reduce the risk of brain necrosis.

Although the RBE of carbon ions was assumed to be 3.0 to set doses, RBE depends on the fraction size, organ, and endpoint. Therefore, the limiting dose of critical organs should be carefully determined, particularly those of the central nervous system. We reported that brain necrosis developed from within the 40 GyE isodose line after C-ion RT for skull base tumors[16]. If the predetermined RBE value was 3.0 and the linear-quadratic model can be applied to C-ion RT, 40 GyE in 16 fractions could be regarded as equal to 44 GyE at a standard fractionation of 2 GyE per fraction with a 3 Gy α/β value. On the other hand, Ruben et al. reported that brain necrosis was unlikely at doses below 50 Gy in 25 fractions after radiotherapy. The RBE for central nervous system tissues could be higher than 3.0.

In this study, radiation-induced facial nerve palsy was not observed in patients with SCC of the EAC and ME who were treated with C-ion RT. Facial nerve palsy is inevitable in patients with advanced tumors who receive surgery. From an aesthetic viewpoint, C-ion RT is superior to surgery.

Several risk factors for the survival of the patients treated with surgery with or without radiotherapy have been reported in the literature. Most reported risk factors are related to tumor extension. Bacciu et al.[18] identified dural involvement an independent risk factor for both disease-specific and relapse-free survival in a series of 45 consecutive

patients with temporal bone SCC. Xie et al.[8] found that parotid invasion, temporomandibular joint (TMJ) involvement, facial nerve palsy, and previous ME surgery for chronic otitis media were associated with poor outcome in 39 patient cases of temporal bone SCC. However, in our study, tumor characteristics such as dural involvement, parotid invasion, TMJ involvement, and T classification were not significant risk factors for LC or OS after C-ion RT. Although young age and male gender were significant risk factors for OS of patients treated with C-ion RT in our study, no reports have identified age or gender as risk factors after surgery or radiotherapy. The repartition of patients with SCC of the EAC and ME according to gender has generally been reported to be 1:1[9, 18]. In this study, the proportion of female patients in the study cohort was 85%. This may have affected the analysis of risk factors for OS.

Of the 6 patients who recurred, 4 patients had local recurrences, all of which developed within the high dose area. The 3-year LC rate of 56.4% was not satisfactory compared with that of non-SCC of the head and neck region after C-ion RT[12]. Although the number of patients was small, univariate analysis revealed that treatment and tumor characteristics were not risk factors for LC. To improve LC, an additional treatment may be needed.

Chemoradiotherapy (CRT) has been shown to improve the outcome of patients with head and neck SCCs such as laryngeal, pharyngeal, and oral SCCs[19, 20]. However, the role of CRT for SCC of the

EAC and ME is still controversial. In a recent meta-analysis, Takenaka et al.[21] reported that definitive CRT may be equivalent to surgical resection in patients with SCC of the EAC and ME. Shiga et al.[22] found that CRT using a TPF (docetaxel, cisplatin, and 5-fluorouracil) regimen was safe and provided a 5-year disease-specific survival rate of 67% for EAC and ME SCC patients with T4 tumors. Therefore, the usefulness of CRT should be examined prospectively. In our study cohort, all patients were treated with C-ion RT alone because the effectiveness and safety of concurrent chemotherapy with C-ion RT has not been established for head and neck SCCs. However, combined C-ion RT and chemotherapy may be considered for improving treatment efficacy in SCC of the EAC and ME and should be evaluated in future clinical trials.

Our study had several limitations. First, the median follow-up period was short. All patients had advanced disease, and most recurrences developed within 1 year after C-ion RT. Consequently, all death events occurred within 2 years. However, the median follow-up period for the seven surviving patients was 32 months, and three of these patients are surviving more than 4 years. Second, this study was a small retrospective case series study. Therefore, further prospective studies with large patient numbers are needed to confirm our findings.

In conclusion, C-ion RT is feasible and effective for patients with locally advanced SCC of the EAC and ME. In particular, this treatment may be a good indication for patients with unresectable tumors or who

refuse surgery.

Conflict of interest statement

None declared.

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Figure Legends

Fig. 1 Local control rate in the patient cohort (n=13).

Fig. 2 A 71-year-old woman presented with squamous cell carcinoma of the right external auditory canal. (a) Magnetic resonance image (MRI) revealed a tumor with intracranial invasion and clivus involvement (T4N0M0). (b) Dose distribution of carbon ion radiotherapy (C-ion RT). C-ion RT was administered at 57.6 GyE/16 fractions. Isodose lines correspond to 96%, 90%, 60%, 50%, 30%, and 10% dose areas. The planning target volume 2 is demarcated by yellow lines. (c) MRI 6 years after C-ion RT. The tumor was controlled. The patient developed localized brain necrosis with mild headache as the only clinical symptom.

Fig. 3 Overall survival and disease-free survival rates in the patient cohort (n=13).

