Chemoradiation therapy for squamous cell carcinoma of the external auditory canal: A meta-analysis

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ABSTRACT: *Background.* The standard treatment for advanced external auditory canal squamous cell carcinoma (SCC) is subtotal temporal bone resection and postoperative radiation therapy (RT), whereas chemoradiation therapy (CRT) is used in some institutions to improve patient prognosis. The purpose of this study was to evaluate the efficacy of CRT in external auditory canal SCC treatment.

Methods. Meta-analyses of external auditory canal SCC studies were performed. We extracted 5-year overall survival rates and number of patients for aggregate patient data, and types of treatment and outcomes for individual patient data.

Results. The 5-year overall survival rate of 752 patients was 57%. In the individual patient data meta-analysis, the 5-year overall survival rates of patients who received surgery ± RT, preoperative CRT, definitive CRT, and postoperative CRT were 53.5%, 85.7%, 43.6%, and 0%, respectively.

Conclusion. Our data suggest that preoperative CRT may improve the survival of surgically treated patients with external auditory canal SCC and that definitive CRT may be equivalent to surgical resection. © 2014 Wiley Periodicals, Inc. *Head Neck* 00: 000–000, 2014

KEY WORDS: external auditory canal, squamous cell carcinoma, chemoradiation therapy, surgery, complication

INTRODUCTION

External auditory canal squamous cell carcinoma (SCC) is a rare disease with a reported incidence of 1 in 1 million persons per year.[1] The rarity of this disease impedes any single institution experience to determine an optimal treatment strategy. However, although no prospective study has been published and no high-level evidence exists, case series of relatively large scales and meta-analyses of the retrospective studies led the following treatment strategies as the standard strategies.[2–5] When classified with the modified Pittsburgh Staging System,[2] the standard therapy is as follows: lateral temporal bone resection or radiation therapy (RT) for a T1 tumor, lateral temporal bone resection, and postoperative RT for a T2 tumor, subtotal temporal bone resection, or total temporal bone resection and postoperative RT for T3 and T4 tumors. In spite of these standardized treatments, the prognosis of the patients with external auditory canal SCC remains poor.

The standard therapy for advanced stage head and neck SCC had been surgery followed by postoperative RT. Recently, however, the role of surgery has been replaced by chemoradiation therapy (CRT).[6] Although CRT has not been shown to be superior to surgery with regard to survival in patients with resectable head and neck SCC, it certainly has the advantage of organ preservation. Moreover, the standard therapy for patients with unresectable head and neck SCC is CRT.

Treatment for advanced external auditory canal SCC requires invasive surgery, such as subtotal temporal bone resection or total temporal bone resection; however, these procedures often cause severe complications, such as meningitis, cerebrospinal fluid leak, encephalitis, and brain infarction,[4,7–9] and deafness and facial palsy are inevitable. Moreover, as the external auditory canal is located adjacent to vital structures, such as the brain and carotid artery, cancer arising there is sometimes unresectable. Considering these factors, it seems appropriate to use CRT for the first-line treatment of external auditory canal SCC. However, the use of CRT for external auditory canal SCC was not reported until 2006. Nakagawa et al[10] reported the effectiveness of preoperative CRT for external auditory canal SCC in 2006. Since then, reports of CRT for external auditory canal SCC have occasionally appeared in the literatures.[11–14] However, all of these reports are case series of less than 20 patients. Therefore, the role of CRT is not yet established. In this study, we examined the recent literature since 2006 concerning the outcomes of external auditory canal SCC treatment to assess the role of CRT for external auditory canal SCC. The main focus of this study was to determine if adjunctive therapy with CRT can improve the survival of surgically treated patients with advanced external auditory canal SCC and if definitive CRT can substitute highly

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invasive surgeries, such as subtotal temporal bone resection and total temporal bone resection.

