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Risk Assessment of Cataract Development in Radiotherapy for Patients with Brain Tumors and Head and Neck Cancer

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The lens is one of the organs at risk (OAR) in radiotherapy for brain tumors and the head and neck cancer. The tolerable dose is low compared to other OARs, and in cases where the tumor is near the lens, the tolerable dose will be exceeded. In this study, we retrospectively investigated the development of cataract after radiotherapy in patients with brain tumors and head and neck cancer. Among 76 patients with brain tumor, maxillary sinus cancer, orbital sarcoma, oral cavity cancer, buccal mucosal cancer, and nasopharyngeal cancer, we reviewed follow-up records of 43 patients (86 lenses). These patients were treated in Hirosaki University Hospital. The lens dose was estimated by dose volume histogram calculated using radiotherapy planning system. Among the 43 patients (86 lenses) investigated, 5 patients (6 lenses) developed cataracts (6.98%). Of which, four lenses were from patients with maxillary sinus cancer, one with orbital sarcoma, and one with nasopharyngeal cancer. The univariate analysis using Cox proportional hazards regression was performed to examine the clinical features of cataract development. Sex, age, smoking, drinking alcohol, and hypertension, which were reported to be associated with the onset of the cataract, were not significantly correlated in this study. Only lens dose classified according to tolerable dosage of 1,000 cGy was significantly associated ($P = 0.048$), with a hazard ratio of 8.830 (95% CI: 1.020–76.440). The cumulative incidence function indicated that the incidence was significantly higher in the sub-group that exceeded the tolerable dose ($P = 0.020$). In addition, there was a negative correlation between lens dose and latent period ($r = -0.521$). The median lens dose was the highest for orbital sarcoma (1973.2 cGy), followed by maxillary sinus cancer (1425.1 cGy). Additionally, the median lens dose in brain tumors exceeded the tolerable dose (1243.4 cGy). In comparison with the 3 dimensional-conformal radiotherapy, the lens dose was lower and no patients developed cataract in the intensity modulated radiotherapy (IMRT) method. Radiotherapy for tumors located in close proximity to the lens often results to a high lens dose, with many instances exceeding the tolerable dose, thereby increasing the risk of developing cataracts. Conversely, employing the IMRT technique has demonstrated the ability to reduce lens dose and risk of cataract development.

Key words: lens, cataract, brain tumor, head and neck cancer

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1. Introduction

The lenses are one of organs at risk (OAR) in external radiotherapy for brain tumor and head and neck cancer. The tolerable dose of lens ranges from 2–10 Gy[1], and is the lowest compared to peripheral OARs. Although the absorbed dose to the lens is minimized by shielding with multi-leaf collimator, radiotherapy for tumors that developed near the lens (e.g., brain tumor and head and neck cancer) tend to exceed the tolerable dose. According to the International Commission on Radiological Protection (ICRP) guidelines, the threshold dose for cataract development (i.e., 1% incidence rate) is 0.5 Gy[2]. The absorbed dose to the lens is considerably higher than this threshold dose in radiotherapy, and developing cataract is one of the most frequent complications. In radiotherapy for orbital pseudotumor at 20 Gy (range, 4.8–40 Gy), the incidence rate of was 10%[3], 19.5% for primary ocular adnexal mucosa-associated lymphoid tissue lymphoma at median dose 37.8 Gy (range, 30.6–45 Gy)[4], and 66.3% for proton beam therapy for uveal melanoma at the lens dosage of 15–20 Cobalt Gray Equivalent[5]. While there are several reports on the development of cataract after radiotherapy, there are few reports outside of ophthalmology. Therefore, additional experience regarding the development of lens cataract and absorbed doses in radiotherapy needs to be reported. In this study, we retrospectively evaluated the incidence of cataract in patients with brain tumor and head and neck cancer following radiotherapy, and the dose volume histogram (DVH) was used for dose assessment of the contoured lenses.

Table 1. Characteristics of the patients. Patient characteristics were reviewed based on medical records.

