapy. Therefore, it is imperative to formulate treatment guideline for these tumors.

In the present study, we performed a retrospective, multi-institutional review of 87 patients with squamous cell carcinoma of the external auditory canal and middle ear. We also investigated the optimal management of these patients, including the role of surgery, radiotherapy, and chemotherapy.

METHODS AND MATERIALS

Patient characteristics

A retrospective review of medical records from 1984 to 2005 identified 87 patients with documented, histologically confirmed, previously untreated squamous cell carcinoma of the external auditory canal and middle ear who were treated with radiotherapy at the following institutions: the Department of Radiology/Radiation Oncology at the University of the Ryukyus Hospital, Kyushu University Hospital, Chiba Cancer Center, Chiba University Hospital, Aichi Cancer Center, and International Medical Center of Japan. The patients ranged in age from 37 to 88 years (median, 67 years). Forty-three patients were male, and 44 patients were female. The Karnofsky performance status of the patients ranged from 40% to 100% (median, 90%). The primary tumor site was in the external auditory canal in 59 patients and in the middle ear in 28 patients. Computed tomography (CT) and/or magnetic resonance imaging (MRI) was performed on all patients before treatment, and of all 87 patients, MRI was performed in 40 (46%).

We used the tumor staging system devised by Stell and McCormick (10) (Table 1), and the node and metastases staging devised by the Union Internationale Contre le Cancer (UICC) (15). In total, there were 13 T1, 37 T2, and 37 T3 tumors. Seventy-nine patients (91%) were N0, and 8 patients (9%) exhibited N1 disease. With regard to T stage, we also applied the staging system devised by Arriaga *et al.* (1) to determine whether it could be properly applied to our patient population. According to Arriaga's staging system, there were 14 T1, 29 T2, 20 T3, and 24 T4 tumors in our group.

Treatments

Fifty-three patients (61%) received surgery and radiotherapy (S + RT group), and the remaining 34 patients were treated with radiotherapy alone (RT group). In the present study there were no definitive treatment policies for squamous cell carcinoma of the external auditory canal and middle ear during the past 20 years; thus treatment was determined by the respective physicians at each institution. In the S + RT group, 23 patients underwent macroscopic total resection with negative surgical margins, 22 patients underwent macroscopic total resection with positive margins, and the remaining 8 patients underwent subtotal or partial resection. Of the 53 patients in the S + RT group, 18 were treated with preoperative radiotherapy, 29 were treated with postoperative radiotherapy, and the remaining 6 patients received both preoperative and postoperative radiotherapy.

Radiotherapy was administered with a ^{60}Co teletherapy unit (n = 2 patients) or a 4, 6, 10-MV linear accelerator. Daily fractions of 1.8–2.0 Gy 5 days per week were used most often. The treatment volume was based on the pretreatment CT or MRI scans, and the planning target volume included the primary tumor (n = 30, RT group), primary tumor bed (n = 29, S + RT group), or primary tumor/primary tumor bed and the lymph node area of the parotid, retroauricular, upper jugular, and upper accessory regions (n = 4, RT group; n = 24, S + RT group). Computed tomography–guided treatment planning was performed in 53 patients (61%). Three patients were treated with hyperfractionated radiotherapy using 2 fractions per day of 1.3–1.6 Gy to a total dose of 42.9–72 Gy. The total dose to the primary site in all 87 patients ranged from 20 to 72 Gy (median, 60 Gy). Two laterally angled, pair wedged fields were used in 54 patients (62%). Nineteen patients received a single lateral field with megavoltage irradiation from the linear accelerator or ^{60}Co teletherapy unit, or 15-MeV electron beam irradiation from a lateral port. The remaining 14 patients were treated with three or more fields with megavoltage irradiation. An immobilization device was used with most of the patients (70 patients, 80%) during radiotherapy. In the RT group with clinically negative lymph node involvement (n = 32), elective neck irradiation was supplemented in 2 patients.

