A retrospective analysis of radiotherapy in the treatment of external auditory canal carcinoma

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Abstract. External auditory canal carcinoma (EACC) is a rare disease. The current study aimed to evaluate the clinical outcomes of patients treated with external beam radiotherapy (EBRT) for EACC. The present study retrospectively reviewed 34 consecutive patients treated for EACC with EBRT between February 2001 and January 2019 at the University of Tokyo Hospital. Clinical staging was performed according to the modified Pittsburgh classification. Of all the included patients, seven patients were in the early stages (I or II) and 27 in the advanced stages (III or IV) of EACC. A total of 16 patients underwent EBRT and surgery (S+RT) pre- and/or postoperatively, while 18 patients underwent definitive radiotherapy (dRT). The median prescribed doses for the S+RT and dRT groups were 66 and 70 Gy, respectively. The median follow-up period for all patients was 22.4 months (range, 2-205 months). The 5-year overall survival rates of the S+RT and dRT groups were 66.7 and 45.1%, respectively. The progression-free survival rate at 5-year was 55.6% (95% confidence interval: 36.5-71.1%) for the entire cohort. A total of 14 patients experienced disease relapse after treatment, consisting of 11 locoregional recurrences and three distant metastases. The current study revealed the clinical outcomes of EBRT for EACC.

Introduction

External auditory canal carcinoma (EACC) is an extremely rare disease with an incidence of approximately one in a million and accounts for <1% of all head and neck cancers (1,2). EACC often requires substantial clinical time from the onset of symptoms to the diagnosis because of its low incidence. The initial clinical symptoms of EACC are nonspecific and include otorrhea, tinnitus, otalgia, hearing loss, clogged ears, and bleeding. In patients with advanced stages of EACC, facial paralysis is also present and is associated with poor survival. Chronic stimulation, such as habitual ear picking, has also been recognized as an important factor in the carcinogenesis of EACC (3).

Squamous cell carcinoma is the most common histological type of EACC and accounts for 80-90% of cases, followed by adenoid cystic carcinoma, basal cell carcinoma, and adenocarcinoma (4). Several criteria have been formulated in the clinical staging system of EACC. According to the 8th edition of the American Joint Committee on Cancer staging manual on the tumor, node, and metastasis staging system, EACC is classified as cutaneous cancers of the head and neck. The Stell and McCormick staging system is based on staging of external auditory canal and middle ear carcinomas (5). The modified Pittsburgh staging system (6) is also widely used in external auditory squamous cell carcinoma, which originates from the Arriaga staging system (7) based on preoperative clinical examination and computed tomography (CT) findings. Although there is no universally accepted staging system, the modified Pittsburgh staging system is valuable for clinical decision-making (8).

Surgery is the mainstay of treatment for early stage EACC (9). Radiotherapy is indicated in the following cases: i) Radical treatment for patients unable to undergo surgery, ii) postoperative treatment for patients who have undergone surgical resection, but having a high risk of recurrence (e.g., positive margins and locally advanced cases), and iii) preoperative treatment for medically operable and locally advanced cases. Multimodal treatment combining local and systemic treatment approaches is advised for locally advanced cases; however, optimal treatment remains controversial.

Performing a large statistical examination is often difficult in a single institution because of the limited number of cases. Hence, careful consideration of these cases is important. This retrospective study aimed to evaluate the feasibility and efficacy of external beam radiotherapy (EBRT) with or without surgery for patients with EACC. We reviewed approximately 20 years of EACC treatment in our institution.

Materials and methods

We retrospectively reviewed 34 consecutive patients with EACC treated by curative EBRT with or without surgery between
February 2001 and January 2019. The inclusion criteria were as follows: histologically confirmed cases of primary EACC, cases treated using EBRT with curative intent, cases with no evidence of distant metastasis at the time of diagnosis, and no prior radiotherapy to the temporal bone region. The exclusion criteria were as follows: Radiotherapy for palliative intent cases and lack of sufficient medical records to confirm EACC or to decide the treatment modality. The clinical staging was performed according to the modified Pittsburgh staging system, because a recent study had been reported the clinical usefulness of that staging system (8). Acute and late adverse events were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.0.

CT of the patients for planning the radiation therapy was performed while wearing a thermoplastic mask. All patients underwent radiotherapy with 4-6 MV photon linear accelerators by radiation technologies of three-dimensional conformal radiotherapy (3D-CRT), static intensity-modulated radiotherapy (IMRT), or volumetric modulated arc therapy (VMAT). The CT image data were reconstructed with a slice thickness of 5 mm for 3D-CRT and 2 mm for IMRT or VMAT. The clinical target volume (CTV) included the primary tumor and clinically positive lymph nodes. The CTV included the tumor bed for the postoperative cases. The planning target volume included the CTV with a minimum added margin of 3-5 mm. No patient received prophylactic irradiation for the clinically negative neck.