Characteristic		Number of patients (n = 43)
Sex		
	Male	27
	Female	16
Site		
	brain tumor	10
	maxillary sinus cancer	14
	orbital sarcoma	2
	oral cavity cancer	2
	buccal mucosa cancer	6
	nasopharyngeal cancer	9
Irradiation technique		
	3D-CRT	31
	IMRT	11
	VMAT	1
Prescribed dose for target (cGy)/fraction		
	3,000/15	1
	5,000/25	1
	5,040/28	1
	6,000/30	9
	6,600/33	23
	7,000/35	8
Smoking		
	Yes	24
	No	19
Drinking		
	Yes	27
	No	16
Hypertension		
	Yes	31
	No	12

2. Methods

2.1. Patients and retrospective analysis

A total of 76 patients (152 lenses) with brain tumor, maxillary sinus cancer, orbital sarcoma, oral cavity cancer, buccal mucosa cancer, or nasopharyngeal cancer received external radiotherapy between 2011 and 2021 at Hirosaki University Hospital. Among the 76 patients, 24 patients (42 lenses) were unknown the absorbed dose of lens as the lens were not contoured in radiotherapy planning system (RTPS). The treatment planning system employed varied depending on the irradiation technique; for three-dimensional conformal radiotherapy (3D-CRT), we used Monaco by Elekta, and for intensity modulated radiotherapy (IMRT) and volumetric modulated ark therapy (VMAT), we used Eclipse by Varian. Among the 76 patients, 9 patients (18 lenses) have no follow-up records. Overall, the demographic and basic information (e.g., age, history of smoking, drinking alcohol, hypertension) of 43 patients (86 lenses) were collected by retrospective review of medical records, and the patients were evaluated for cataract development, latent period of cataract development, irradiation technique, and treatment regimens. Noted that if a history of cataract was found in the medical records, the patient was judged as cataract development. In addition, latent period was defined the time span between completion of radiotherapy and cataract development. The lens dose was estimated using DVH, with the lens dose represented by the mean dose. This study was approved by the institutional review board of Hirosaki University Graduate School of Medicine Ethics Committee (approved number: 2023-001).

2.2. Statistical analysis

Univariate analysis was performed using Cox proportional hazards regression to examine the association between clinical features and cataract development. The age of the patients and absorbed dose were classified into sub-groups using the median value (i.e., 66 years old) and tolerable dose of lens (i.e., 1,000 cGy), respectively. The cumulative incidence function (CIF) curves were calculated and the

Table 2. Characteristics of the patients who developed cataract. Five patients (six lenses) developed cataract. Note: Case no. 3 and 4 were the same patient.

Characteristic	Case no.					
	1	2	3	4	5	6
Sex	Male	Male	Male	Male	Female	Male
Age (y/o)	51	49	51	51	31	71
Site	maxilalry sinus	maxilalry sinus	maxilalry sinus	maxilalry sinus	orbital	nasopharyngeal
Prescribed dose (cGy)/fraction	6,600/33	6,600/33	6,600/33	6,600/33	3,000/15	6,600/33
Irradiation technique	3D-CRT	3D-CRT	3D-CRT	3D-CRT	3D-CRT	3D-CRT
Lens dose (cGy)	4,743.2	5,966.3	2,905.2	7,618.1	3,073.5	231
Latent period (months)	35	31	25	41	47	60
Smoking	No	No	Yes	Yes	No	No
Drinking	No	Yes	No	No	No	No
Hypertension	No	Yes	No	No	No	Yes

sub-groups were statistically compared using a Gray's test. Welch's t-test was used to compare two groups, and multiple comparisons were performed using Steel-Dwass test after Kruskal-Wallis test. All statistical analyses were performed using Easy R (EZR) version 1.52 (Saitama Medical Center, Jichi Medical University). A $P < 0.05$ indicate a statistically significant difference.