Table 1. Patient and treatment characteristics

Patient characteristics	
Gender	
Male/Female	2/11
Age (y)	
Median/Range	53/45-71
Primary site	
external auditory canal	11
middle ear	2
Tumor grade	
well-differentiated	9
moderately-	2
poorly-	1
unknown	1
T-classification	
T3/T4	4/9
N-classification	
N0/N1/N2b	10/2/1
Facial nerve palsy	
Yes/No	5/8
Dural involvement	
Yes/No	8/5
Parotid invasion	
Yes/No	8/5
TMJ involvement	
Yes/No	6/7
Treatment characteristics	
Gross tumor volume (ml)	
Median/Range	41/6-84
Planning target volume (ml)	
Median/Range	159/70-310
Prescribed dose	
57.6 GyE/16 fractions	8
64.0 GyE/16 fractions	5

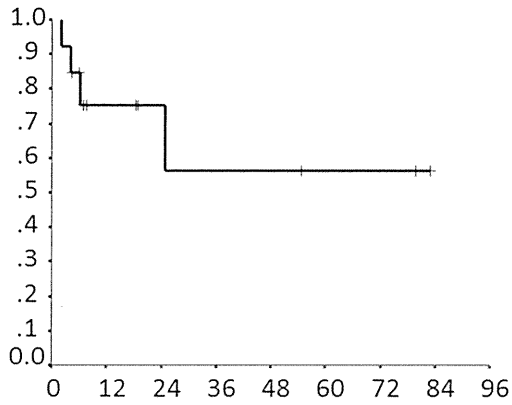
Abbreviation: TMJ,temporomandibular joint

Table 2. Univariate analysis for the local control and overall survival rates

Clinical factor	No. of patients	LC p-value	OS p-value
Age			
≥53y.o.	7		
<53y.o.	6	0.0343*	0.0011*
Gender			
Male	2		
Female	11	0.0933	0.0016*
Primary site			
external auditory canal	11		
middle ear	2	0.3692	0.4166
Tumor grade			
well	9		
moderately or poorly	3	0.3385	0.5697
unknown	1		
T-category			
T3	3		
T4	10	0.3378	0.9049
Lymph node status			
positive	3		
negative	10	0.1753	0.1298
Facial nerve palsy			
Yes	5		
No	8	0.0967	0.9889
Dural involvement			
Yes	8		
No	5	0.1757	0.8032
Parotid invasion			
Yes	8		
No	5	0.6834	0.4166
TMJ involvement			
Yes	6		
No	7	0.3352	0.9879
Dose			

57.6 GyE	8		
64.0 GyE	5	0.6041	0.7566
Goss tumor volume			
≥41ml	6		
<41ml	7	0.2363	0.2632
Planning target volume			
≥159ml	6		
<159ml	7	0.9863	0.4948

Abbreviation: TMJ,temporomandibular joint; *, significant value.



Local control rate in the patient cohort (n=13).
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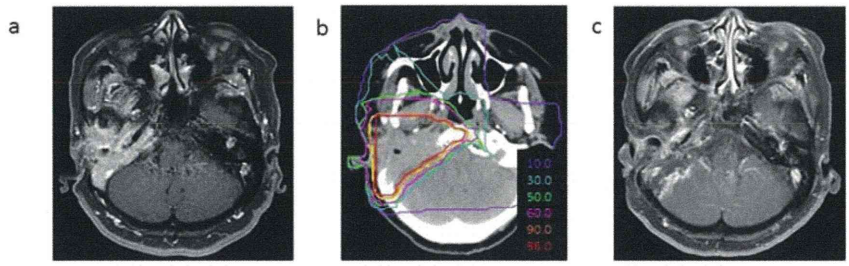

A 71-year-old woman presented with squamous cell carcinoma of the right external auditory canal. (a) Magnetic resonance image (MRI) revealed a tumor with intracranial invasion and clivus involvement (T4N0M0). (b) Dose distribution of carbon ion radiotherapy (C-ion RT). C-ion RT was administered at 57.6 GyE/16 fractions. Isodose lines correspond to 96%, 90%, 60%, 50%, 30%, and 10% dose areas. The planning target volume 2 is demarcated by yellow lines. (c) MRI 6 years after C-ion RT. The tumor was controlled. The patient developed localized brain necrosis with mild headache as the only clinical symptom.
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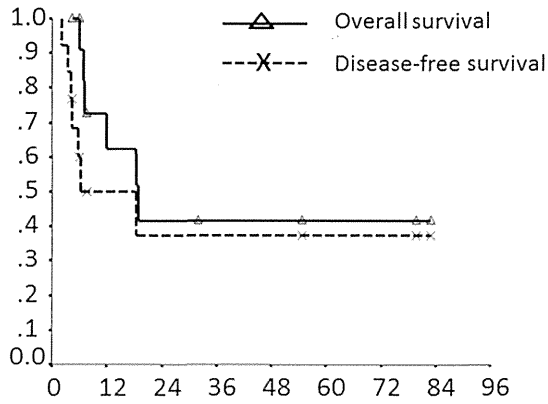

Overall survival and disease-free survival rates in the patient cohort (n=13).
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Particle beam therapy

Feasibility of carbon ion radiotherapy for locally advanced sinonasal adenocarcinoma

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ABSTRACT

Background and purpose: To evaluate the safety and efficacy of carbon ion radiotherapy (CIRT) for locally advanced sinonasal adenocarcinoma.