MATERIALS AND METHODS

Search strategy

We performed a literature search regarding external auditory canal SCC using electronic databases for articles published between January 1, 2006, and September 30, 2013. The databases used were PubMed (www.ncbi.nlm.nih.gov/pubmed), Scopus (www.elsevier.com/online-tools/scopus), which has 100% coverage of MEDLINE and EMBASE, and Ichushi-Web (http://login.jamas.or.jp/), which contains bibliographic information and abstracts of articles in Japanese journals (Japan Medical Abstracts Society). Furthermore, the references in the retrieved articles were manually searched for associated studies.

Selection criteria

We collected articles regarding external auditory canal SCC treatment and outcome that included the 5-year overall survival rate or individual patient data of histological types, follow-up period, and final outcome. Nonhuman studies and those in languages other than English and Japanese, or with a mixed histology of SCC and other malignancies were excluded. Case reports, meta-analyses, and reviews were also excluded.

Data extraction

Two of the authors (Y.T. and H.C.) extracted data. For the aggregate patient data, 5-year overall survival and the number of patients were extracted. For the individual patient data, sex, age, Moody's modified Pittsburgh stage[2] (in some cases, the stage was estimated from the described disease extent), type of treatment modality, type of surgery, follow-up period, and final outcome were extracted.

Statistical analysis

Survival was estimated from individual patient data using the Kaplan–Meier method and examined using the log-rank method. Multivariate analysis was performed using the Cox proportional hazard model. A probability (p) value $< .05$ was considered statistically significant. Individual patient data analyses were performed using the JMP version 9 statistical software (IBM Japan, Tokyo, Japan).

For the aggregate patient data analysis, DerSimonian and Laird's random-effects model was used to pool the 5-year survival rate. Proportions from the 5-year survival dataset were converted into a quantity using the Freeman–Tukey transformation. Meta-analyses were performed using Comprehensive Meta-Analysis (Biostat, Englewood, NJ).

RESULTS

Literature search results

Electronic database searches retrieved 1226 records (see Figure 1). We examined the titles and abstracts, and excluded duplicated entries, case reports, and review articles. Three additional articles were obtained by a manual search. Thus, we found 37 case series regarding external auditory canal SCC but no controlled trials. After applying the exclusion criteria, 29 articles were included in this study.[3,5,7–10,12–34] Among them, 1 article did not show 5-year overall survival because of short a follow-up period.[12] Thus, the remaining 28 articles were analyzed for the aggregate patient data meta-analysis.[3,5,7–10,13–34] Nineteen articles presented the individual patient data and were analyzed for the individual patient data meta-analysis.[3,7,8,10,12–14,17,18,20,22,24–26,28,29,31,33,34] These 19 articles included data of 274 cases. The T classifications of these cases were 59 cases for T1, 41 for T2, 46 for T3, and 128 for T4. For the individual patient data meta-analysis, data of locally advanced external auditory canal SCC cases, namely, 174 cases with T3 or T4 disease were used for subsequent individual patient data analysis.

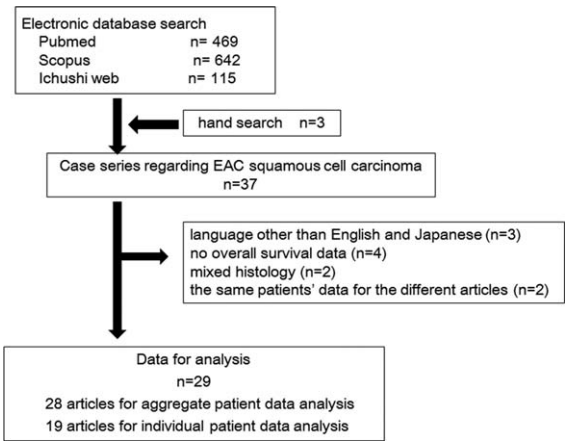

FIGURE 1. Flow diagram of article selection. EAC, external auditory canal.

Aggregate patient data analysis

Among the 28 analyzed articles in which 752 cases were reported, the 5-year overall survival rate for patients with external auditory canal SCC was 20% to 90% (see Figure 2). The weighted estimate of 5-year survival in the 752 cases using a random effect model was 57% (95% confidence interval, 50% to 63%). This data included patients with all stages of external auditory canal SCC with any treatment modalities. Because of the small number of cases in each article, we could not perform aggregate analyses according to either tumor stages or treatment modalities.