Three patients were treated with high-dose-rate intracavitary brachytherapy in addition to external beam radiotherapy. After 30–50-Gy external beam radiotherapy, 15–42-Gy ^{192}Iridium high-dose-rate brachytherapy with a 370-GBq source (MicroSelectron; Nucletron, Veenendaal, The Netherlands) was supplemented for boost treatment with a single dose of 3 Gy at 5–7-mm applicator distance with 5 fractions (1 patient with a T2 tumor) or 10 fractions (2 patients with T1 tumors) per week.

Thirty-four patients (39%) received various regimens and doses of intravenous or oral chemotherapy before, during, and/or after

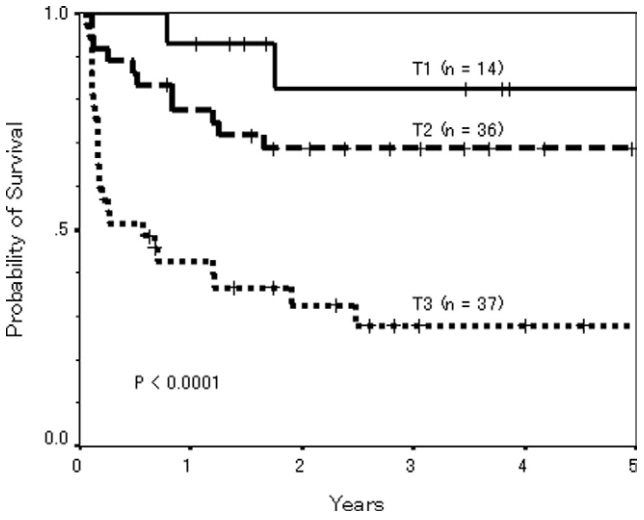

Fig. 1. Actuarial disease-free survival rates according to the T stage classification proposed by Stell *et al.* (10).

radiotherapy. The most commonly used regimen was concurrent intravenous 5-fluorouracil (250 mg/m^2 daily dose during radiotherapy) or oral fluoropyrimidine (TS-1) administration at a daily dose of 65 mg/m^2 for 4 weeks starting from the onset of radiotherapy (20 patients). The next most common was a combination of cisplatin (40–80 mg/m^2, 2–3 times) and 5-fluorouracil (250–750 mg/m^2, 2–17 times) in 6 patients. The remaining 8 patients received other chemotherapeutic regimens with the following agents either alone or in combination: carboplatin (20–200 mg/m^2, 1–20 times), bleomycin (15 mg, 12–20 times), and/or peplomycin (5 mg, 3–15 times).

Statistical analysis

The biologic effective dose (BED) and linear–quadratic effective dose (LQED) for early-responding tissues were calculated, and the BED converted to a LQED for a 2-Gy fraction (16). The BED and LQED were calculated using the LQ equation. For the LQ calculation, a value of $\alpha/\beta = 10$ was assumed for tumors (Gy_{10}), and $\alpha/\beta = 3$ was used for late complications (Gy_3) (17). Acute toxicities were graded according to the National Cancer Institute Common Toxicity Criteria version 3.0. Late complications were graded in accordance with the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) criteria (18).

The median follow-up period for 52 surviving patients was 42 months (range, 2–174 months), and no patients were lost to follow-up. Overall survival and disease-free survival (DFS) rates were calculated actuarially according to the Kaplan-Meier method (19) and were measured starting from the day of initial treatment. Differences between groups were estimated using the chi-square test and the log–rank test (20). Multivariate analysis was performed using the Cox regression model (21). A probability level of 0.05 was chosen for statistical significance. Statistical analysis was performed with the SPSS software package (version 11.0; SPSS, Chicago, IL).