Statistical analysis. The R statistical package (The R Foundation for Statistical Computing, Vienna, Austria) was used for data analyses. For comparison of the proportions of patient's characteristics in two groups, the Fisher exact test was used. Overall survival (OS), progression-free survival (PFS), and cancer-specific survival (CSS) rates were calculated from the first day of initial therapy by the Kaplan-Meier method. PFS was defined as the time from initial therapy to first evidence of radiological or clinical tumor progression, or until death from any cause. A univariate Cox proportional hazard analysis was performed, since a small sample size made it difficult to conduct a multivariate analysis to reach a valid conclusion. The P-values of <0.05 were considered statistically significant.

Results

In this study, 34 patients were retrospectively analyzed. The median follow-up period for these patients was 22.4 months (range: 2-205 months). The pathological diagnosis of all patients was undifferentiated carcinoma (1 patient), followed by adenoid cystic carcinoma (1 patient), undifferentiated carcinoma (1 patient), and poorly differentiated adenocarcinoma (1 patient). Of all the patients, 18 received definitive radiotherapy (dRT) and 16 received EBRT combined with surgery (S+RT). The median follow-up period for the dRT and S+RT groups was 15.3 (range: 2-205 months) and 75.1 months (range: 5-169 months), respectively. Patient characteristics for both the groups are presented in Table I. The S+RT group had a higher ratio of male patients and better Karnofsky Performance Status (KPS) compared to the dRT group. No statistically significant difference was observed between the two groups in terms of patient age, clinical stage, pathology, and prescribed dose. The entire cohort consisted of 19 men and 15 women, with a median age of 66 years (range: 32-86 years). According to the modified Pittsburgh staging system, 21% of the patients were classified in early stage and 79% in advanced stage of EACC.

The radiotherapy characteristics of the patients are shown in Table II. In the dRT group, 13 patients underwent EBRT concurrently with chemotherapy or biotherapy, which consisted of the docetaxel platinum plus 5-fluorouracil (DCF) regimen, platinum plus 5-fluorouracil (CF) regimen, single-agent platinum regimen, and cetuximab.

The S+RT group underwent postoperative radiotherapy (n=10) and pre- and/or postoperative radiotherapy (n=6). According to the surgical treatment modalities, one patient underwent mastoidectomy, seven patients underwent lateral temporal bone resection, and eight patients underwent subtotal temporal bone resection. All patients who received postoperative radiotherapy underwent EBRT without chemotherapy. In total, there were six patients in the pre- and/or postoperative radiotherapy group; four patients received radiation therapy alone (without chemotherapy), one patient received a daily low-dose of cisplatin concurrently undergoing the pre- and/or postoperative radiation therapy, and one patient received neoadjuvant chemotherapy consisting of cisplatin and 5-fluorouracil prior to preoperative radiotherapy. The median prescribed doses for the S+RT and dRT groups were 66 (range: 50-70 Gy) and 70 Gy (range: 60-70 Gy), respectively.

Of all the patients, 19 (56%) patients were alive at the time of this analysis; the 5-year OS and CSS rates for the entire cohort were 55.2 (95% confidence interval [CI]: 35.7-71.1%) and 57.1% (95% CI: 37.0-72.9%), respectively (Fig. 1). The 5-year OS rates for the early and advanced stages were 85.7 and 45.6%, respectively (Fig. 2A). There was no significant statistical difference between the 5-year OS rates of both the groups (Fig. 2B, 66.7 vs. 45.1%, P=0.104). With reference to the univariate analysis (Table III), a factor associated with a favorable OS rate included a good performance status of over or equal to 90% (hazard ratio: 0.137, 95% CI: 0.043-0.434, and P<0.001).

Of all the patients, 14 (41.2%) developed recurrences, including nine with local recurrences, two with combined locoregional recurrences, and three with distant metastases. The PFS rate at 5-year was 55.6% (95% CI: 36.5-71.1%) for the entire cohort. A wide variety of metastatic sites, including the lungs, liver, and bone, was observed in cases with distant metastases. Salvage surgery was performed in one patient, while chemotherapy was performed in three patients for patients with recurrence. The remaining patients selected the option of best supportive care. Among the patients treated with chemotherapy, one patient received the CF regimen and two patients received oral S-1 administration. The median survival time after recurrence in patients with recurrence was 2.9 months (range: 0.2-23 months). Severe (Grade 3 or higher) radiation-induced late complications were not observed.