Material and methods: Twenty-two patients with sinonasal adenocarcinoma were treated with CIRT. CIRT was the primary treatment for 16 patients. Four patients received CIRT for local recurrence after surgery and two for residual tumour after surgery or chemotherapy. At the start of CIRT, 1 patient had T-classification (T) 2 disease, 2 had T3 disease, 5 had T4a disease, and 14 had T4b disease. Fourteen patients were treated with 57.6 Gy equivalent (GyE)/16 fractions, and 8, with 64.0 GyE/16 fractions.

Results: The median follow-up period was 43 months for all patients. The 3-year local control and loco-regional control rates for all patients were 76.9% (95% confidence interval [CI] = 56.7–97.1%) and 61.3% (95% CI = 38.5–84.1%), respectively. The 3-year overall survival and disease-specific survival rates were 59.1% (95% CI = 38.6–79.6%) and 65.6% (95% CI = 44.9–86.3%), respectively. Acute reactions of grade 3 of the skin and mucosa were observed in 2 and 4 patients, respectively. Late reactions included lateral visual loss (5 patients), mucosal ulceration (1 patient), and brain necrosis with clinical symptoms (1 patient). In the 5 patients who developed visual loss, the optic nerve was close to the tumour.

Conclusions: CIRT was effective and generally safe for locally advanced sinonasal adenocarcinoma.

Malignant tumours of the sinonasal tract are relatively rare, accounting for 3% of all head and neck malignancies. Adenocarcinomas account for 10–20% of all primary malignant tumours of the nasal cavity and paranasal sinuses [1].

Although surgery is the most important treatment for sinonasal adenocarcinoma, postoperative radiotherapy remains the treatment of choice for locally advanced sinonasal adenocarcinoma [2–4]. In a large study on sinonasal adenocarcinoma, Choussy et al. showed a significant survival advantage with surgery alone or in combination with radiotherapy, when compared with radiotherapy alone [2]. In the literature, the 5-year overall survival (OS) rate of sinonasal adenocarcinoma patients treated with surgery, with/without radiotherapy, ranged from 43% to 79% [2,3,5–8]. However, there are few reports on the clinical outcomes of radiotherapy alone for sinonasal adenocarcinoma. Waldron et al. reported on the outcome of 29 patients with ethmoid sinus carcinoma, including 9 with adenocarcinomas treated with radiotherapy alone. Of these 9 patients, 3 had T-classification (T) 1 disease, 5 had T2 disease, and 1 had T4 disease. Three patients developed local recurrence and 6 patients survived with a median follow-up period of 6.1 years [9].

Carbon ion radiotherapy (CIRT) was initiated at the National Institute of Radiological Sciences in 1994. Carbon ions exhibit high linear energy transfer and display good dose-localising properties compared to other ion species and photons [10,11].

We found that CIRT showed promising results for locally advanced head and neck cancer in a phase II clinical trial [12]. In that study, the 5-year local control (LC) and OS rates for 27 patients with adenocarcinoma of the head and neck region were 73% and 56%, respectively. Accordingly, this treatment protocol was used to treat head and neck carcinomas thereafter.

Clinical data for determining the effect of radiotherapy, including CIRT, on locally advanced sinonasal adenocarcinoma is insufficient. Accordingly, the objective of this study was to evaluate the effectiveness and safety of CIRT for patients with locally advanced sinonasal adenocarcinoma.

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Materials and methods

Eligibility criteria and ethics

The treatment protocol for head and neck cancer was reviewed and approved by the National Institute of Radiological Sciences Ethics Committee on Human Clinical Research, and all patients provided written informed consent. The eligibility criteria of the patients received definitive CIRT for head and neck cancer were as follows: (1) histologically confirmed carcinoma, (2) medically inoperable tumour as deemed by the referring surgeons or declined surgery, (3) age between 15 and 79 years, (4) Karnofsky performance status score of >60, (5) N0M0 status, (6) grossly measurable tumour, (7) no prior radiotherapy to the carbon ion treated area, (8) no chemotherapy within the past 4 weeks, and (9) no serious medical or psychological conditions precluding safe administration of treatment. Of the eligible patients, only those with sinonasal adenocarcinoma were selected and analysed in this study.

Carbon ion radiotherapy

Doses of carbon ions were expressed in photon-equivalent doses (Gray equivalent [GyE]), defined as the physical doses multiplied by the RBE of the carbon ions [10]. The biological flatness of the spread-out Bragg peak (SOBP) was normalised by the survival fraction of the human salivary gland tumour cells at the distal region of the SOBP, where the RBE of carbon ions was assumed to be 3.0. CIRT was administered on a fractionation schedule comprising 64.0 GyE/16 fractions for 4 weeks. When a wide range of skin or mucosa was included in the target volume, a dose of 57.6 GyE/16 fractions for 4 weeks was used. In cases where the tumours showed subcutaneous, nasopharyngeal, or oral cavity invasion, a lower dose was often used.