RESULTS

We applied two staging systems, Stell's staging system (Fig. 1) and Arriaga's staging system (Fig. 2), to examine DFS. According to Stell's classification, the 5-year actuarial DFS rate was 83%, 69%, and 28% for T1, T2, and T3 tumors, respectively ($p < 0.0001$). According to Arriaga's staging system, the 5-year actuarial DFS rate was 83%, 65%, 55%, and 27% for T1, T2, T3, and T4 tumors, respectively ($p = 0.001$). Therefore, both staging systems could be applied properly to our patient population.

Of 87 patients, 34 (39%) died during the analysis period. Thirty-one patients died of their disease, whereas the remaining 3 died of other causes without any sign of clinical recurrence (1 T2-stage patient died of pneumonia, 1 T1-stage patient died of rectal cancer, and 1 T1-stage patient died of unknown causes). Of the 87 patients, 38 experienced recurrence: 34 patients with local recurrence, 3 with neck lymph node recurrence, and 1 with distant metastasis (lung) as a first failure. The 5-year actuarial overall survival and DFS rates for all 87 patients were 55% and 54%, respectively.

On univariate analysis, T stage (Stell's classification) ($p < 0.0001$), treatment modality (S + RT vs. RT) ($p = 0.002$), and Karnofsky performance status ($p = 0.03$) all had significant impact on DFS. On multivariate analysis, T stage ($p < 0.0001$) and treatment modality ($p < 0.0001$) were also found to be significant prognostic factors (Table 2). Other factors, such as tumor site and chemotherapy, did not influence DFS. The 5-year DFS rate for T1, T2, and T3 patients was 83%, 45%, and 0 in the RT group ($p < 0.0001$) (Fig. 3) and 75%, 75%, and 46% in the S + RT group ($p = 0.13$) (Fig. 4), respectively.

Because radiotherapy alone may be reserved for less fit patients or those with poor chance of respectability, we further compared DFS between the S + RT group and RT group according to T stage (Stell's) and Karnofsky performance status (Table 3). In T3 patients or those with KPS ≥70%, the S + RT group had significantly better DFS compared with those in the RT group, but in T1 and T2

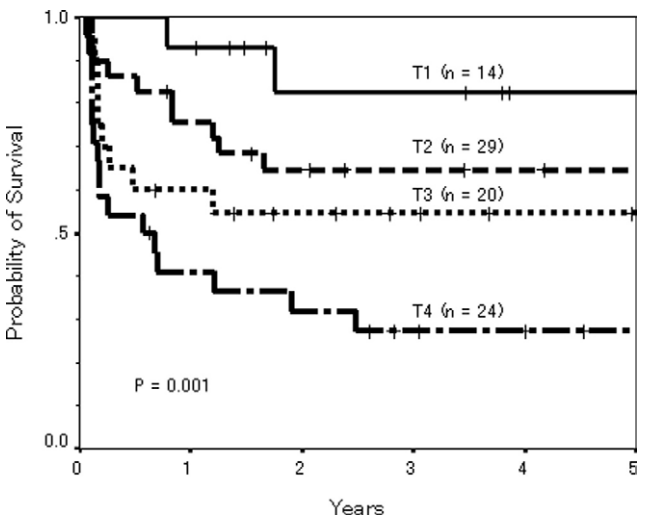

Fig. 2. Actuarial disease-free survival rates according to the T stage classification proposed by Arriaga *et al.* (1).

Table 2. Univariate and multivariate analysis of various potential prognostic factors for disease-free survival in patients with squamous cell carcinoma of the external auditory canal and middle ear