Discussion

Our study evaluated the clinical outcomes of patients treated with EBRT for EACC. Our results were consistent with those of previous reports. A meta-analysis of 742 patients reported...
that patients with external auditory canal squamous cell carcinoma treated with chemoradiotherapy had a similar survival rate (10). A multi-institutional review of 87 patients that focused primarily on the roles of surgery and radiotherapy in these patients discovered that the 5-year OS and disease-free survival rates were 55 and 54%, respectively (11). Furthermore, this review indicated that the clinical stage and treatment modality were significant prognostic factors.

To the best of our knowledge, there are no prospective or randomized trials about EACC treatment. For the patient in early stage EACC, surgical resection with tumor free margin is the most standard treatment (12,13). Radical conventional radiotherapy also achieves favorable outcome, which was considered as treatment option (14). Murai et al reported the effectiveness of the stereotactic radiotherapy for a new treatment option of EACC (15).

However, there is no clear consensus about treatment strategies in advanced cases. Surgical resection in combination with perioperative radiotherapy is more effective compared to a single modality treatment (16-18). Nakagawa et al used preoperative radiotherapy; their study revealed that the tumor-free surgical margin had a significant correlation with patient survival in locally advanced cases (19). In another study conducted by Choi et al they considered the necessity of postoperative radiotherapy in accordance with the clinical stage (20). The disease control rates for patients with early vs. advanced stages were 55.6 vs. 50% in the postoperative radiotherapy group and 66.7 vs. 37.5% in the dRT group. In this study, while the 5-year OS rate was higher in the S+RT group, the difference did not reach statistical significance (66.7 vs. 45.1%, P=0.104).

Despite the aggressive multidisciplinary treatment, locoregional failure remains the most frequent recurrence; Yoon et al reported a high propensity for locoregional failure of EACC (21). Furthermore, they reported nine local recurrences, eight regional recurrences, and three distant metastases among 20 patients with recurrence. In our study, locoregional failure was detected in 76% of patients with recurrence. Therefore, a more aggressive local therapy could be beneficial to some extent. Hayashi et al reported the clinical outcome of carbon ion radiotherapy for external auditory canal and middle ear carcinomas in a retrospective multicenter study (22). They revealed that the 3-year local control and OS rates were 55 and 59%, respectively.

The optimal chemotherapy regimen for concurrent chemoradiotherapy in definitive radiotherapy is still

Table I. Patient characteristics of 34 patient with external auditory canal carcinoma in our institution.

| Characteristics                  | dRT group (n =18) | S+RT group (n =16) | P-value |
|----------------------------------|-------------------|--------------------|---------|
| Age, median (range)              | 68 (46-86)        | 65 (32-75)         | 0.925   |
| Sex                              |                   |                    |         |
| Male                             | 7 (39%)           | 12 (75%)           | 0.045   |
| Female                           | 11 (61%)          | 4 (25%)            |         |
| KPS, median (range)              | 80 (70-100)       | 90 (80-100)        | 0.008   |
| Clinical stage                   |                   |                    | 0.214   |
| Early (I/II)                     | 2 (11%)           | 5 (31%)            |         |
| Advanced (III/IV)                | 16 (89%)          | 11 (69%)           |         |
| Pathology                        |                   |                    | 0.591   |
| SqCC                             | 17 (94%)          | 14 (88%)           |         |
| ACC                              | 0                 | 1 (6%)             |         |
| Others                           | 1 (6%)            | 1 (6%)             | 0.446   |
| Prescribed dose, median (range)  | 70 Gy (50-70 Gy)  | 66 Gy (60-70 Gy)   |         |

KPS, Karnofsky Performance Status; dRT, Definitive radiotherapy; S+RT, surgery plus radiotherapy; SqCC, Squamous cell carcinoma; ACC, Adenoid cystic carcinoma; Gy, gray (a derived unit of ionizing radiation dose).