The patients were positioned in customised cradles (Moldcare; Alcare, Tokyo, Japan) and immobilised using a low-temperature thermoplastic shell (Shellfitter; Kuraray, Osaka, Japan). A set of computed tomography (CT) images of 2.5-mm thickness was obtained for treatment planning with the immobilisation devices. Magnetic resonance imaging (MRI) was routinely performed for the identification of the tumour, after planning CT image fusion. Determination of the gross tumour volume (GTV) was based on contrast-enhanced MRI. The clinical target volume (CTV) had a minimum margin of 5 mm added around the GTV. In case of possible tumour invasion to adjacent sites, CTV1 included whole anatomical sites and CTV2 was limited to the GTV. The planning target volume (PTV) 1 and PTV2 had margins of 3–5 mm added around the CTV1 and CTV2, respectively. The PTV1 was irradiated initially with 36 GyE/9 or 10 fractions, and thereafter, PTV2 was irradiated to a total dose of 64.0 or 57.6 GyE/16 fractions. The target reference point dose was defined as the isocentre, and the PTV was encompassed by the minimum 90% dose line of the reference point dose.

The limiting doses for critical normal tissues were defined as a maximum point dose of 30 GyE for the spinal cord and brain stem and 40 GyE for the chiasm and optic nerve. A limiting dose was not established for the brain. The CTV and PTV margins of areas close to critical organs such as the brain, brain stem, and optic nerve were reduced as necessary. When the ipsilateral optic nerve was located near the GTV, the dose limitation for optic nerve was ignored. Multi-portal irradiation was planned fundamentally to avoid severe normal tissue reactions. Three-dimensional treatment planning was performed using original HIPLAN software. A representative dose distribution is shown in Fig. 1.

During the CIRT, patients received no concomitant therapy, and after completion, patients received no adjuvant therapy such as surgery or chemotherapy. In cases of local recurrence and/or distant metastasis, treatment methods for these tumours had no limitations.

Evaluation and follow-up examinations

All patients were re-staged according to the seventh edition TNM staging system (International Union Against Cancer; UICC, 2009). All patients underwent a CT and MRI examination before treatment to determine the TNM stage. Acute reactions in normal tissues were classified according to the Radiation Therapy and Oncology Group (RTOG) scoring system. Late reactions were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Effect version 3.0. LC was defined as no evidence of tumour re-growth in the PTV1. Regional control was defined as no evidence of recurrence in both the sinonasal region outside of the PTV1 and regional lymph nodes. The oncological status was followed using both clinical nasal endoscopic examinations and CT or MRI every 2–3 months for the first 2 years after CIRT and every 3–6 months thereafter.

Statistics

LC, loco-regional control (LRC), OS, disease-specific survival (DSS), and disease-free survival (DFS) rates were determined using the Kaplan–Meier method, and the different subgroups were compared using the log-rank test. All analyses were calculated from the first day of CIRT. Differences were considered significant if the P value was less than 0.05. Statistical analysis was performed using SPSS software version 11 (SPSS Inc., Chicago, IL).

Results

Patient and treatment characteristics

A total 22 patients with sinonasal adenocarcinoma were enrolled in the study between June 1997 and January 2010. The characteristics of the patients and treatment are summarised in Table 1. All patients had N0M0 status. Four patients were diagnosed as having intestinal type and 18 as having non-intestinal type adenocarcinoma. Of the 8 patients with intracranial invasion, 6 had brain invasion and 2 had dura invasion.

Local control and survival

The median observation period was 43 months (range, 4–126 months) for all patients and 58 months (range, 36–110 months) for the 9 surviving patients. No patients were lost to follow-up.

The 3-year and 5-year LC rates were 76.9% (95% confidence interval [CI] = 56.7–97.1%) and 68.4% (95% CI = 44.5–92.3%), respectively (Fig. 2). The 3-year and 5-year LRC rates were 61.3% (95% CI = 38.5–84.1%) and 54.5% (95% CI = 30.7–78.3%), respectively. Five patients developed local recurrence. Of the 3 patients who developed regional recurrence, 2 had marginal recurrence and 1 had both marginal and lymph node recurrence (Table 1S). Of the 5 patients with local recurrence, 1 received salvage surgery and 1 re-CIRT. These 2 patients were alive without disease. Of the 5 patients who had distant metastasis, 3 patients remained without local recurrence.

The 3-year and 5-year OS rates were both 59.1% (95% CI = 38.6–79.6%) (Fig. 2). The 3-year and 5-year DSS rates were both 65.6% (95% CI = 44.9–86.3%). The 3- and 5-year disease-free survival rates were 45.5% (95% CI, 24.6–66.3%) and 40.4% (95% CI, 20.0–61.1%), respectively. The median survival period for all patients was 68.1 months. Of the 13 patients who died, 10 died of original disease and 3 of intercurrent causes without active disease.