		Univariate analysis		Multivariate analysis	
Variable	No. of patients	5-y DFS rate (%)	*p*	RR (95% CI)	*p*
T stage			<0.0001	0.183 (0.089–0.375)	<0.0001
T1, T2	51	74			
T3	36	25			
Treatment modality			0.002	3.577 (1.816–7.048)	<0.0001
RT	34	38			
Surgery + RT	53	65			
KPS (%)			0.03	0.577 (0.260–1.279)	0.18
≥70	75	58			
<70	12	28			
N stage			0.07	0.417 (0.171–1.018)	0.06
N0	79	57			
N1–3	8	25			
Tumor site			0.15	—	
External auditory canal	59	61			
Middle ear	28	41			
Total radiation dose (Gy)			0.16	—	
≤60	53	50			
>60	34	61			
Use of CT-based treatment planning			0.53	—	
Yes	62	53			
No	25	60			
Gender			0.54	—	
Female	44	56			
Male	43	52			
Age (y)			0.86	—	
<75	50	53			
≥75	17	60			
Use of chemotherapy			0.98	—	
Yes	34	57			
No	53	54			
Use of immobilization device during RT			0.99	—	
Yes	70	55			
No	17	53			

Abbreviations: DFS = disease-free survival; RR = relative risk; CI = confidence interval; RT = radiotherapy; KPS = Karnofsky performance status.

patients or those with KPS <70%, no significant difference was found between the groups.

Concerning surgical margin status in the S + RT group, the 5-year DFS rate in patients with negative surgical margins, those with positive margins, and those with macroscopic residual disease was 83%, 55%, and 38%, respectively (Fig. 5; $p = 0.007$). Concerning the timing of radiotherapy in the S + RT group, the 5-year DFS rate in patients treated with preoperative, postoperative, and both pre- and postoperative radiotherapy was 64%, 71%, and 50%, respectively ($p = 0.75$). Although there was a trend toward greater negative surgical margins in the preoperative group, there were no significant differences with the timing of radiotherapy and surgical margin status (Table 4) ($p = 0.06$).

With regard to local control, the 5-year local control rate in T1, T2, and T3 patients was 83%, 45%, and 0, respectively, in the RT group ($p < 0.0001$). Of 10 patients with T1 stage tumors (total, 10 patients), 9 had no local recurrence, and 2 of these 9 patients were treated with external beam

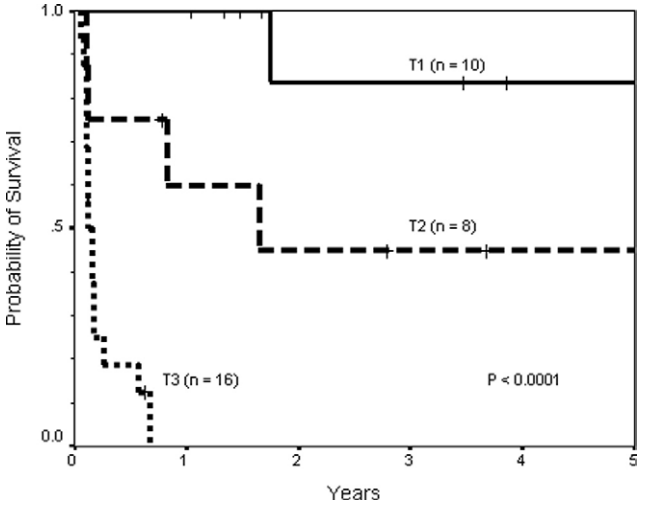

Fig. 3. Actuarial disease-free survival rates in patients treated with radiotherapy, according to T stages proposed by Stell *et al.* (10).

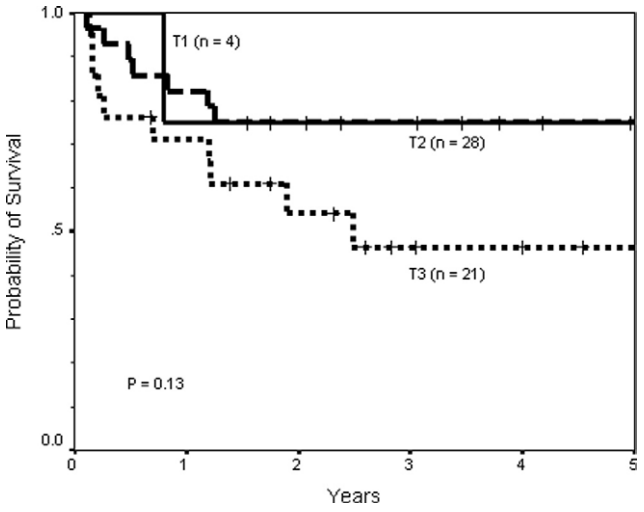

Fig. 4. Actuarial disease-free survival rates in patients treated with surgery and radiotherapy, according to T stages proposed by Stell *et al.* (10).