3. Results

3.1. Patient characteristics and radiotherapy regimens

We identified 43 patients (86 lenses) who received radiotherapy for brain tumor and head and neck cancer, and their medical records were reviewed (Table 1). The median age was 66 years (range, 17–83 years), comprising 27 males and 16 females. The patient's ages were distributed with seven under 40, five in their 50s, twelve in their 60s, eighteen in their 70s, and one in their 80s. Among them, 10 patients received radiotherapy for brain tumor, 14 for maxillary sinus cancer, two for orbital sarcoma, two for oral cavity cancer, six for buccal mucosa cancer, and nine for nasopharyngeal cancer. The radiotherapy regimens for a patient with orbital sarcoma, maxillary sinus cancer, and brain tumor was prescribed with a dosage of 3,000 cGy/15, 5,000 cGy/25, and 5,040 cGy/28 fractions, respectively. The other nine patients with brain tumor were prescribed with 6,000 cGy/30 fraction. Twenty-three patients including nine with maxillary sinus cancer (one received IMRT), two with oral cavity cancer, six with buccal mucosa cancer (one received IMRT), and six with nasopharyngeal cancer (two received IMRT) received 6,600 cGy/33 fraction. The remaining eight patients, including four with maxillary sinus cancer, one with orbital sarcoma, and three with nasopharyngeal cancer received 7,000 cGy/35 fraction. These eight patients were prescribed using the IMRT technique, with one of them receiving VMAT.

3.2 Cataract development after radiotherapy correlated with lens dose

Among the 43 patients (86 lenses) included in the analysis, five (six lenses) developed cataract (6.98%). This comprises three patients (four lenses) with maxillary sinus cancer, one patient with ocular sarcoma, and one patient with nasopharyngeal cancer. All patients who developed cataract received 3D-CRT. The characteristics of these patients were summarized in Table 2. The median latent period was 38 months (range, 25–60 months), median age of 51 years (range 31 to 71 years), and median lens dose of 3908.4 cGy (range, 231.0–7,618.1 cGy). Only for patient (one lens) with nasopharyngeal cancer has a lens dose below the tolerable dose (i.e., 231.0 cGy). Meanwhile, the lens dose in four patients (five lenses) with maxillary sinus cancer and orbital sarcoma was approximately equivalent to the prescribed dose to the target.

To investigate the association between the patient characteristics and development of cataracts, univariate analysis was performed using a Cox proportional hazards regression model. Only lens dose was found to be associated with the hazard ratio (HR) [8.830 (95% CI 1.020–76.44, $P = 0.048$, Table 3)]. These patients were classified based on a tolerable dosage of 1,000 cGy. In addition, the CIF indicated that cataracts are significantly induced in a sub-group, which exceeded the tolerable dose (Fig. 1, $P = 0.020$), and the latent period was negatively correlated with lens dose (Fig. 2, $r = -0.512$). The lens dose for each disease site (Fig. 3) indicated that the lens dose of brain tumor (15 lenses, 75%), maxillary sinus cancer (23 lenses, 82%) and orbital sarcoma (2 lenses, 50%) exceeded the tolerable dosage. Meanwhile, for prescribe targets located in the oral cavity site, the dose was maintained below the tolerable dose. When comparing the lens dose by irradiation technique (Fig. 4), the median dose for IMRT/VMAT was 648.1 cGy

Table 3. Univariate analysis of cataract incidence. Univariate analysis was performed using cox hazard proportional regression model.

Parameters	HR (95% CI)	p-value
Sex	0.330 (0.038 to 2.835)	0.312
Age > 66 y/o	0.305 (0.036 to 2.622)	0.280
Smoking	0.455 (0.083 to 2.503)	0.365
Drinking	0.201 (0.023 to 1.727)	0.144
Hypertension	0.848 (0.153 to 4.712)	0.851
Lens dose > 10 Gy	8.830 (1.020 to 76.440)	0.048