Table 2S shows the results of univariate analysis for LC and OS risk factors. None of the factors evaluated correlated with LC. However, intracranial invasion significantly correlated with OS ($P < 0.05$; Fig. 3). The median survival periods for patients with and without intracranial invasion were 32.5 months and 126.4 months, respectively.

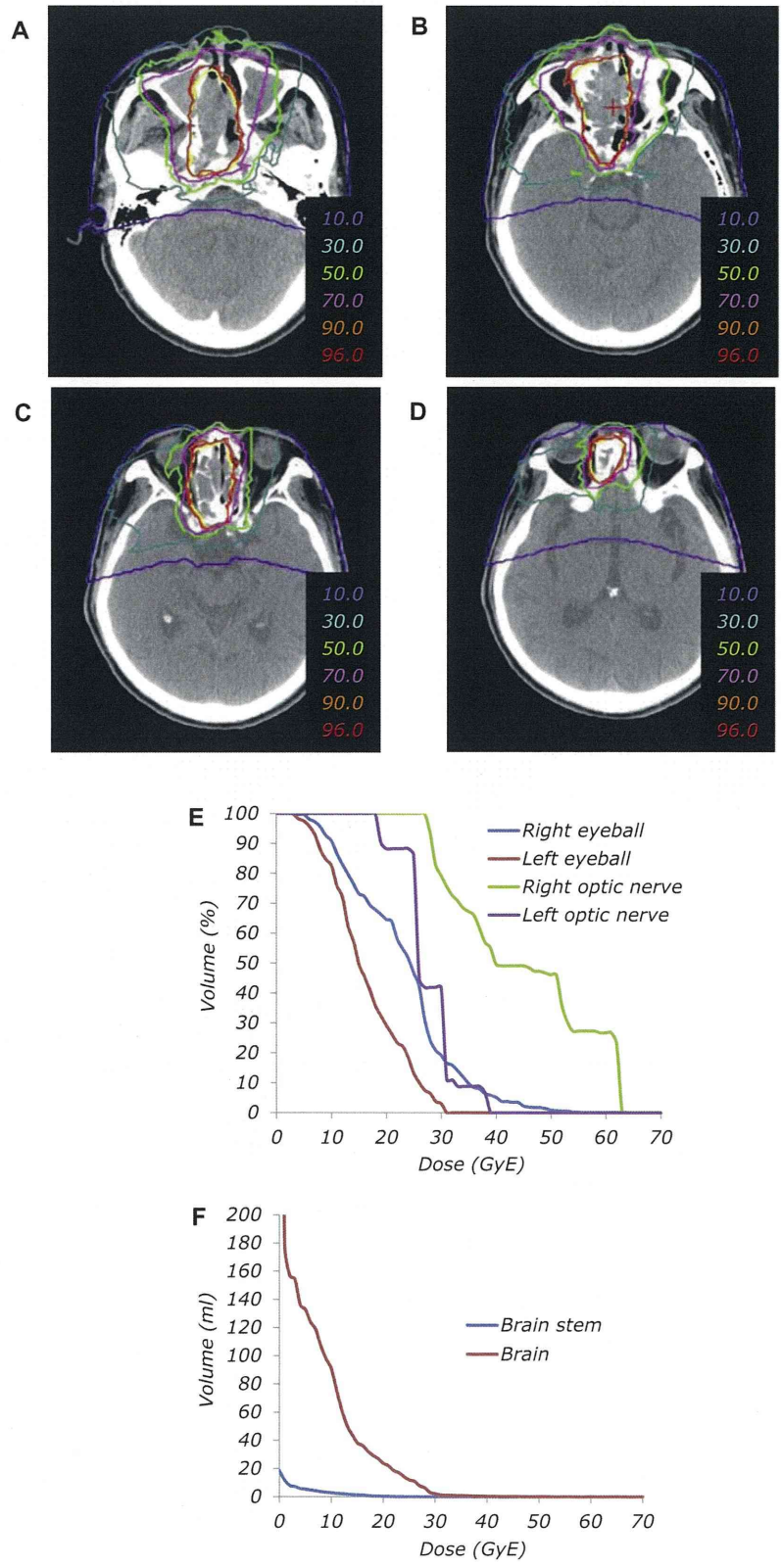

Fig. 1. Computed tomography images showing the dose distribution for a 66-year-old male patient who had ethmoid sinus adenocarcinoma with nasopharyngeal invasion (T4bN0M0). Carbon ion radiotherapy was delivered at 64.0 GyE/16 fractions from 3 directions. Isodose lines correspond to 96%, 90%, 70%, 50%, 30%, and 10% dose areas. The planning target volume 2 is demarcated by yellow lines. The local tumour was controlled for 70 months until death due to distant metastases. Right blindness occurred 2.5 years after treatment. (A) Dose distribution at the nasopharyngeal level. (B) Dose distribution at the tumour centre level. (C) Dose distribution at the optic nerve level. (D) Dose distribution at the lacrimal gland level. (E) Dose–volume histograms of the right eyeball, left eyeball, right optic nerve, and left optic nerve. (F) Dose–volume histograms of the brain stem and brain including the cerebrum and cerebellum.