Table II. Radiotherapy characteristics of 34 patient with external auditory canal carcinoma in the University of Tokyo Hospital.

| Treatment type                           | N | Percentage (%) |
|------------------------------------------|---|----------------|
| Definitive radiotherapy                  | 18| 53             |
| Bioradiotherapy (cetuximab)              | 1 |                |
| CCRT                                     | 12|                |
| Docetaxel + Cisplatin + 5FU (DCF)        | 8 |                |
| Cisplatin + 5-FU (CF)                    | 2 |                |
| Daily Cisplatin                          | 2 |                |
| RT alone                                 | 5 |                |
| Radiotherapy with surgery                | 16| 47             |
| Postoperative (RT alone)                 | 10|                |
| Pre + postoperative                      | 6 |                |
| RT alone                                 | 4 |                |
| Chemoradiotherapy (including NAC)        | 2 |                |

CCRT, concurrent chemoradiotherapy; NAC, neoadjuvant chemotherapy; 5-FU, 5-fluorouracil; DCF, docetaxel cisplatin plus 5-fluorouracil; CF, cisplatin plus 5-fluorouracil; RT, radiotherapy.
Table III. Univariate Cox proportional hazard analysis of overall survival.

| Covariables                | N   | Hazard ratio | 95% CI           | P-value |
|----------------------------|-----|--------------|------------------|---------|
| Age                       |     |              |                  |         |
| ≤65 years old             | 16  | 1            |                  |         |
| >65 years old             | 18  | 1.529        | 0.542-4.312      | 0.422   |
| Sex                       |     |              |                  |         |
| Female                    | 15  | 1            |                  |         |
| Male                      | 19  | 0.647        | 0.234-1.788      | 0.401   |
| Performance status        |     |              |                  |         |
| <90%                       | 10  | 1            |                  |         |
| ≥90% (local recurrence)   | 24  | 0.137        | 0.043-0.434      | <0.001  |
| Clinical stage            |     |              |                  |         |
| Early                     | 7   | 1            |                  |         |
| Advanced                  | 27  | 2.493        | 0.558-11.130     | 0.231   |
| Pathological type         |     |              |                  |         |
| SqCC                      | 31  | 1            |                  |         |
| non SqCC                  | 3   | 0.976        | 0.127-7.525      | 0.982   |
| Surgery                   |     |              |                  |         |
| No                        | 18  | 1            |                  |         |
| Yes                       | 16  | 0.406        | 0.137-1.204      | 0.104   |
| Chemotherapy              |     |              |                  |         |
| No                        | 20  | 1            |                  |         |
| Yes                       | 14  | 1.300        | 0.460-3.679      | 0.621   |

CI, confidence interval; SqCC, Squamous cell carcinoma.

Figure 1. Kaplan-Meier curve for (A) overall survival and (B) cancer-specific survival in patients with external auditory canal carcinoma treated in our institution. A vertical bar indicates a censored case.

Figure 2. Kaplan-Meier curves for (A) overall survival stratified clinical stage: Early vs. advanced) and (B) treatment strategy: dRT vs. S+RT. A vertical bar indicates a censored case. dRT, Definitive radiotherapy; S+RT, surgery plus radiotherapy; OS, overall survival.
controversial. Several anticancer drugs, such as cisplatin, carboplatin, fluorouracil, docetaxel, and mitomycin, are widely used (10). Nagano et al reported that the DCF regimen was potentially the most effective method, with reference to their study that revealed a 100% 2-year OS and locoregional control rate in six patients with advanced EACC who had received this regimen (23). Other studies supported the use of an intra-arterial cisplatin infusion in combination with radiotherapy for locally advanced cases of EACC (24,25).

Several limitations existed in our study. First, the most important limitation of present study is the low number of cases and the retrospective nature of the study could have produced a selection bias. Second, a long observation period resulted in a substantial heterogeneity of treatment modality, such as chemotherapy regimens, treatment modality, radiation technology, and surgical procedure. Third, there was unclarity about decision making process of the therapeutic strategies at the time of the treatment because of retrospective data analysis. Fourth, our study included different pathological types, which could have caused inaccurate results in the study. Fifth, our data were dependent on the medical records, which may be insufficient for accurately describing all the patient characteristics and events, especially in adverse event detection. This factor limited the availability of patient covariates, and unmeasured confounding variables most likely existed during the study.

In conclusion, our retrospective study reported the clinical outcomes of EACC in our institution. No statistically significant difference between the dRT and S+RT groups was observed. However, the S+RT group had a better prognosis tendency than the dRT group, which was consistent with a previous report. Further studies and accumulation of data are needed to determine the optimal treatment strategy for EACC in the future.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Authors' contributions
AK was a major contributor to writing this report. AK collected and assembled the data. HY and AK analyzed and interpreted the clinical data. HY conceived of this study and collected and assembled the data. HY and AK analyzed and interpreted the clinical data. HY and AK contributed to the acquisition of data. OA and KN made substantial contributions to interpretation of data. RT, HY, MA, MY, TA, OA and KN revised this report critically for important intellectual content. All authors have read and approved the final manuscript.

Ethics approval and consent to participate
Written informed consent was obtained from all patients. The current study was approved the institutional review board in the University of Tokyo Hospital (Tokyo, Japan).

Patient consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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