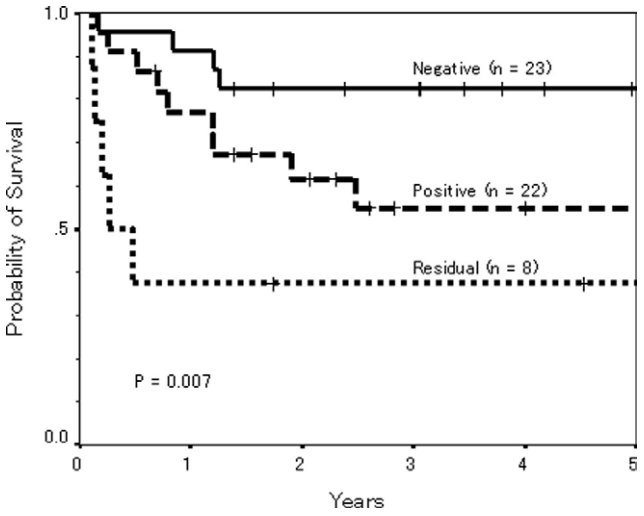

Fig. 5. Actuarial disease-free survival rates in patients treated with surgery and radiotherapy, according to surgical margin status.

radiotherapy and intracavitary brachytherapy. The remaining 1 patient with T1 disease had local recurrence with marginal field recurrence and was treated with a ^{60}Co teletherapy unit without the use of CT-based treatment planning. The BED for T1 patients ranged from 72 Gy_{10} to 90.6 Gy_{10} (median, 84 Gy_{10}), and LQED for the T1 patients ranged from 60 to 76 Gy (median, 70 Gy). In the RT + S group, the 5-year local control rate in T1, T2, and T3 patients was 75%, 79%, and 53%, respectively ($p = 0.32$). Concerning surgical margins, the 5-year local control rate in patients without negative surgical margins, those with positive margins, and those with macroscopic residual disease was 95%, 55%, and 38%, respectively ($p < 0.0002$). Concerning neck control in the RT group, only 1 of 32 patients (3%) with N0 disease developed neck recurrence at the time of analysis.

Concerning acute toxicity, 77 patients had Grade 2 or less dermatitis, and 10 patients had Grade 3 dermatitis. However, there were no treatment-related deaths for any of the patients. In addition, most patients had no late complications ($n = 80$) or RTOG/EORTC Grade 1–2 late complications ($n = 5$). However, 2 patients experienced radiation-induced Grade 4 late complications. One patient experienced osteoradionecrosis with a total dose of 72 Gy in conventional fractionation (BED = 115 Gy_3), and the other had ulceration with a total dose of 67.2 Gy in 2 fractions per day of 1.6 Gy (BED = 103 Gy_3). No other severe radiation-induced complications were observed at the time of the analysis. With regard to T1 tumors, no apparent hearing impairment was documented after treatment for either the S + RT group or the RT group.

Table 3. Comparison of DFS in patients treated with S + RT and those treated with RT according to T stage and KPS

	No. of patients		5-y DFS rate (%)		
	S + RT	RT	S + RT	RT	*p*
T stage (Stell's [10])					
T1	4	10	75	83	0.98
T2	28	8	75	45	0.12
T3	21	16	46	0	<0.0001
KPS (%)					
≥70	47	28	69	39	0.003
<70	6	6	25	33*	0.50

Abbreviations: DFS = disease-free survival; S = surgery; RT = radiotherapy; KPS = Karnofsky performance status.
* 3-y DFS rate.

