Analysis of Visual Loss Due to Radiation-Induced Optic Neuropathy After Particle Therapy for Head and Neck and Skull Base Tumors Adjacent to Optic Nerves

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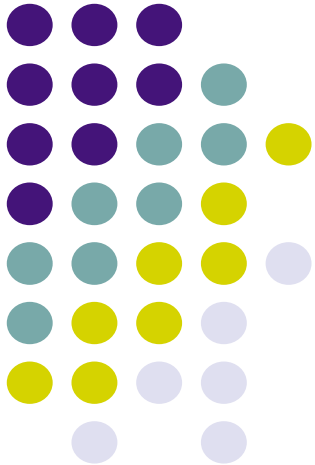
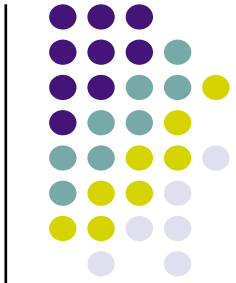


Background (1)

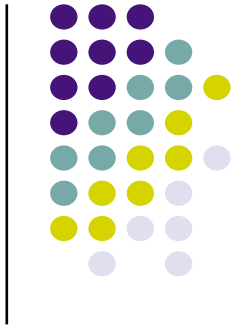


- Radiotherapy is often used for treating head and neck or skull base tumors for preservation of function or cosmetic reason.
- Particle beams, such as carbon ion and proton beams, have superb dose distribution compared to photon beam and are able to spare risk organs.
- It is, however, sometimes difficult even for particle therapy to avoid optic nerves (ONs) when tumors exist adjacent to them.

Background (2)

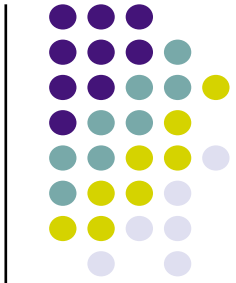
- Preservation of visual acuity is crucial for patients' QOL after treatment.
- Not many reports have been published regarding tolerance dose of ON for particle therapy.
- Hyogo Ion Beam Medical Center is the only medical institution where both carbon ion and proton therapies are available, thus clinical comparison between them is possible.

Purpose



- To assess the incident rates of VL due to radiation-induced optic neuropathy (RION) after particle therapy in terms of comparison of carbon ion and proton.
- To evaluate the factors that can affect the occurrence of VL.

Materials and Methods (1)



- From August 2001 to August 2006, 104 patients with head and neck or skull base tumors adjacent to ONs were treated with carbon ion or proton beam at Hyogo Ion Beam Medical Center.
- Carbon ion therapy 57.6 GyE/16 fr or proton therapy 65 GyE/26 fr were used to treat the patients.
- After the treatment, the patients were followed-up periodically and the diagnosis of VL (counting fingers or severer) due to RION was confirmed by ophthalmologists and radiation oncologists based on ophthalmologic exams and Gd-enhanced MRI.

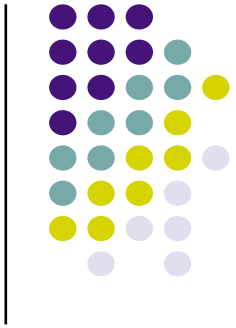
Materials and Methods (2)

- Among 104 patients, 112 ONs of 72 patients, which had >12 months follow-up periods and were irradiated with >50% of prescribed doses, were analyzed.
- The incident rate of VL was determined by the Kaplan-Meier method.
- Maximum doses (D_{max}) to ONs were obtained from dose-volume histograms (DVHs).
- The biologic effective doses at α/β = 3 GyE (BED_3) were calculated using the following formula.

$$BED_3 = (\text{total dose}) \times \{1+\text{daily dose}/3\}$$

- Logrank test and Cox proportional hazards model were used for statistical analyses. P-values of <0.05 were considered to be significant.