Patient background

To evaluate the role of CRT in advanced stage diseases, we performed meta-analyses of individual patient data from 174 patients with T3 or T4 disease. Table 1 shows the characteristics of individual patient data. The median patient age was 63 years and the male to female ratio was 1.0 T classification defined by Moody's classification indicated 46 T3 cases and 128 T4 cases, respectively. Lymph node metastasis was observed in 34 cases (11% T3 cases and 23% T4 cases). There were 42 and 132 cases of stage III (T3N0) and stage IV (T3N1, T4N0,

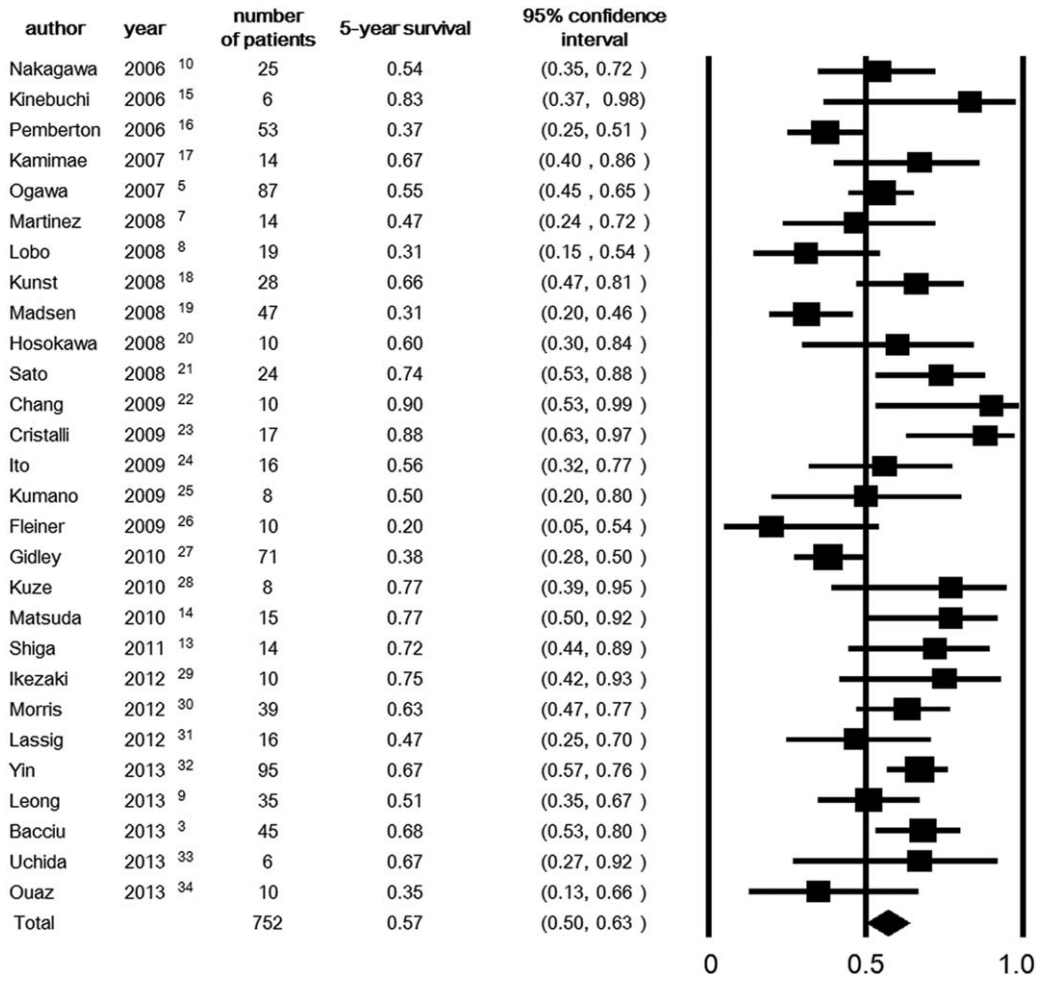

FIGURE 2. A forest plot showing the probability of 5-year overall survival. A total of 752 cases in 28 articles were analyzed.

or T4N1), respectively. Surgery was performed in 124 cases. Of the patients who underwent surgery, 7 received preoperative CRT and 8 received postoperative CRT. Definitive CRT was performed in 37 patients. The surgical procedures were subtotal temporal bone resection or total temporal bone resection for 52 patients, lateral temporal bone resection for 65 patients, and other types of surgery for 7 patients.