DISCUSSION

A rational comparison of treatment strategies from the literature on squamous cell carcinoma of the external auditory canal and middle ear is difficult, owing to heterogeneity of staging classification and the types of treatment used (12). Although many classification methods have been proposed, none has been accepted by the UICC. Of the various staging systems, the one proposed by Stell and McCormick (10) is based on 47 tumors of the external auditory canal and middle ear, and several investigators have used this staging system for classification (14, 22–24). Arriaga *et al.* (1) also proposed a staging system based on pretherapeutic radiologic findings in CT scans and clinical examination. This staging system correlated well to the histopathologic tumor extension (25) and has been used for classification in several reports (3, 4, 12, 26, 27). In the present study we applied these two staging systems and found that they corresponded well and were applicable to our patients. Several other reports also indicated that these staging classifications were a reproducible and objective method of subdividing patients for evaluation of efficacy of treatment (3, 4, 10, 13, 14, 26–28). We believe that these two staging systems can be used to properly classify squamous cell carcinoma of the

Table 4. Mode of radiotherapy and surgical margin status in patients with squamous cell carcinoma of the external auditory canal and middle ear

Timing of RT	Total no. of patients	Surgical margin status		
		Negative	Positive	MRD
Preoperative	18	11	6	1
Median RT dose (Gy)		50 (20–60)	50 (40–70)	50
Pre- and postoperative	6	1	5	0
Median RT dose (Gy)		60	70 (63–72)	—
Postoperative	29	11	11	7
Median RT dose (Gy)		55.2 (45–60)	60 (50–70)	66 (50–70)
Total no. of patients	53	23	22	8

Abbreviations: RT = radiotherapy; MRD = macroscopic residual disease. Values in parentheses are ranges.

external auditory canal and milled ear. Recently, MRI has been frequently performed in patients with these tumors, and information from MRI may provide useful information regarding the precise staging of tumors. Further studies are required to elucidate whether a more appropriate staging system can be formulated using additional information, such as from MRI.

In the present study, the patient's T stage was found to be an independent prognostic factor for DFS. This result is consistent with those of previous reports, and it is widely accepted that local tumor extension is an important prognostic factor for squamous cell carcinoma of the external auditory canal and middle ear (1, 4–11, 25, 29, 30). For early-stage tumors, several investigators have also reported favorable results. Arriaga *et al.* (1) reported a survival rate of 100% in 5 cases of T1 disease drawn from 39 cases of external auditory canal squamous cell carcinoma that they studied. Austin *et al.* (4) have reported a survival rate of 100% in 3 cases of T1 disease in which surgical resection and adjuvant radiotherapy were performed. On the other hand, for advanced tumors, there is a significantly worse prognosis than for those with early-stage tumors (1, 5, 26, 31, 32). Prasad *et al.* (32) reviewed 96 reports and selected 26 reports containing information on 144 comparable patients. They noted that in cases of advanced disease, only 2 of 144 patients survived more than 5 years. Many investigators also reported that advanced tumors with the presence of bone erosion or invasion had decreased survival rates compared with those without bone erosion or invasion (1, 4, 5, 8, 33). These results imply that early diagnosis is an important factor for improving prognosis.

The present study also indicated that the treatment modality (S + RT vs. RT) was an independent prognostic factor for DFS. Previous reports have also indicated that a combination of surgery and radiotherapy is better than radiotherapy alone for these tumors (4, 26, 30). Testa *et al.* (26) reported that the 5-year survival rate for patients who underwent radiotherapy was 29%, but for patients who underwent a combination of surgery and radiotherapy it was 63%. Austin *et al.* (4) indicated that combination therapy involving surgery and radiotherapy provided a higher 5-year survival rate than either surgery or radiotherapy alone. In the present study, the 5-year DFS rate in patients treated with surgery and radiotherapy (65%) was significantly higher than in those treated with radiotherapy (38%). These results indicate that the combination of surgery and radiotherapy is a preferable treatment to radiotherapy alone for these tumors.