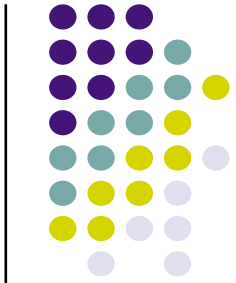
Patient Characteristics (1)



Characteristic	Total (n = 72)	Carbon (n = 13)	Proton (n = 59)
Age (year), median (range) (15-85)	61 (15-85)	57 (23-73)	62 (15-85)
Gender, *n* (%) Male	33 (46)	5 (38)	28 (47)
Female 39 (54)	8 (62)	31 (53)	
Tumor site, *n* (%)			
Nasal cavity and PNS	49 (68)	10 (77)	39 (66)
Skull base	10 (14)0 (0)	10 (17)	
Pterygopalatine fossa	5 (7)2 (15)	3 (5)	
Nasopharynx and PPS	5 (7)0 (0)	5 (8)	
Orbita	3 (4)1 (8)	2 (3)	

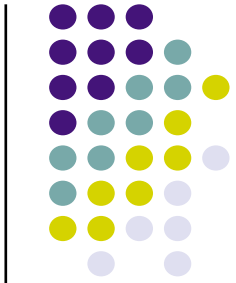
Abbreviations: PNS, Paranasal sinus; PPS, Parapharyngeal space.

Patient Characteristics (2)



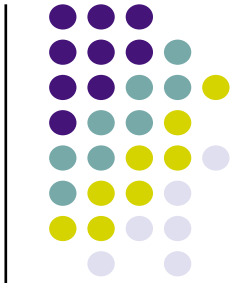
Characteristic	Total (n = 72)	Carbon (n = 13)	Proton (n = 59)
Histology, *n* (%)			
Adenoid cystic carcinoma	20 (28)	3 (23)	17 (29)
Malignant melanoma	16 (22)	5 (38)	11 (19)
Squamous cell carcinoma	7 (10)	0 (0)7 (12)	
Olfactory neuroblastoma	6 (8)	2 (15)	4 (7)
Chordoma	6 (8)0 (0)	6 (10)	
Adenocarcinoma	5 (7)1 (8)	4 (7)	
Undifferentiated carcinoma	3 (4)0 (0)	3 (5)	
Osteosarcoma/chondrosarcoma	2 (3)1 (8)	1 (2)	
Meningioma	2 (3)0 (0)	2 (3)	
Others	5 (7)1 (8)	4 (7)	

Patient Characteristics (3)



Characteristic	Total (n = 72)	Carbon (n = 13)	Proton (n = 59)
Treatment history, *n* (%)			
None	53 (74)	9 (69)	44 (75)
Chemotherapy	15 (21)	4 (31)	11 (19)
Surgery	4 (6)	0 (0)	4 (7)
Diabetes mellitus, *n* (%)			
(-)	69 (96)	12 (92)	57 (97)
(+)	3 (4)	1 (8)	2 (3)
Hypertension, *n* (%)			
(-) 61 (85)	10 (77)	51 (86)	
(+) 11 (15)	3 (23)	8 (14)	

Optic Nerve Characteristics (1)



Characteristic	Total (n = 112)	Carbon (n = 20)	Proton (n = 92)
Age (year), median (range) (15-85)	61 (15-85)	58 (23-73)	61
Gender, *n* (%) Male	52 (46)	8 (40)	44 (48)
Female 60 (54)	12 (60)48 (52)		
Treatment history, *n* (%)			
Nothing	83 (74)14 (70)	69 (75)	
Chemotherapy	23 (21)6 (30)	17 (18)	
Surgery	6 (5)0 (0)	6 (7)	

Optic Nerve Characteristics (2)