Overall survival according to tumor extent and types of surgery

Figure 3 shows the overall survival curves of the individual patient data estimated by the Kaplan–Meier method. The 5-year overall survival rates for T3 and T4 cases were 72.5% and 35.8%, respectively ($p < .001$; Figure 3A). Patients with lymph node metastasis had worse survival compared with patients without lymph node metastasis, although not statistically significant (37.1% vs 47.8%, respectively; $p = .372$; Figure 3B). The 5-year survival rates for stage III and IV diseases were 75.4% and 35.8%, respectively (Figure 3C; $p < .001$). When survival was analyzed according to the types of surgery, subtotal temporal bone resection or total temporal bone resection obtained a 5-year survival rate of 45.7% (Figure 3D). Paradoxically, less curative surgery, mostly lateral temporal bone resection, obtained a better survival rate of 58.2%. On the other hand, the survival rate of patients who did not undergo surgery was 29.0%. These patients received palliative therapy, RT alone, chemotherapy alone, or CRT.

Chemoradiation therapy containing treatment versus conventional treatment

Several reports have shown good treatment outcomes after CRT.[10–14] The details of CRT regimen used in the articles analyzed in this study are summarized in Table 2. To evaluate the role of CRT in the treatment of advanced external auditory canal SCC, we compared the survival rates of patients receiving surgery and those receiving CRT in multimodality treatment strategies. Intra-arterially or intravenously administered platinum-based regimens were mainly used for definitive CRT. As shown in Figure 3E, the 5-year overall survival rate of the definitive CRT group was comparable with that of the standard treatment group (ie, in surgery with or without RT 43.6% and 53.3%, respectively; $p = .210$). Of note, some of the

definitive CRT cases were treated nonsurgically because of unresectability.[10] In particular, the definitive CRT group contained a proportion of patients with poorer prognosis. When CRT was combined with surgery, the effect of CRT on survival depended on settings. Compared with the standard treatment, the 5-year survival rate was better in preoperative CRT settings (85.7%; $p = .131$) and worse in postoperative CRT settings (0%; $p = .327$), although these differences were not statistically significant. The regimens used in preoperative and postoperative settings were fluorouracil-based regimen and intravenously administered platinum-based regimens, respectively (Table 2).

Multivariate analysis

To further investigate the effect of CRT on survival, the Cox proportional hazard model was used (Table 3). T classification was an independent factor for poor survival (hazard ratio [HR], 2.53; $p = .002$), whereas lymph node metastasis was not associated with survival (HR, 0.95; $p = .875$). The types of surgery did not significantly affect survival (HR, 0.75; $p = .327$). The HR of definitive CRT was comparable with that of subtotal temporal bone resection or total temporal bone resection with or without RT (HR, 0.93; $p = .939$). Preoperative CRT was significantly associated with better prognosis (HR, 0.18; $p = .030$), whereas postoperative CRT did not affect survival (HR, 1.30; $p = .617$).

TABLE 1. Patient characteristics.

Characteristics	No. of patients	%
Age		
Median, 63 y		
Range 30–93		
Sex		
Male	74	46
Female	72	45
N/A	28	9
T classification		
3	46	26
4	128	74
N classification		
Negative	140	80
Positive	34	20
Stage		
III	42	24
IV	132	76
Types of treatment		
Preoperative CRT + surgery	7	4
Postoperative CRT +surgery	8	5
Definitive CRT	37	21
Surgery ± RT	109	63
Other	13	7
Surgery		
Subtotal temporal bone resection, total temporal bone resection	52	30
Lateral temporal bone resection	65	37
Other	7	4
None	50	29

Abbreviations: N/A, not available; CRT, chemoradiation therapy; RT, radiation therapy.

