Dosimetric Analysis for Otitis Media With Effusion Due to Eustachian Tube Dysfunction After Carbon-ion Radiation Therapy for Head and Neck Cancers

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Abstract

Purpose: This study aimed to clarify the predictive factors for otitis media with effusion (OME) due to Eustachian tube dysfunction in patients treated with carbon-ion radiation therapy (CIRT) for head and neck cancers.

Methods and Materials: We investigated patients with head and neck cancer whose Eustachian tube was irradiated by CIRT between October 2013 and December 2018 at our institution. OME severity was assessed by the proportion of mastoid cell opacification of magnetic resonance or computed tomography imaging (grade 0: <5% of volume of mastoid cell with opacification by fluid collection; grade 1: 6%-33%; grade 2: 34%-67%; and grade 3: 68%-100%). Clinical factors and dosimetric parameters affecting the development of grade 2 to 3 OME were analyzed using a log-rank test and Cox proportional hazards model.

Results: In total, 141 patients were analyzed. The median follow-up period was 25.2 months. Grade 2 to 3 OME was observed in 65 patients, with a median incidence period of 6.5 months. According to the multivariate analysis, the mean dose of the cartilage part was a significant independent predictive parameter of grade 2 to 3 OME. The 2-year incidence rate of patients with a mean dose of the cartilage part of <40.59 Gy (relative biological effectiveness) and ≥40.59 Gy (relative biological effectiveness) was 24.2% (95% confidence interval, 15.1%-37.4%) and 66.4% (95% confidence interval, 54.5%-78.0%), respectively.

Conclusions: Our findings may be useful to predict the risk of grade 2 to 3 OME due to Eustachian tube dysfunction before CIRT.

Introduction

Otitis media with effusion (OME) is a major concerning adverse event for patients with head and neck cancers treated with radiation therapy (RT), producing various clinical symptoms, such as earache, chronic purulent secretion, tinnitus, hearing loss, and reduced quality of
life.1-3 Approximately 10% to 30% of patients with head and neck cancer treated with RT developed OME.4 There are 2 potential mechanisms for OME development: Eustachian tube dysfunction and direct radiation-induced damage of the middle ear cavity and/or mastoid cell mucosa.5 Several articles report on the association between dosimetric factors and OME in RT.5-8

Compared with photons, carbon ions are characterized by higher linear energy transfer and greater values of relative biological effectiveness (RBE).9 Carbon ions also have improved dose localization properties due to the Bragg peak and small lateral scattering.9 Therefore, carbon-ion RT (CIRT) has been effective against radioresistant tumors due to its high biological effectiveness and high dose irradiation.10-13 Moreover, CIRT can deliver doses consistent with the irradiation field, and is expected to reduce adverse events, especially by improving the surrounding medium dose area (Fig. 1). In the head and neck regions, CIRT can be used to irradiate deep tumors, such as sinonasal and pharyngeal tumors, with reduced doses to the mastoid cells and middle ear, but we encountered a case of OME due to Eustachian tube dysfunction where the tumor was in close proximity. However, there are no reports on the risk factors for OME due to

Figure 1  Example of otitis media with effusion after carbon-ion radiation therapy (RT). A 40-year-old woman was diagnosed with adenoid cystic carcinoma of the maxillary sinus. Six months after receiving carbon-ion RT, grade 3 otitis media with effusion was observed. A–F) Contouring of the cartilage part (red), bone part (blue), and mastoid cell (green); G) representative dose distribution of carbon-ion RT, with a prescribed dose of 64.0 Gy (relative biological effectiveness)/16 fractions; H) T2-weighted image before carbon-ion RT; and I) T2-weighted image 6 months after carbon-ion RT.
Eustachian tube dysfunction in CIRT, and dose constraints on the Eustachian tube are unknown.

This study aimed to determine the predictive factors for OME related to Eustachian tube dysfunction in patients treated with CIRT for head and neck cancers.

Methods and Materials

Study participants

Patients with head and neck cancers treated with CIRT between October 2013 and December 2018 at our institution were evaluated. To exclude OME cases caused by direct inflammation of the middle ear cavity or mastoid cell, patients with deep site tumors, such as those located in the pharynx and sinonasal or oral cavity, were included in this study. The exclusion criteria were as follows: 1) <6 months of follow up; 2) presence of mastoid cell opacification and/or tumor invasion to the Eustachian tube; 3) presence of inflammatory findings around the Eustachian tube; 4) <10 Gy (RBE) irradiation of the bilateral Eustachian tube; 5) planning target volume (PTV), including middle ear or mastoid cell; and 6) a history of previous RT to the head and neck regions. In total, 141 patients were enrolled in this study. In these patients, we analyzed the Eustachian tube on the side that received the higher dose.