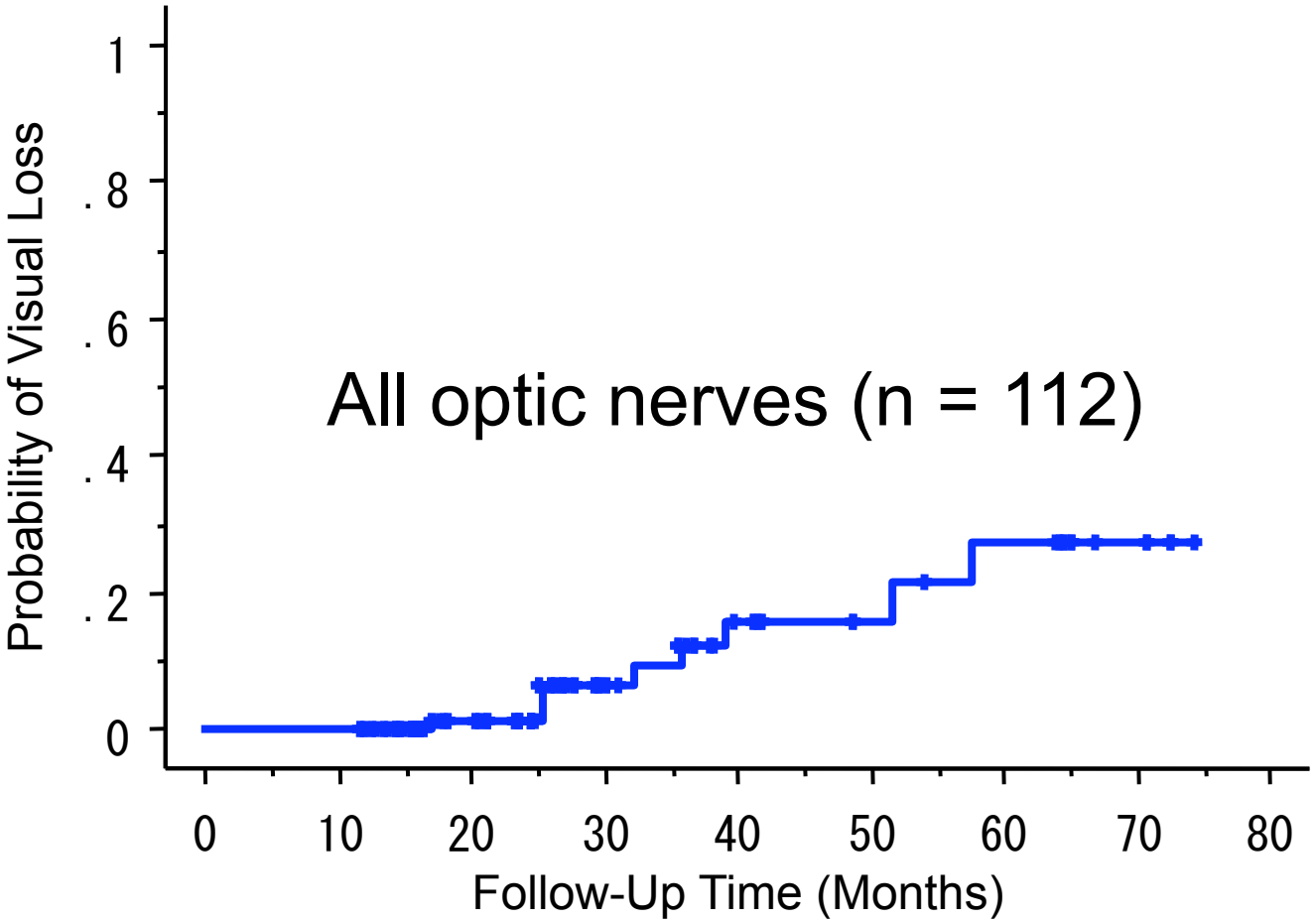
Characteristic	Total (n = 112)	Carbon (n = 20)	Proton (n = 92)
Diabetes mellitus, *n* (%)			
(-)	107 (96%)	19 (95%)	88 (96%)
(+)	5 (4%)	1 (5%)	4 (4%)
Hypertension, *n* (%)			
(-)	95 (85%)	15 (75%)	80 (87%)
(+)	17 (15%)	5 (25%)	12 (13%)
D_{max} to ON (GyE), median (range)	54.3 (31.7-59.8)	55.9 (32.6-67.6)	
D_{max} to ON (GyE_3), median (range)	97 (46-134)	116 (53-134)	96 (46-126)

Abbreviations: D_{max}, maximum dose; ON, optic nerve.