Although the combination of therapy and radiotherapy is generally more effective than radiotherapy alone, the role of radical radiotherapy for early-stage tumors remains controversial. Previous reports have indicated that radiotherapy alone is inadequate as a primary therapy regardless of extent of disease and that most patients so treated present with rapid local recurrence (2, 4, 34, 35). On the other hand, recent reports have suggested the usefulness of radical radiotherapy for early-stage disease. Hashi *et al.* (22) indicated that disease control was 100% in 8 patients with T1 disease when treated with radiotherapy alone. Pemberton *et al.* (14) analyzed 123 patients treated with radiotherapy alone, and the 5-year cancer-specific survival rate was 85% for 27 patients with early-stage disease (T1 by Stell's classification). In the present study, the 5-year disease rate in 10 T1 patients treated with radiotherapy was 83%, and 9 of 10 patients had no local recurrence at the time of analysis. The remaining 1 patient had local recurrence at the marginal radiation field and was treated with ^{60}Co teletherapy without CT-based treatment planning. Moreover, radical radiotherapy did not seem to impair hearing function in patients with T1-stage tumors. These results indicate that radical radiotherapy is a viable treatment modality for T1-stage tumors, as well as surgery plus radiotherapy. Using external beam radiation based on three-dimensional CT treatment planning, tumoricidal doses can be administered without a serious threat of brainstem damage and brain injury. Although the optimal dose of radiotherapy remains uncertain, several investigators indicated that total doses of 65–75 Gy were sufficient to control disease (22). In the present study, total doses (LQED) of radiotherapy for T1-stage patients ranged from 60 to 76 Gy (median, 70 Gy). A dose of 70 Gy for radical radiotherapy seems to be appropriate for achieving local control for early-stage tumors.

However, a total dose of 70 Gy or more may cause late complications, such as osteoradionecrosis of the temporal

bone and ulcerations (36, 37). In the present study, 2 patients suffered radiation-induced complications. These patients were treated with more than 70 Gy (BED = 115 Gy_3) in conventional fractionation or approximately 70 Gy (BED = 103 Gy_3) in accelerated hyperfractionated radiotherapy. Several investigators also indicated that when a total dose of 70 Gy in conventional fractionation is used, the risk of complications, such as osteoradionecrosis, increases (36, 37). Therefore, it is necessary to reduce the occurrence of late complications when treating with radical radiotherapy. Recently, brachytherapy has emerged as an attractive boost treatment that can be applied for curative intent when the disease is locally confirmed or with a recurrent tumor (12, 38). With the use of multiple fractions, one may deliver a dose sufficient for local control while decreasing the risk of unacceptable side effects and late complications (38). In the present study, 3 patients treated with external beam radiotherapy and brachytherapy had no local recurrence without serious late complications (T1: 2 patients; T2: 1 patient). Suzuki *et al.* (39) also treated a patient with early-stage carcinoma of the external auditory canal by high-dose-rate intracavitary brachytherapy irradiation (20 Gy/8 fractions) followed by 40-Gy external beam irradiation. They found no severe side effects, and the tumor disappeared after treatment. These results suggest that the additional use of brachytherapy followed by external beam radiotherapy may be useful in achieving curative therapy without serious late complications for early-stage diseases. Recently, advanced techniques such as intensity-modulated radiotherapy have also been emerging as an attractive method for achieving local control while effectively sparing normal tissues. These advanced techniques may also help to improve the patient's quality of life by avoiding late complications or preserving hearing function.