Table 1
Patient and treatment characteristics.

Patient characteristics	
Gender	
Male/female	11/11
Age (y)	
Median/range	61/26–73
Karnofsky performance status	
Median/range	90/70–90
Tumour characteristics	
Primary site	
Ethmoid sinus	11
Nasal cavity	6
Maxillary sinus	5
Histology subtype	
Intestinal/non-intestinal	4/18
T classification	
T2/T3/T4a/T4b	1/2/5/14
Intracranial invasion	
Yes/No	8/14
Cribriform plate invasion	
Yes/No	11/11
Previous treatment	
None	16
Recurrence after surgery	4
Partial resection	1
Chemotherapy	1
Treatment characteristics	
Gross tumour volume (ml)	
Median/range	63.3/10.6–143.6
Planning target volume (ml)	
Median/range	217.9/66.4–483.6
Prescribed dose (16 fractions)	
57.6 GyE/64.0 GyE	14/8
Number of portals	
2 portals/3 portals	3/19
Treatment period (days)	
Median/range	28/23–29

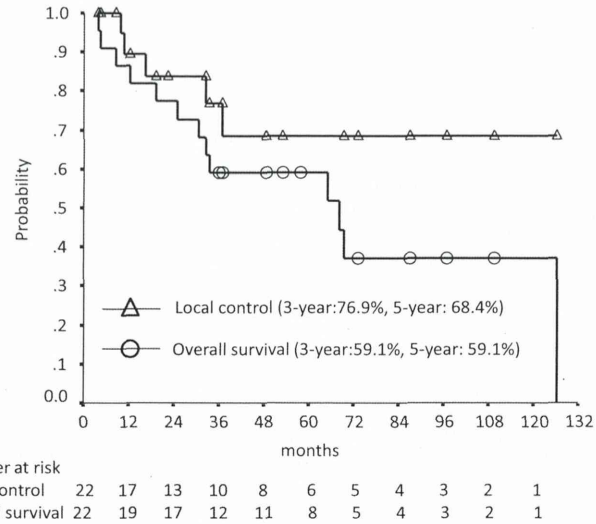

Fig. 2. Local control and overall survival rates for all patients enrolled in the present study ($n = 22$).

Reactions of normal tissues

Regarding acute reactions, grade 3 mucosal reactions were observed in 4 patients, and grade 3 skin reactions, in 2. Grade 4 mucosal and skin reactions were not observed in any patients. Grade 2 or higher eye toxicities were not observed, although some patients developed grade 1 conjunctivitis and/or tearing.

Late reactions included lateral visual loss (grade 4) in 5 patients in whom the optic nerve was close to the tumour. Of these patients,

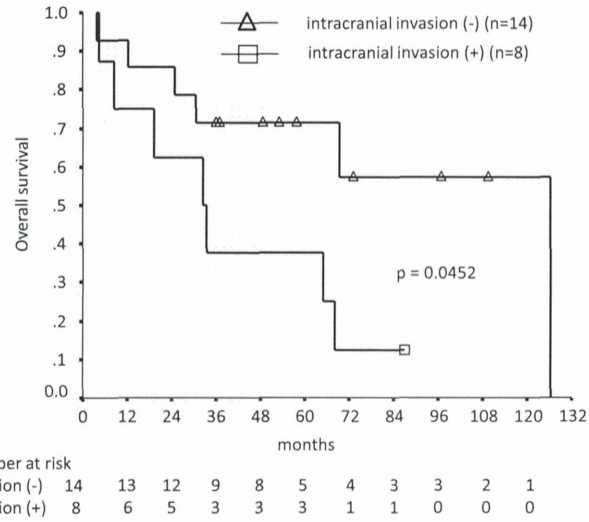

Fig. 3. Overall survival rate according to the intracranial invasion. Five-year overall survival rates with and without intracranial invasion were 37.5% and 71.4%, respectively.

1 had both ipsilateral blindness and contralateral visual impairment caused by tumour invasion into the bilateral optic nerves before CIRT. This patient then developed contralateral blindness after CIRT. Treatment-related blindness in these 5 patients was caused by radiation-induced optic neuropathy and 4 of these were treated with a dose of 57.6 GyE. The median percentages of the volume of the optic nerves receiving more than 40 GyE (V40 [%]) in patients with and without blindness were 73.6% and 9.0%, respectively. Severe toxicities of the eyeballs were not observed. Five patients developed brain necrosis, as seen on MRI, 1 of whom developed convulsions that needed to be controlled by medical treatment (grade 2). The remaining 4 patients did not develop any clinical symptoms (grade 1). The median volumes of the brain receiving more than 50 GyE (V50) in patients with and without necrosis were 7.4 ml and 0.8 ml, respectively. Of the 9 surviving patients, 2 developed asymptomatic brain necrosis; 1, lateral blindness; and 1, both asymptomatic brain necrosis and lateral blindness. Nasopharyngeal mucosal ulceration was observed in 1 patient (grade 2), and osteonecrosis of the mandible (grade 1), in 1.