All patients provided informed consent, authorizing the use of their clinical information for study purposes. This retrospective study was approved by the institutional review board of our institution (approval number 20-0012), and was conducted in accordance with the Declaration of Helsinki.

Carbon-ion radiation therapy

The carbon-ion dose is expressed as the photon-equivalent dose in Gy (RBE), and defined as the physical dose multiplied by the carbon-ion RBE.9 Detailed treatment planning has been previously described.13 The treatments were planned on a computed tomography (CT)-based 3-dimensional treatment planning system using the XiO-N (ELEKTA, Stockholm, Sweden; Mitsubishi Electric, Tokyo, Japan).14 The median prescribed dose was 64 Gy (range, 57.6-70.4 Gy; RBE). All patients were treated with a schedule of 16 fractions, with 4 fractions per week.

Follow up and evaluation of otitis media with effusion

After CIRT for head and neck cancers, patients received follow up with CT or magnetic resonance imaging (MRI) every 3 months for the first 2 years and 3 to 6 months thereafter. OME was assessed based on the proportion of mastoid cell opacification of MRI T2-weighted imaging or CT with bone setting imaging. The grade was rated as follows: Grade 0, <5% of the volume of mastoid cell was opacified by fluid collection; grade 1, 6% to 33%; grade 2, 34% to 67%; and grade 3, 68% to 100%.5

Dose–volume histogram analysis

To identify the dosimetric parameters to develop OME, we contoured the cartilage and bone parts of the Eustachian tube and mastoid cell on each axial slice of planning CT imaging. Since no well-known contouring atlas about the Eustachian tube exists, we defined contouring as a columnar structure of 4 mm in the radius from the center line of the Eustachian tube cavity. We included the middle ear cavity in mastoid cell contouring. Dose–volume histogram (DVH) parameters, which were mean dose ($D_{\text{mean}}$), maximum dose ($D_{\text{max}}$), and volume receiving 10 to 60 Gy (RBE; $V_{10-60}$) of each structure, were generated using MIM Maestro, version 7.0 (MIM Software Inc, Cleveland, OH). The dose–response curve of the association between grade 2 to 3 OME incidence rate and a DVH parameter was calculated with the following integral logistic model15:

$$P = 1 - 1/(1 + \exp(a + bD))$$

where $P$ is the probability of grade 2 to 3 OME, $D$ the irradiated dose of organs at risk, and $a$ and $b$ the constants calculated by binary logistic regression analysis.

Statistical analyses

All incidence periods were calculated from the first day of CIRT. The 2- and 3-year incidence rates were determined using the Kaplan–Meier method. A Mann–Whitney U test was used to evaluate the relationship between the DVH parameters and grade 2 to 3 OME. A Pearson’s correlation analysis was used to assess the correlation of DVH parameters. The area under the receiver operating characteristic curve (AUC) values were calculated to select the DVH parameters with the highest sensitivity and specificity for grade 2 to 3 OME. Clinical factors and dosimetric parameters affecting the development of grade 2 to 3 OME were analyzed. Each factor was considered a binary variable.

Continuous variables, such as age, gross tumor volume, PTV, structure volume, and DVH parameters, were divided into 2 groups by median value. For the univariate analyses, the log-rank test was used to compare the incidence rates of grade 2 to 3 OME between the 2 groups. All factors with statistically significant differences in the univariate analysis were included in a multivariate analysis using the Cox proportional hazards model. Statistical
significance was set at 2-tailed $P < .05$. All statistical analyses were performed using the Statistical Package for the Social Sciences software, version 23 (IBM, Armonk, NY).

Results

Patient characteristics

The characteristics of patients, tumors, treatments, and structure volumes are summarized in Table 1. A total of 42 patients received concurrent chemotherapy. These patients all had mucosal malignant melanoma and received a dacarbazine, nimustine hydrochloride, and vincristine sulfate regimen.