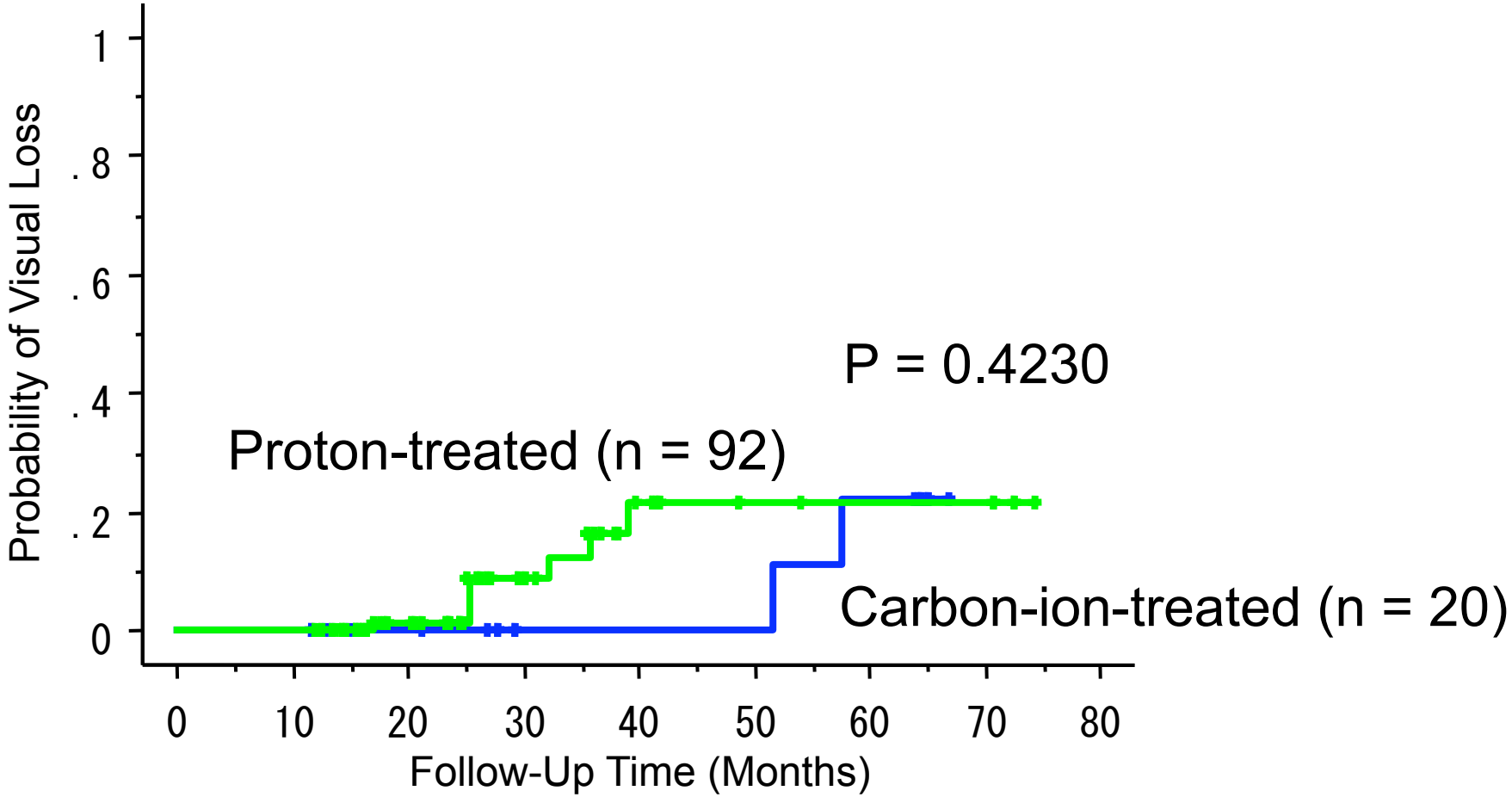
Incident Rate of Visual Loss (1)

- Median follow-up periods:
  - All patients 25 months
  - Carbon-treated 28 months
  - Proton-treated 24 months
- Incident rates of VL:
  - All ONs 8% (9/112)
  - Carbon-treated 10% (2/20)
  - Proton-treated 8% (7/92)
- Time to onset of VL: median (range)
  - All ONs 33 months (17-58 months)
  - Carbon-treated 55 months (52-58 months)
  - Proton-treated 26 months (17-39 months)