Discussion

To date, the effectiveness of radiotherapy alone for sinonasal adenocarcinoma has not been extensively studied. Although several studies have examined the clinical results of radiotherapy for sinonasal tumours, these studies have included a number of different histologies [9,13,14]. Our study was uniform with respect to histology, tumour staging system, and treatment regimens, and the use of CIRT yielded promising results for locally advanced sinonasal adenocarcinoma.

Late toxicities of grade 2 or higher were observed in 7 patients (31.8%), including 5 patients who developed visual loss. The frequency and degree of the late reactions seemed to be of an acceptable degree, considering that 14 tumours (63.6%) were diagnosed as T4b. The patients had been made aware of possibilities before treatment because the tumours were very close to at-risk organs. In the 5 patients who developed visual loss (grade 4), the optic nerve was very close to the tumour and had been irradiated with the full dose. We previously reported that a dose of 20% of the volume of the optic nerve (D20) was a risk factor for developing blindness after CIRT and that the radiation dose associated with a 10% probability of blindness was approximately 40 GyE of D20 [15].

In this study, a maximum dose of 40 GyE was used as the limiting dose for the optic nerve. The median V40 (%) values of the optic nerve for patients with and without blindness were 73.6% and 9.0%, respectively. Madani et al. [14] reported that 6 out of 70 patients with sinonasal tumours who received postoperative intensity-modulated radiotherapy (IMRT) with 70 Gy/35 fractions developed grade 3 visual impairment; however, none developed blindness due to the IMRT. A hypofractionated regimen of 16 fractions for 4 weeks was used in our study. If the predetermined RBE values were correct and the linear-quadratic model can be applied to CIRT, 57.6 GyE in 16 fractions can be regarded as equal to 76 GyE in a standard fractionation regimen of 2 GyE per fraction with a 3 Gy α/β value. Regarding the brain, dose constraints were not set, not only in this study, but also in other IMRT studies [14,17]. We recently demonstrated that the brain V50 (GyE) was an independent risk factor for developing brain necrosis after CIRT using a 16-fraction regimen [16]. In this study, the median brain V50 (GyE) values in patients with and without brain necrosis were 7.4 ml and 0.8 ml, respectively. In the IMRT studies of sinonasal tumours with a median dose of 70 Gy, the incidence of brain necrosis was 4–5% [14,17]. In this study, brain necrosis was observed in 5 patients (23%). A high dose and hypofractionation schedule might increase the risk of brain necrosis, although 4 of the 5 patients did not show any clinical symptoms. Other major late toxicities were less common, possibly as exposure of normal tissues outside of the PTV was reduced with the superior dose distribution of CIRT compared to photons.

The gold standard treatment for sinonasal adenocarcinoma is surgery with or without radiotherapy. However, T4 tumours have a very poor prognosis [2]. Table 3S summarises research on the treatment result after surgery with or without radiotherapy for sinonasal adenocarcinoma [2,3,5–8]. The reported 5-year OS rate ranged from 43% to 79%, and the percentage of T4 tumours ranged from 27% to 65%. Nineteen tumours (86%) were classified as T4 in this study. It is notable that the 5-year OS rate was 59.1% after CIRT alone, although it would be preferable to have a longer median follow-up period.

Lund et al. described that local recurrence after primary treatment may reduce the survival rate of patients with sinonasal adenocarcinoma [4]. In this study, although 16 patients (64%) had T4b tumours, the 3-year LC and LRC rates were 76.9% and 61.3%, respectively. Of the 5 patients who developed local recurrence, 4 were treated with a dose of 57.6 GyE in 16 fractions. A high prescribed dose may achieve a better LC rate than a low dose, although the prescribed dose was not a significant predictive factor for LC in this study. The prescribed doses are based on the results of our phase I/II trial, which was conducted between 1994 and 1997 [18]. Accordingly, a dose of 57.6 GyE was recommended when a wide range of skin or mucosa was included in the target volume. Since then, advancements in treatment techniques and clinical experience have made sparing of skin or mucosa technically easier, and we are therefore using a dose of 64.0 GyE as frequently as possible.

Three patients developed marginal recurrence and the recurrence sites were not close to the edge of the irradiated fields. These recurrences might be skip lesions or metastases. The usefulness of prophylactic irradiation to the regional lymph nodes is not clear. In this study, prophylactic cervical lymph node irradiation was not performed, and regional lymph node recurrence was observed in only 1 patient who also had marginal recurrence.

Sinonasal adenocarcinomas were categorised as intestinal type or non-intestinal type. The former are generally locally aggressive tumours [19], and in our study, 4 patients had intestinal-type adenocarcinoma. However, the histological subtype was not a risk factor for LC and OS in univariate analysis. Choussy et al. reported, in a series of 418 patients with adenocarcinoma of the ethmoid sinus, that the pathological subtype was not a risk factor for survival [2]. In their study, the survival rate was significantly influenced by the size of the lesion (T4 classification and lymph node metastasis) and extension to the brain or dura.