DISCUSSION

In the present study, we observed improved survival of patients with external auditory canal SCC compared with previous meta-analyses.[4,35] A meta-analysis of the literature between 1976 and 2008 showed a 5-year overall survival rate of 57.5% and 22.9% for T3 and T4 external auditory canal SCC, respectively.[35] In contrast, our present meta-analysis of the literature between 2006 and 2013 showed a 5-year overall survival of 72.5% for T3 cases and 35.8% for T4 cases, respectively. Although the treatment outcomes explicitly improved, they remain poor, particularly in cases with T4 tumors. To ameliorate treatment outcomes, several institutions use CRT, either preoperatively, postoperatively, or definitively. The results of this meta-analysis suggested the following: (1) preoperative CRT may improve survival in advanced external auditory canal SCC; (2) definitive CRT may be an effective alternative for surgical treatment; and (3) postoperative CRT may not be effective enough to salvage patients with worse prognoses.

Local failure is frequent after surgical treatment for external auditory canal SCC. The risk of failure is particularly high in patients with positive surgical margins. The survival rate for patients with positive margins was poorer despite postoperative radiation.[2] To reduce the rate of locoregional failure after surgery, the standard approach for high-risk head and neck SCC patients is postoperative CRT using high-dose cisplatin.[36] In our meta-analysis, 8 patients received postoperative CRT; however, the results were unfavorable. The 5-year overall survival rate for patients receiving surgery followed by CRT was as low as 0%. One possible reason for this poor result is that patients receiving postoperative CRT were at high-risk and, irrespective of adjuvant therapy, their prognoses were poor. Among the 8 cases with postoperative CRT in this study, 4 received postoperative CRT as a routine for resected T3/T4 disease,[33] 3 for positive margin,[10,29,31] and 1 for aggressive disease.[26] Another possible reason is that the chemotherapy regimens they received were different from the standard regimen for head and neck SCC (ie, high-dose cisplatin). Hence, the benefits of postoperative CRT seem to be scarce. Other strategies, such as definitive CRT or preoperative CRT, should be considered if resection with a tumor-free margin is unlikely.

Nakagawa et al[10] used a different approach to deal with surgical margin status, in which they diminished tumors and obtained tumor-free surgical margin by applying preoperative CRT. In addition, they concomitantly used fluorouracil or its derivative (TS-1) with radiation and topical bleomycin. Their approach seemed to be successful. Negative surgical margins were obtained in 5 of 6 cases, and local disease was controlled in all cases. However, it is notable that their surgical subjects were relatively selected, and they did not resect T4 tumors that invaded the pyramidal apex, carotid canal, or dura. Moreover, their CRT regimen was unique. Only platinum-based regimens have been shown to be effective for head and neck SCC in randomized controlled trials and meta-analyses.[37] In addition, no preoperative therapy was shown to improve the survival of patients with head and neck SCC. The effectiveness of fluorouracil-based preoperative CRT should be verified in controlled trials.