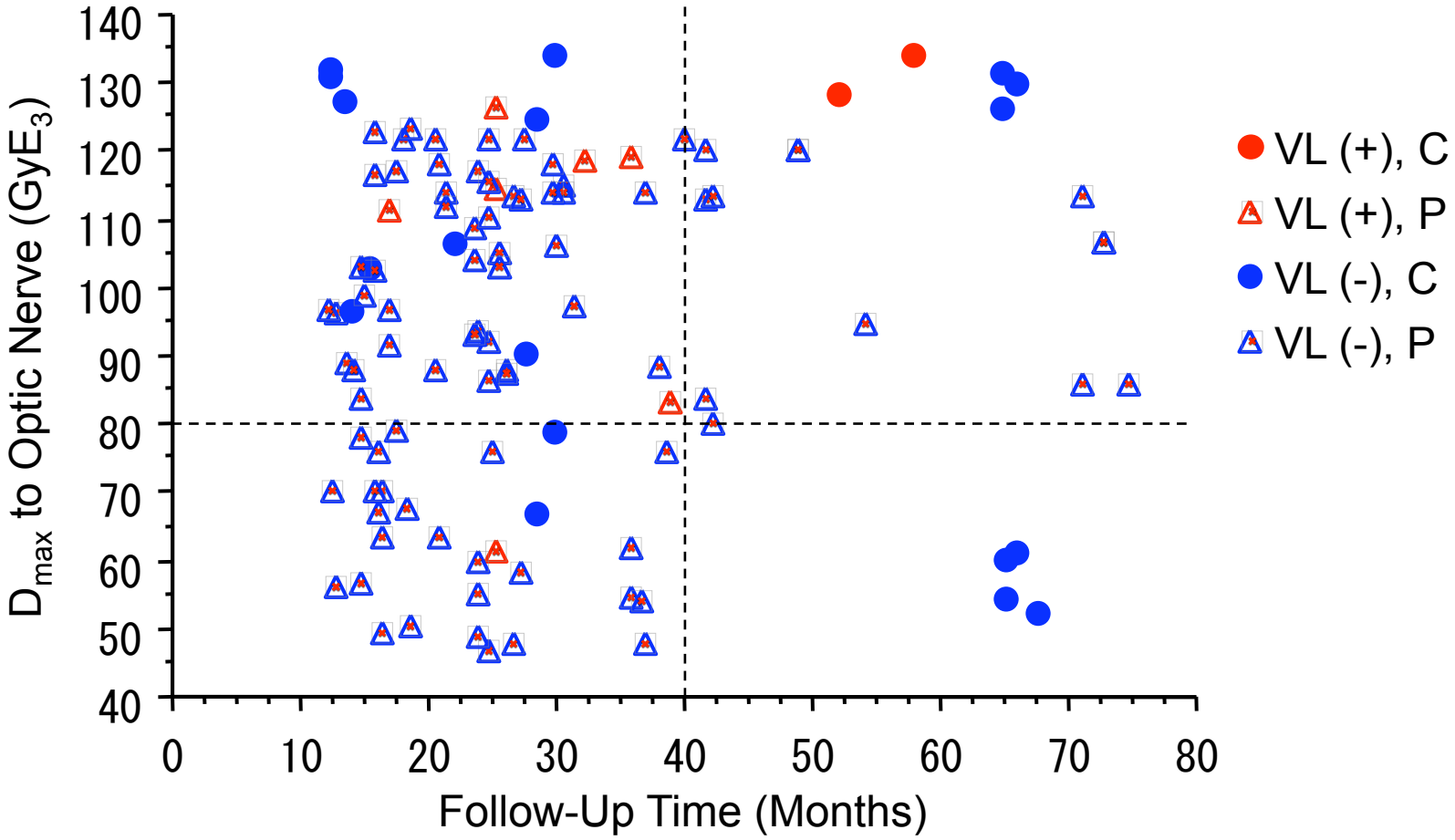
Incident Rate of Visual Loss (2)