Incidence of otitis media with effusion

The median follow-up period was 25.2 months (range, 6.0-76.1 months). OME was observed in 76 patients (54%) on follow-up CT or MRI evaluation. Grades 1, 2, and 3 OMEs were observed in 11 (8%), 20 (14%), and 45 (32%) patients, respectively. The median incidence period of grade 2 to 3 OME in 65 patients was 6.5 months (range, 0.9-64.4 months). The 2-year incidence rate of grade 2 to 3 OME was 45.2% (95% confidence interval [CI], 36.8%-54.5%). Of the 65 patients who developed grade 2 to 3 OME, 11 had ventilation tube insertion, 5 underwent tympanostomy, 2 received oral medicine, and 5 experienced spontaneous recovery.

Risk factors for otitis media with effusion

The mean DVH curves of the cartilage, bone, and mastoid cell for patients with grade 0 to 1 OME and grade 2 to 3 OME are shown in Supplementary Figure 1. The mean values for the DVH parameters in the grade 0 to 1 and grade 2 to 3 groups, as well as the $P$-values from the Mann–Whitney $U$ test, are shown in Supplementary Table 1.3. There were significant differences in all DVH parameters. Each DVH parameter was highly correlated and confounded by the Pearson’s correlation analysis (Suppl. Table 4.6); therefore, AUC values were calculated (Suppl. Table 7).

$D_{\text{mean}}$ was the parameter with the largest AUC value at the cartilage part, bone part, and mastoid cell, and was included in the univariate and multivariate analyses of risk factors for grade 2 to 3 OME incidence. The results of the univariate and multivariate analyses are shown in Table 2. In the univariate analysis, concurrent chemotherapy, gross tumor volume, PTV, volume of bone part, and $D_{\text{mean}}$ of the cartilage part, bone part, and mastoid cell

| Table 1 | Characteristics of study patients (N = 141) |
|----------------|------------------------------------------|
| Characteristic | Data                                      |
| Age, years, median (range) | 65 (18-90) |
| Sex, $n$ (%) |                                          |
| Male | 74 (52) |
| Female | 67 (48) |
| Tumor site, $n$ (%) |                                          |
| Nasal cavity | 64 (45) |
| Maxillary sinus | 31 (22) |
| Oral cavity | 18 (13) |
| Ethmoid sinus | 11 (8) |
| Nasopharynx | 9 (6) |
| Oropharynx | 5 (4) |
| Sphenoid sinus | 3 (2) |
| Pathologic type, $n$ (%) |                                          |
| Adenoid cystic carcinoma | 55 (39) |
| Mucosal malignant melanoma | 51 (36) |
| Adenocarcinoma | 6 (4) |
| Olfactory neuroblastoma | 6 (4) |
| Mucoepidermoid carcinoma | 3 (2) |
| Others | 20 (14) |
| Lesional side, $n$ (%) |                                          |
| Left | 76 (54) |
| Right | 65 (46) |
| Irradiation method, $n$ (%) |                                          |
| Passive | 52 (37) |
| Scanning | 89 (63) |
| Dose of protocol, $n$ (%) |                                          |
| 57.6 Gy (RBE)/16 fractions | 50 (35) |
| 60.8 Gy (RBE)/16 fractions | 6 (4) |
| 64.0 Gy (RBE)/16 fractions | 77 (55) |
| 70.4 Gy (RBE)/16 fractions | 8 (6) |
| Concurrent chemotherapy, $n$ (%) |                                          |
| No | 99 (70) |
| Yes | 42 (30) |
| Gross tumor volume, cc, median (range) | 27.24 (0.19-145.76) |
| Planning target volume, cc, median (range) | 137.54 (20.77-313.70) |
| Cartilage part, cc, median (range) | 1.51 (1.04-2.19) |
| Bone part, cc, median (range) | 1.25 (1.01-1.64) |
| Mastoid cell, cc, median (range) | 19.45 (3.31-48.22) |