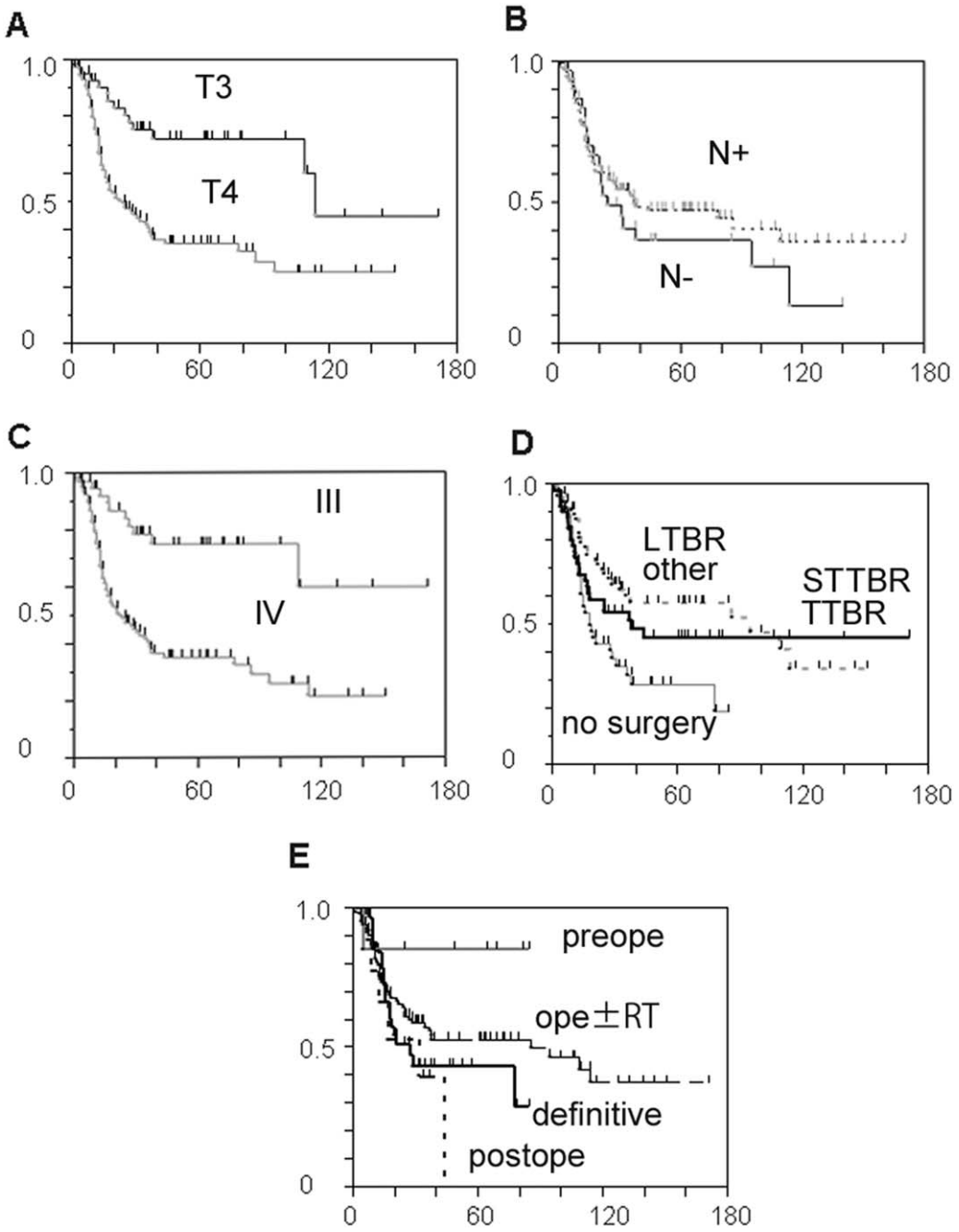

FIGURE 3. The overall survival rate estimated with the Kaplan–Meier method. (A) Comparison of patients with T3 and T4 tumors. (B) Comparison of patients with and without lymph node metastasis. (C) Comparison of patients with stage III and IV tumors. (D) Effect of surgery types on survival. Patients receiving subtotal temporal bone resection (STTBR) or total temporal bone resection (TTBR), those receiving lateral temporal bone resection (LTBR) or other types of surgery, and those without surgery were compared. (E) Effect of chemoradiation therapy (CRT) on survival. Patients receiving conventional treatment (surgery ± radiation therapy [RT]), those receiving preoperative CRT followed by surgery, those receiving definitive CRT, and those receiving surgery followed by postoperative CRT were compared.