Incident Rate of Visual Loss (3)



Scatter Plot for Incidence of Visual Loss



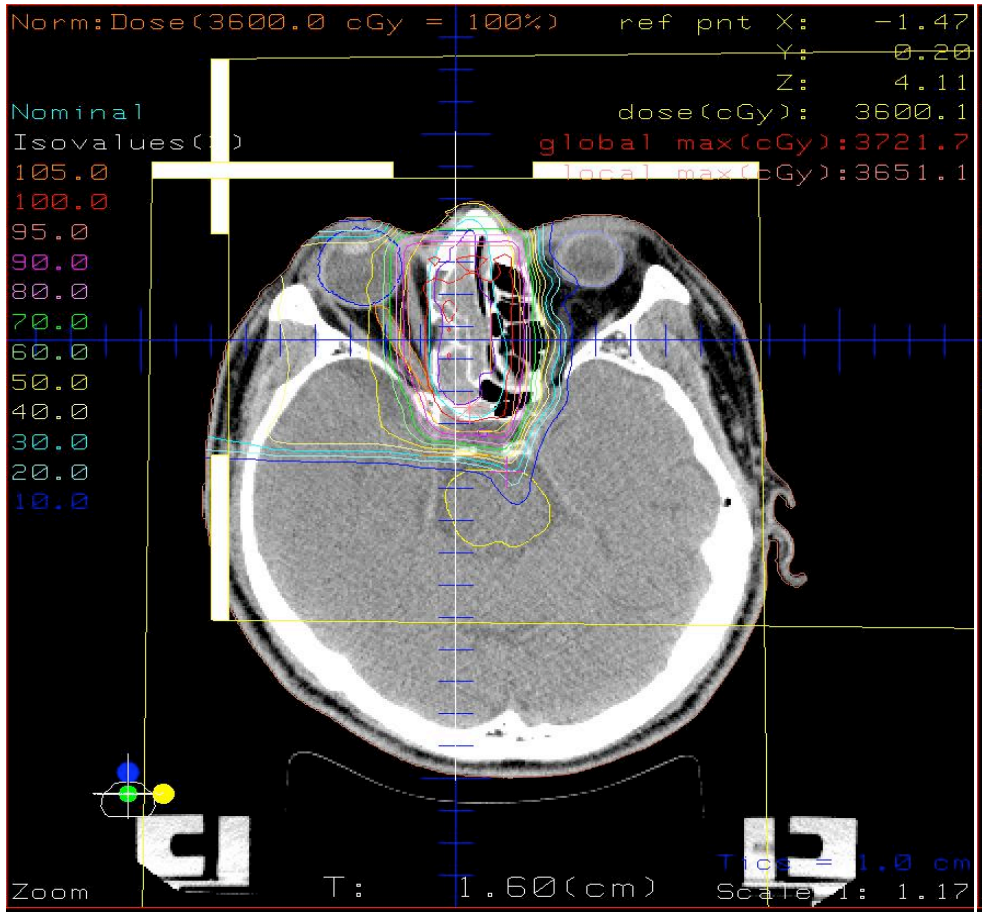
Patients Who Experienced Visual Loss

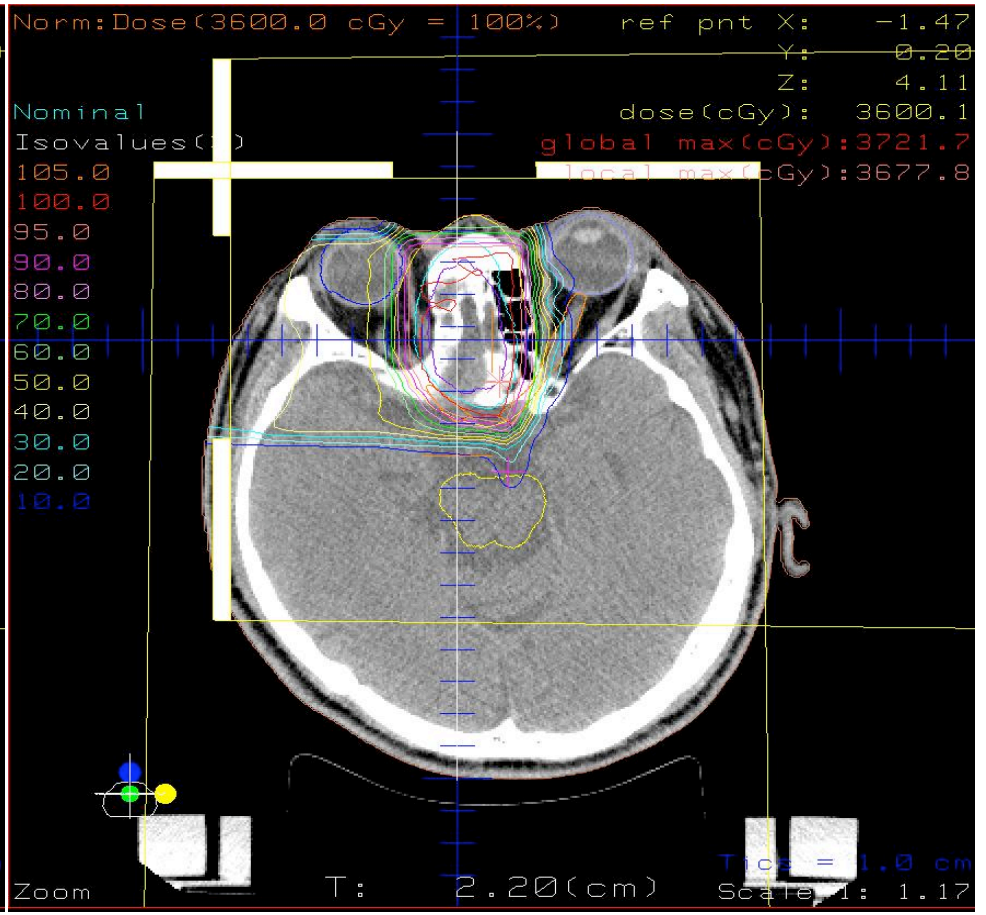
No.	Age (mo)	Gender	Tumor site	Histology	DM	Tx	D_{max} to ON (GyE_3)	Effect	Rec	Time to VL
1	42	F	PPF	ACC	-	C	134	CR	-	58
2	66	M	Nasal	ONB	-	C	129	SD	-52	
3	70	F	Sphenoid	ONB	-P	119	PR	-	36	
4	73	F	Nasal	MM	-P	118	PR	Local	33	
5	78	F	Ethmoid	MM	-P	82	PR		-39	
6*	78	F	Ethmoid	ACC	+P	61, 126	CR	-	26	
7	60	F	Skull base	Meningioma	-P	111	SD		-17	
8	76	F	Skull base	Chordoma	-P	114	SD		-26	

Abbreviations: DM, diabetes mellitus; Tx, therapy; D_{max}, maximum dose; ON, optic nerve; BED, biologic effective dose, Rec, recurrence; VL, visual loss; M, male; F, female; PPF, pterygopalatine fossa; ACC, adenoid cystic carcinoma; ONB, olfactory neuroblastoma; MM, malignant melanoma; C, carbon ion; P, proton; CR, complete response; PR, partial response; SD, stable disease.

*This patient experienced visual loss of both sides at the same time.