RBE, relative biological effectiveness
| Factor                              | Univariate        |          | Multivariate          |          | Hazard ratio (95% confidence interval) |
|------------------------------------|-------------------|----------|-----------------------|----------|---------------------------------------|
|                                    | n                 | P-value  | n                     | P-value  |                                       |
| Age, y                             |                   | .428     |                       |          |                                       |
| <65                                | 73                |          |                       |          |                                       |
| ≥65                                | 68                |          |                       |          |                                       |
| Sex                                |                   | .979     |                       |          |                                       |
| Male                               | 74                |          |                       |          |                                       |
| Female                             | 67                |          |                       |          |                                       |
| Lesional side                      |                   | .765     |                       |          |                                       |
| Left                               | 76                |          |                       |          |                                       |
| Right                              | 65                |          |                       |          |                                       |
| Irradiation method                 |                   | .276     |                       |          |                                       |
| Passive                            | 52                |          |                       |          |                                       |
| Scanning                           | 89                |          |                       |          |                                       |
| Total prescribed dose              |                   | .140     |                       |          |                                       |
| <64.0 Gy (relative biological      | 56                |          |                       |          |                                       |
| effectiveness)                     |                   |          |                       |          |                                       |
| ≥64.0 Gy (relative biological      | 85                |          |                       |          |                                       |
| effectiveness)                     |                   |          |                       |          |                                       |
| Concurrent chemotherapy            |                   | .036     | .144                  |          |                                       |
| No                                 | 99                |          |                       |          |                                       |
| Yes                                | 42                |          |                       |          |                                       |
| Gross tumor volume, cc             |                   | .001     | .161                  |          |                                       |
| <27.24                            | 70                |          |                       |          |                                       |
| ≥27.24                            | 71                |          |                       |          |                                       |
| Planning target volume, cc         |                   | .001     | .139                  |          |                                       |
| <137.54                           | 70                |          |                       |          |                                       |
| ≥137.54                           | 71                |          |                       |          |                                       |
| Cartilage part, cc                 |                   | .413     |                       |          |                                       |
| <1.51                             | 70                |          |                       |          |                                       |
| ≥1.51                             | 71                |          |                       |          |                                       |
| Bone part, cc                      |                   | .029     | .056                  |          |                                       |
| <1.26                             | 72                |          |                       |          |                                       |
| ≥1.26                             | 69                |          |                       |          |                                       |
| Mastoid cell, cc                   |                   | .761     |                       |          |                                       |
| <19.45                            | 70                |          |                       |          |                                       |
| ≥19.45                            | 71                |          |                       |          |                                       |
| D<sub>mean</sub> of the cartilage part | < .001 | .007     |                       |          | 3.540 (1.417-8.850)                    |
| <40.59                            | 70                |          |                       |          |                                       |
| ≥40.59                            | 71                |          |                       |          |                                       |
| D<sub>mean</sub> of the bone part  | < .001 | .820     |                       |          |                                       |
| <12.56                            | 70                |          |                       |          |                                       |
| ≥12.56                            | 71                |          |                       |          |                                       |
| D<sub>mean</sub> of the mastoid cell | < .001 | .348     |                       |          |                                       |
| <1.27                             | 70                |          |                       |          |                                       |
| ≥1.27                             | 71                |          |                       |          |                                       |

D<sub>mean</sub>: mean dose
were risk factors. However, in the multivariate analysis, the D_{mean} of the cartilage part was a significant independent predictive factor for grade 2 to 3 OME. The 2-year incidence rates of patients with a D_{mean} of the cartilage part of <40.59 Gy (RBE) and $\geq 40.59$ Gy (RBE) were 24.2% (95% CI, 15.1%-37.4%) and 66.4% (95% CI, 54.5%-78.0%), respectively (Fig. 2).

A dose–effect curve was generated for the D_{mean} of the cartilage part. The result of partial regression constant of -2.595 was substituted as a, and the partial regression constant of 0.061 as b in the above formula. The odds ratio for the partial regression coefficient (D_{mean} of cartilage part) was 1.063 (95% CI, 1.040-1.086) with P = .000. The adjusted curve between the grade 2 to 3 OME incidence rate and D_{mean} of the cartilage part is presented in Figure 3. As the value of the D_{mean} increased, the frequency of OME gradually increased.

Discussion

OME after RT decreases the patient’s quality of life; however, since there are treatment methods for OME, such as myringotomy, the priority in treatment is not high compared with visual impairment. With CIRT, with the introduction of spot scanning irradiation, finer irradiation is possible, and reducing the dose to minute areas, such as the Eustachian tube, has become possible. In this study, we revealed that the D_{mean} of the cartilage part is a significant independent predictive factor for OME grade 2 to 3. To the best of our knowledge, this is the first study to investigate the predictive factors associated with OME-related Eustachian tube dysfunction after CIRT for head and neck cancers.