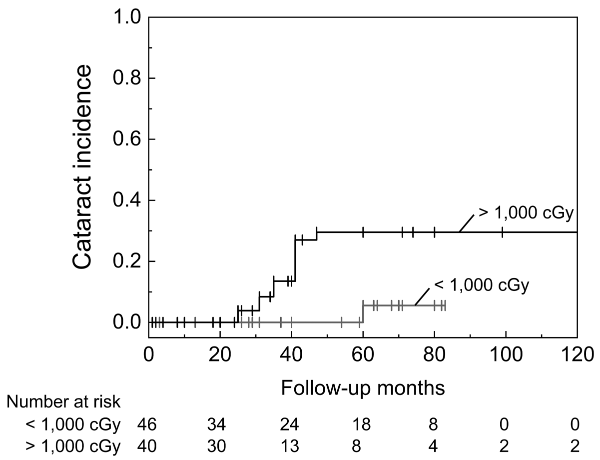

Fig. 1. CIF curves of cataract incidence. Patients were divided into sub-groups based on excess or not excess tolerable dose of 1,000 cGy. The black solid line indicates the > 1,000 cGy sub-group and the gray solid line indicates the < 1,000 cGy sub-group.

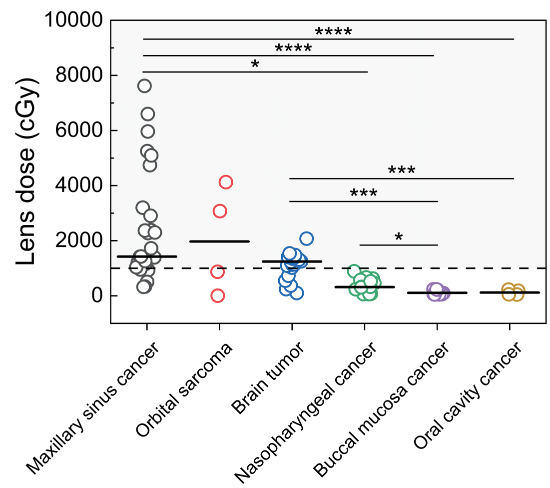

Fig. 3. Lens dose of each disease site. The dot line indicates tolerable dosage of 1,000 cGy and horizontal lines indicate the median dose. The asterisks represent significant differences of *P < 0.05, ***P < 0.001, and ****P < 0.0001 between the two groups. P-value was indicated by Steel-Dwass test.

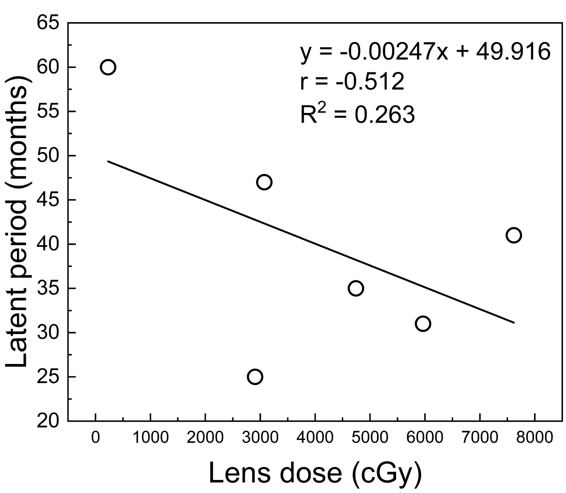

Fig. 2. The correlation between the latent period and lens dose. The equation shows approximate formula, r is Pearson's correlation coefficient, and R^2 is coefficient of determination.

(range, 157.2–4,127.5 cGy), which is lower than that for 3D-CRT (median dose 1,032.5 cGy; range, 6.6–7,618.1 cGy, Fig. 4A). Meanwhile, 32 lenses (52%) and seven lenses (29%) exceeded the tolerable dose in 3D-CRT and IMRT/VMAT, respectively. Lens doses were also compared for maxillary sinus and nasopharyngeal cancers, which were statistically comparable (Fig. 4B). While there was a significant dose reduction in maxillary sinus cancer, it was increased in nasopharyngeal cancer in IMRT technique. The maximum lens dose prescribed for nasopharyngeal cancer with IMRT was 666.5 cGy, which was not excess the tolerable dose. These results indicate that the patients with brain tumor, maxillary sinus cancer and ocular sarcoma were at increased risk of developing cataracts. The implementation of IMRT/VMAT may potentially reduce risk.