On the other hand, our study showed that patients with advanced disease (T2 and T3) did poorly when treated by radical radiotherapy alone (4, 10, 29). Several investigators also indicated that combination therapy with surgery and radiotherapy provided a higher 5-year survival rate than surgery or radiotherapy alone (4, 10, 24, 29, 35). Wagenfield *et al.* (35) indicated that the 4-year survival rate for patients treated with surgery and radiotherapy was 67% but was 0 for those treated with radiotherapy alone. Pemberton *et al.* (14) indicated that the 5-year survival rate was only 44% for 96 patients with advanced-stage tumors when treated with radiotherapy alone. In the present study, the 5-year DFS rate was 45% and 0, respectively, in patients with T2 and T3 tumors treated with radiotherapy, whereas a significantly higher rate of 75% and 46% was seen in patients with T2 and T3 tumors treated with both surgery and radiotherapy. These results indicate that surgery and radiotherapy should be recommended as a standard treatment for advanced (T2–3) disease.

Concerning the method of surgery, most investigators agree that wide en bloc resection of the tumor with free surgical margins is the optimal treatment (3, 4, 12, 27, 40–42). Pfreundner *et al.* (12) indicated that patients with completely resected tumors had a 5-year survival rate of 100%, and the rate was 66% for patients with tumors extending beyond surgical margins. Yin *et al.* (27) indicated that positive surgical margins provided a 5-year survival rate of 20.8%, which was significantly lower than the 5-year survival rate of 76.5% for free margins. In the present study, the 5-year disease-free survival rate was significantly higher in patients who had negative surgical margins than for those with positive surgical margins or macroscopic residual disease. These results indicate that surgery with negative surgical margins may be the preferable treatment for these diseases.

On the other hand, optimal timing of radiotherapy (preoperative or postoperative) has not been established for squamous cell carcinoma of the external auditory canal and middle ear (3, 8, 24, 26). Several investigators emphasized the effectiveness of postoperative radiotherapy to control residual tumors at the margins (3, 4, 7, 8, 12, 13, 29, 43). Concerning postoperative radiotherapy, the recommended doses were 54–60 Gy for patients with radical tumor resection and 66 Gy or more for patients with tumors beyond the surgical margins, owing to hypoxia and reduced sensitivity to radiation of the tumor cells at the margin of resection (12, 26, 30). However, several investigators indicated that incomplete resection was the major cause of recurrence and that postoperative radiotherapy was not beneficial (25, 44). In the present study, patients who were treated with preoperative radiotherapy tended to have more negative margins at operation than those who were treated with postoperative radiotherapy, but there were no significant differences with regard to DFS among patients with preoperative, postoperative, or both pre- and postoperative radiotherapy. Further studies are required to clarify the optimal management of radiotherapy when combined with surgery.

The role of chemotherapy in the management of squamous cell carcinoma of the external auditory canal and middle ear also remains uncertain. Because distant metastases are not commonly reported from these tumors, systemic chemotherapy is not routinely used (8, 25, 43). In the present study, the use of chemotherapy did not affect DFS. However, our results concerning chemotherapy should be interpreted with caution owing to the variability in chemotherapy regimens, doses, and timing that were used. Recently, to obtain a negative surgical margin at operation, several investigators have tried using both radiotherapy and chemotherapy (3, 27). When combined, chemotherapy may enhance the radiotherapeutic effects. Several randomized clinical trials for various tumors comparing concurrent chemoradiotherapy with radiotherapy alone have shown that concurrent chemoradiotherapy improved local control and often resulted in the absence of a tumor at the surgical margin and sometimes in no residual tumor at all (45–47). Further clarification on the role of chemotherapy is necessary for these tumors.

In conclusion, our results indicate that radical radiotherapy is the treatment of choice for patients with early-stage squamous cell carcinoma of the external auditory

canal and middle ear. In addition, surgery, with negative surgical margins if possible, and radiotherapy are recommended as the standard care for cases of advanced-stage disease. We did not find the effectiveness of chemotherapy in the present study. However, this was a retrospective study comprising a relatively small number of patients, and further studies with a larger number of patients are necessary to confirm our results concerning squamous cell carcinoma of the external auditory canal and middle ear.

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