Several studies have reported OME after RT. Nishimura et al. evaluated the incidence rate of radiation-induced otomastoiditis according to the proportion of the high-signal intensity area using T2-weighted MRI, and reported that the incidence rate of otomastoiditis increased with the irradiation dose of the temporal bone $>50$ Gy. In another study classifying MRI, Walker et al. reported that a mean photon irradiation dose of $>30$ Gy to the mastoid cell or posterior nasopharynx was associated with otomastoid opacification in patients treated with RT for skull base tumors. Wang et al. assessed OME by the variation of pure tone audiometry and impedance audiometry tests for nasopharyngeal carcinomas, and concluded that a D_{mean} of $>52$ Gy to the isthmus of the Eustachian tube and a D_{mean} of $>46$ Gy to the middle ear cavity increased the morbidity factors for OME. Yao et al. reported that a D_{30%} of $>52.75$ Gy of the Eustachian tube and a D_{0.5 cc} of $>41.04$ Gy of the mastoid cell were associated with ear symptoms, posing difficulty in daily life and/or requiring treatment.

Although these studies report on the association between irradiation dose and adverse events related to ear function, the study designs and conclusions vary. These reports may have a mix of 2 components: Eustachian tube dysfunction and middle ear inflammation. With CIRT, irradiation is possible with a reduced dose to the temporal bone, even in the treatment of tumors of the nasal sinuses and pharynx. Therefore, the current study focused on Eustachian tube dysfunction. In fact, the median dose of the D_{mean} of the mastoid cell was only 1.27 Gy (RBE), and the effects of inflammation of the middle ear cavity and mastoid cell were minimized.

Most OMEs develop within the 1st year after CIRT. Therefore, the obstruction or dysfunction of the Eustachian tube in the acute inflammation phase is related to the major mechanisms of OME. The mucociliary function of the Eustachian tube plays an important role in fluid clearance, which is produced and pools in the middle ear cavity. Ohashi et al. reported on pathologic mucociliary changes after photon irradiation. In studies with
guinea pigs that had their Eustachian tube and middle ear cavity irradiated with 30 Gy, ciliary activities were found to be statistically lower than those of the control group from day 0. Several pathologic changes, such as swelling of the cilia, compound cilia, cytoplasmic protuberance, and expansion of the intercellular space, were also observed.

Takahashi et al. also reported on similar pathologic changes in a specimen from a human patient who received photon RT for oropharyngeal carcinoma. The dysfunction of ciliary activities after photon irradiation was found at a relatively low dose of ≤4 Gy. Consequently, disorder of gas change by obstruction or mucositis around the Eustachian tube causes negative pressure, and increases effusion in the middle ear cavity and mastoid cell. In the late phase, histologic changes due to the production of collagenous fibrous tissue, loss of capillaries, and stenosis of the Eustachian tube by irradiation were reported and caused gas change impairment. The involvement of trismus in the Eustachian tube due to myogenic impairments of the tensor veli palatini muscle has also been reported.

The dose dependence of OME was recognized, but gradual (Fig. 3), which may be due to the fact that there is more than one cause for OME, as described. Moreover, dose dependence of OME may also be affected by swelling of the soft tissue around the Eustachian tube and the effects of surrounding infections. Notably, there is a risk of OME even at low doses clinically.

Treatment of radiation-induced OME remains controversial. Patients with OME experience hearing loss, aural fullness, tinnitus, and dizziness. Ventilation tube insertion is performed as a treatment for radiation-induced OME, but may lead to persistent otorrhea and permanent ear drum perforation. According to a review by Schwarz et al., the initial management for OME is observation, and ventilation tube insertion should be considered for patients with persistent symptoms. In our study, 20% and 9% of patients with grade 2 and 3 OME, respectively, recovered spontaneously. Corticosteroids to reduce inflammation caused by RT and the valsalva maneuver to keep Eustachian tubes open might both be effective to prevent the development of OME. There is no clear consensus on therapeutic efficacy for radiation-induced OME treated with corticosteroids and the valsalva maneuver.

This study has some limitations. First, this study was conducted using single-institutional retrospective data. Second, our study evaluated only MRI or CT findings without considering clinical symptoms and functional examinations, such as pure audiometry, tympanometry, and sonotubometry. Adding clinical symptoms to the assessment may lead to different results. Third, due to the hypofractionated regimen of CIRT, comparing our data with that of conventional fractionated photon RT may be difficult. However, the trend in the results of this study is expected to also be observed in conventionally fractionated photon RT.

Conclusions

The Dmean of the cartilage part was a risk factor to develop grade 2 to 3 OME after CIRT. Our findings may be useful to predict the risk of OME due to Eustachian tube dysfunction. Cumulative data from prospective studies are required to validate our findings.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2022.101115.

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