Intracranial invasion was a significant risk factor for OS but not for LC in this study. Previously, we reported our clinical results using CIRT to treat head and neck sarcomas [20]. In the report, tumour volume was a risk factor for OS and not for LC, because patients with a large tumour volume developed distant metastasis more frequently than did those with a small tumour volume. In the current study, of the 8 patients with intracranial invasion, 3 developed distant metastases and 1, a regional recurrence. It is important to prevent regional recurrence or metastases to improve survival following advanced disease such as intracranial invasion and T4b. In future, a combination of CIRT and systemic chemotherapy or molecular targeted therapy should be considered.

Our study was limited by its retrospective nature and small sample size; however, CIRT was administered to all patients using the same protocol. Sinonasal adenocarcinoma is very rare, and therefore, it is difficult to perform a prospective clinical study.

In conclusion, CIRT is effective and safe for patients with inoperable sinonasal adenocarcinoma or those who refuse surgery. Further studies on larger numbers of patients and long-term follow-up will define the usefulness of CIRT for locally advanced sinonasal adenocarcinoma.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2014.09.009.

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Lipoprotein Subfractions Highly Associated With Renal Damage in Familial Lecithin:Cholesterol Acyltransferase Deficiency

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Objective—In familial lecithin:cholesterol acyltransferase (LCAT) deficiency (FLD), deposition of abnormal lipoproteins in the renal stroma ultimately leads to renal failure. However, fish-eye disease (FED) does not lead to renal damage although the causative mutations for both FLD and FED lie within the same *LCAT* gene. This study was performed to identify the lipoproteins important for the development of renal failure in genetically diagnosed FLD in comparison with FED, using high-performance liquid chromatography with a gel filtration column.

Approach and Results—Lipoprotein profiles of 9 patients with LCAT deficiency were examined. Four lipoprotein fractions specific to both FLD and FED were identified: (1) large lipoproteins (>80 nm), (2) lipoproteins corresponding to large low-density lipoprotein (LDL), (3) lipoproteins corresponding to small LDL to large high-density lipoprotein, and (4) to small high-density lipoprotein. Contents of cholesteryl ester and triglyceride of the large LDL in FLD (below detection limit and 45.8±3.8%) and FED (20.7±6.4% and 28.0±6.5%) were significantly different, respectively. On in vitro incubation with recombinant LCAT, content of cholesteryl ester in the large LDL in FLD, but not in FED, was significantly increased (to 4.2±1.4%), whereas dysfunctional high-density lipoprotein was diminished in both FLD and FED.

Conclusions—Our novel analytic approach using high-performance liquid chromatography with a gel filtration column identified large LDL and high-density lipoprotein with a composition specific to FLD, but not to FED. The abnormal lipoproteins were sensitive to treatment with recombinant LCAT and thus may play a causal role in the renal pathology of FLD. (***Arterioscler Thromb Vasc Biol.* 2014;34:1756-1762.)**

Key Words: chromatography, gel ■ LDL ■ lecithin acyltransferase deficiency ■ renal insufficiency

Lecithin:cholesterol acyltransferase (LCAT)–deficiency syndromes are rare autosomal recessive diseases, characterized by hypo-α-lipoproteinemia and corneal opacity.[1,2] They are caused by mutations in the *LCAT* gene, of which 88 have been reported to date.[3] Severe mutations lead to familial LCAT deficiency (FLD), mild mutations lead to fish-eye disease (FED). In FLD, the mutant LCAT enzyme is either absent in plasma (not secreted from the hepatocyte or rapidly degraded on secretion) or exhibits no catalytic activity on any lipoprotein; in FED, LCAT cannot esterify cholesterol on high-density lipoprotein (HDL; loss of α-activity) but retains its activity on lipoproteins containing apolipoprotein B (β-activity).[1,2] Likely, the molecular difference is causal to the major clinical difference between FLD and FED: patients with FLD develop renal failure, whereas patients with FED do not.[2,4]

To prevent renal failure in patients with FLD, replacement therapy with recombinant enzyme is currently being developed.[5–8] Alternatively, we are developing a long-lasting gene therapy by transplantation of human *LCAT* gene-transduced autologous adipocytes.[7,9] Recombinant LCAT (rLCAT) secreted by the *LCAT* gene-transduced adipocytes corrected abnormal HDL subpopulations in sera of FED patients in vitro.[10]

LCAT catalyzes the esterification of cholesterol with acyl groups hydrolyzed from phospholipids, predominantly on HDL particles. This leads to mature lipoproteins with cores filled with cholesterol ester. LCAT dysfunction leads to decreased maturation of the HDL particle and to increased levels of both its substrates: unesterified cholesterol and phosphatidylcholine. In the absence of LCAT activity, abnormal lipid particles have been observed throughout lipoprotein fractions.[11–14] The HDL fraction contains disk-shaped particles in rouleaux and small spherical particles. Density-gradient ultracentrifugation followed by electron microscopy

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