4. Discussion

We retrospectively investigated the lens cataract

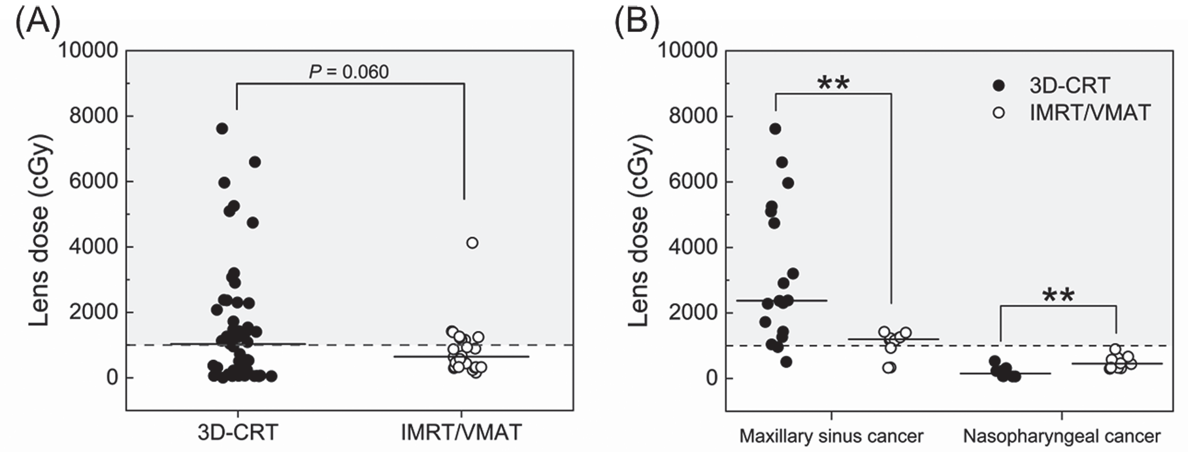

Fig. 4. Lens dose comparison by irradiation technique. Lens dose of (A) all disease sites and (B) maxillary sinus and nasopharyngeal cancer are shown. The gray dot line indicates tolerable dosage of 1,000 cGy and horizontal solid lines indicate the median dose. The asterisks represent significant differences of **P < 0.01 between two groups. P-value was indicated by Welch's t-test.

developments after radiotherapy for brain tumors and head and neck cancer. The incidence rate of cataract development was 6.98%, and is association only with lens dose. Regarding irradiation technique, all patients who developed cataract were prescribed using 3D-CRT, and had higher lens dose than IMRT/VMAT (Fig. 4). IMRT can achieve a high probability of local control without excessive risk for acute or late adverse events[6]. In head and neck cancer, IMRT technique is employed to avoid osteoradionecrosis, which is a severe side effect[7]. In addition, IMRT for ocular adnexal lymphoma can reduce long-term late grade 2 toxicities (i.e., dry eye and cataract) compared with conventional procedures[8]. In this retrospective study, cataract was not observed in patients with head and neck cancer who were prescribed using IMRT method. This suggests that IMRT/VMAT have an advantage in reducing the risk of developing cataracts.