Definitive CRT has become the mainstay of head and neck SCC treatment and is used to improve survival for unresectable diseases and preserve organ function in resectable diseases. Our meta-analysis revealed that definitive CRT was also effective for external auditory canal SCC. The survival rates of definitive CRT, estimated by the Kaplan–Meier method, and the hazard for death calculated by the Cox proportional hazard model, were comparable with those of the standard therapy, although definitive CRT cases had more extensive diseases. In the articles we reviewed, various anticancer drugs were used, such as cisplatin, carboplatin, fluorouracil, docetaxel, and mitomycin.[10–14,26,28,33,34] In 10 of 36 definitive CRT cases, intra-arterial cisplatin infusion was used.[11,12,14] This method was reported by Robbins et al[38] in 1996, who reported the use of targeted infusions of supradose

TABLE 2. Details on chemoradiation therapy.

Year	Author	Chemotherapy	Radiation (Gy)	No. of cases	Results	Adverse events
Preoperative						
2006	Nakagawa[10]	Topical bleomycin 5-FU 250 mg daily TS-1 65 mg/m2, daily	40	T3 2 T4 4	1 NED, 1 DOD 3 NED, 1 AWD	N/A
Postoperative						
2009	Fleiner[26]	CBDCA 2 cycles	66	T4 1	1 DOD	N/A
2013	Uchida[33]	CBDCA 60 mg/m2 wk	50–70	T3 2 T4 2	2 NED 2 DOD	N/A
2013	Ouaz[34]	CDDP based	N/A	T4 1	1 alive	N/A
Definitive						
2006	Nakagawa[10]	Topical bleomycin 5-FU 250 mg daily TS-1 65 mg/m2, daily	70	T3 1 T4 8	1 NED 4 NED, 4 DOD	N/A
2009	Ueda[11]	Intra-arterial CDDP	60	T2 2	2 NED	No osteoradionecrosis
2010	Matsuda[14]	100–150 mg/body 4 cycles		T4 3	2 NED, 1 DOC	No thromboembolic events
2009	Fleiner[26]	5-FU, mitomycin CBDCA Mitomycin	78 60 N/A	T4 1 T4 1 T4 1	1 DOD 1 DOD 1 DOD	N/A N/A N/A
2010	Kuze[28]	Docetaxel 10 mg/m2 wk	74	T4 1	1 NED	N/A
2011	Sugimoto[12]	Intra-arterial CDDP 100–150 mg/body 2–4 cycles	60–66	T3 1 T4 4	1 DOD 3 NED, 1 AWD	Neutropenia 4 cases Dermatitis 5 cases Alopecia 4 cases
2011	Shiga[13]	TPF (docetaxel 50 mg/m2, CDDP 60 mg/m2, 5-FU 600–700 mg/m2) 2 cycles	70	T4 9	6 NED 2 DOD 1 DOC	Granulocytopenia 9 cases Anemia 9 cases Elevation of liver enzyme 5 cases Hyponatremia 6 cases
2013	Ouaz[34]	CDDP-based regimen	N/A	T4 1	1 DOD	N/A

Abbreviations: 5-FU, 5-fluorouracil; NED, no evidence of disease; DOD, died of disease; AWD, alive with disease; N/A, not applicable; CBDCA, carboplatin; CDDP, cisplatin; DOC, died of other causes; TPF, docetaxel, cisplatin, and 5-fluorouracil.

cisplatin combined with concomitant radiotherapy (RADPLAT) against malignancies invading the temporal bone, resulting in a complete response in all 4 cases. They enabled infusion of high-dose cisplatin by neutralizing with intravenously injected sodium thiosulfate. The treatment outcomes of RADPLAT for head and neck SCC in a case series and a phase II trial were promising. To verify the superiority over standard CRT regimen, a phase III trial to compare RADPLAT with intravenous CRT for unresectable head and neck SCC was performed.[39] However, RADPLAT was not found to be superior to intravenous CRT, although subset analysis revealed that it had significantly better local control against tumors that did not extend across the midline.[40] Based on the anatomic characteristics, external auditory canal SCCs rarely extend across the midline; therefore, external auditory canal SCC is a good candidate for RADPLAT. Other definitive CRT regimens[10,13,26,28] were uncommon; thus, their effectiveness should be assessed in further trials.