Radiation cataract is a tissue reaction and has a threshold dose. Some epidemiological studies have shown HR or odds ratio (OR) per Gy. Little et al. reported the risk of cataract incidence in a cohort of US radiologic technologists, and exhibited an excess HR/mGy of 0.69×10^{-3} (95% CI 0.27×10^{-3} to 1.16×10^{-3})[9]. Allodji et al. investigated the risk of cataract after radiotherapy for non-retinoblastoma solid cancer in childhood, and the HR increased by 39-fold (95% CI, 12.0- to 127.9-fold) at 10 Gy exposure to the eyes compared to that in the no radiation exposure group[10]. In our results, the HR was 8.830 (95% CI 1.020–76.44), and tended to be lower than that in previous studies. This may be attributed to the short follow-up period in this study (median follow-up of 39 months; range, 1–122 months) compared with that in previous studies. The time of development of radiation-induced cataract ranges from 6 months to several years, and typically diagnosed by ophthalmologist within 2–3 years[11]. The cataract in the present study was determined based on the follow-up medical records, and thus it cannot be detected unless the patient had subjective symptoms such as obvious opacity. In addition, markedly long-term follow-up is difficult owing to the censoring depending on the prognosis due to clinical stage of disease. Therefore, the incidence rate presented in this study may be underestimated.

Moreover, we investigated the clinical features for developing cataracts after radiotherapy and only lens dose was associated with developing cataracts in this study. Zetterberg et al. indicated that women are more likely to have opaque lenses[12]. Meanwhile, Aina et al. highlighted the correlation between estrogen and the development of cataracts, and that the incidence of cataract increases after estrogen is decreased during menopause[13]. In terms of age, older people gradually develop more severe and frequent cataracts[14]. Several reports indicated that smoking increases the risk of cataracts by 2–3 times[15-17]. Additionally, drinking alcohol increases the risk of nuclear, cortical, and posterior subcapsular cataracts and pose a toxic effect on the lens[18, 19]. Regarding hypertension, early clinical studies of cataract formation in diabetes mellitus indicated a high prevalence of arterial hypertension[20]. Moreover, hypertension, which is associated with diabetes, induces cataract development[21, 22]. In this study, we performed univariate analysis including these clinical features, and found that only lens dose associated to cataract development (Table 2). This may be due to the small number of cases with a history of cataract.

This study has certain limitation, including the fact that we cannot rule out age-related cataracts. Multivariate analysis can be used to examine the relationship between age and cataract development, but this was not possible due to the small number of developments. Radiation-induced cataract can be differentiated from age-related cataract by the site of lens (i.e., posterior subcapsular opacification)[23, 24]. However, there were no records of the cataract site of lenses. The prevalence of age-related cataract among Japanese in their 50s is 37–54%, which is considerably higher than the incidence rate reported in this study (6.98%). Additionally, more than 70% of the patients surveyed were over 60 years old (31 patients). Therefore, it should be noted that there were too few age-related cataracts in the patients investigated in this study. Based on the lens dose dependence of latent period ($r = -0.512$) and incidence rate ($P < 0.05$) (Figs. 1 and 2), radiation-induced cataracts are highly possible. Meanwhile, the excess risk cannot be assessed.

5. Conclusion

In this study, we retrospectively investigated the cataract incidence after radiotherapy for brain tumors and head and neck cancer. The incidence rate was 6.98%, which is lower than that in previous studies that investigated the adverse events after radiotherapy. This could be attributed to the short follow-up period. The HR for the lens surpassing tolerable dose was 8.830, indicating an increased risk of cataracts. The tolerable dose may be exceeded for brain tumors, maxillary sinus cancer, and orbital sarcoma, particularly when the onsets are in close proximity to the lens. Treating these targets requires an acceptance of risk, while opting for IMRT/VMAT can reduce the dose of OARs and risk of developing cataract.

Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contributions

R.S., M.O., M.A. and Y.H. designed the study, R.S., H.Okabe., H.Obara, F.K. performed retrospective analysis, R.S. and H.Okabe performed statistical analysis. M.A. diagnosed patients and gathered patient data. R.S. and H.Okabe wrote the manuscript, M.O., M.A. and Y.H. supervised the study. All authors reviewed the manuscript.

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None.

Data availability

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The human data was recruited with the ethics approval (approval number: 2023-001) by Hirosaki University Graduate School of Medicine Ethics Committee. Informed consent was obtained from all subjects.

Consent to publish

All authors have consented for the publication of the manuscript.

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