Generally, surgical approaches recommended for external auditory canal SCC are lateral temporal bone resection for T1/T2 disease and subtotal temporal bone resection or total temporal bone resection for T3/T4 disease.[41] However, in actual clinical settings, lateral temporal bone resection or other less invasive surgeries were used more frequently against T3/T4 disease than subtotal temporal bone resection or total temporal bone resection (Table 1). Moreover, cases with lateral temporal bone resection or other surgeries had better survival than those with subtotal temporal bone resection or total temporal bone resection (see Figure 2). This is probably because lateral temporal bone resection was performed for less extensive disease and subtotal temporal bone resection was performed for more extensive disease. Therefore, lateral temporal bone resection may be considered as the choice of treatment for selected T3/T4 cases. However, selection of surgery should be carefully done because incomplete resection results in poor outcome.[2]

Surgical therapy against advanced external auditory canal SCC may be associated with major intracranial complications.[41] Extensive brain retraction can result in lower cranial nerve palsy, cerebellar or temporal lobe edema, and cerebral infarction. Resection of the dura occasionally causes cerebrospinal fluid leakage, resulting

TABLE 3. Multivariate analysis of factors associated with prognosis.

Covariate	Hazard ratio	95% confidence interval	*p* value
T classification			
T3	1		
T4	2.53	(1.38–4.96)	.002
Lymph node metastasis			
Negative	1		
Positive	0.95	(0.52–1.66)	.875
Types of treatment			
Subtotal temporal bone resection or total temporal bone resection ± RT	1		
Lateral temporal bone resection or other surgery ± RT	0.75	(0.41–1.34)	.327
Preoperative CRT + surgery	0.18	(0.01–0.88)	.030
Surgery + postoperative CRT	1.30	(0.43–3.21)	.617
Definitive CRT	0.93	(0.50–1.72)	.806

Abbreviations: RT, radiation therapy; CRT, chemoradiation therapy.

in meningitis. Intracranial hemorrhage may occur after cranial base surgery and can lead to cerebral edema, brain stem herniation, or even death. As consequences of these complications, the perioperative mortality of patients with tumors invading the middle ear treated by total temporal bone resection or subtotal temporal bone resection was as high as 18.7%.[4] In contrast, CRT-associated complications seem to be acceptable, even though a few studies have reported adverse events[12–14] (Table 2). No treatment-related death occurred among the CRT cases analyzed in this study.[10,12,13] The reported adverse events were granulocytopenia and anemia in patients who received docetaxel, cisplatin, and 5-fluorouracil (TPF) regimens, and neutropenia, dermatitis, and alopecia in those who received intra-arterial cisplatin. However, the reports on CRT lack information on late complications. Pemberton et al[16] reported that 5% of the patients treated with primary radical RT developed bone necrosis, 2% developed soft tissue necrosis, and the median time from RT to necrosis was 4.6 years. As CRT is more intense than RT, late complications may occur more frequently in patients who undergo CRT. Therefore, assessment of late complications is required to discuss the pros and cons of CRT.

In this study, we demonstrated the roles of CRT in external auditory canal SCC; however, there were several limitations. First, there was no control trial that compared CRT and conventional therapy. Because of the low evidence level of cited articles, this meta-analysis should not be recognized as having a high evidence level. Therefore, the conclusions suggested here should be verified in future clinical trials. Second, the CRT regimens and selection criteria of patients receiving definitive CRT differed among studies, which caused a substantial discrepancy in treatment outcomes. Definitive CRT with RADPLAT or TPF obtained good prognoses, whereas those with other regimens were unfavorable (Table 2). Last, approximately one-third (9 of 29) of the analyzed articles were written in Japanese. However, we believe it is important to include reports other than those written in English. Bias could be introduced in reviews exclusively based on English-language reports because authors are more likely to report in an international, English-language journal if results are positive, whereas negative findings are more often published in local journals.[42]

In conclusion, our data suggest that preoperative CRT may improve the survival of patients with external auditory canal SCC and that definitive CRT may be an effective alternative for surgical treatment. Because of the limited number of patients, trials by single institutes are difficult to conduct. Prospective multicenter studies are required to verify the role of CRT, establish the best regimen, and improve the survival of patients with external auditory canal SCC.

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