Case No.2:
66 y.o., Male, DM (-), Carbon ion

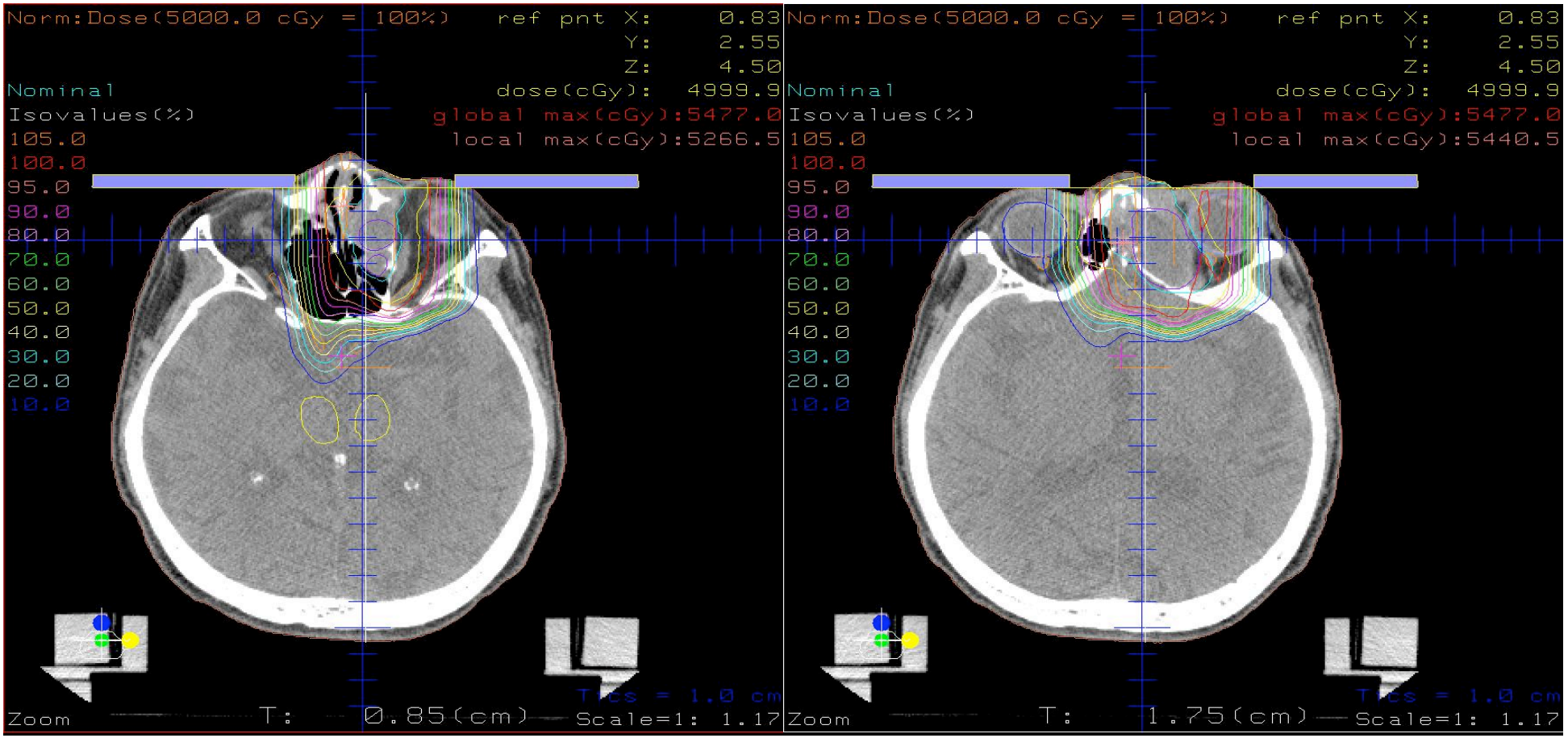




Rt) D_{max} = 58.2 GyE (129 GyE_3)
Time to **visual loss** = 52 months

Lt) D_{max} = 57.5 GyE (126 GyE_3)
No visual loss

Case No.6:
78 y.o., Female, DM (+), Proton



Rt) D_{max} = **40.1** GyE (60 GyE_3)
Time to visual loss = 26 months

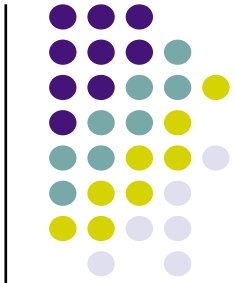
Lt) D_{max} = 67.6 GyE (126 GyE_3)
Time to visual loss = 26 months

Univariate Analysis for Visual Loss (Logrank Test)

Covariate	P-value
Age (year: ≤65 vs >65)	**0.0062**
Gender (male vs female)	0.0699
Previous treatment (yes vs no)	0.3312
Chemotherapy (yes vs no)	0.5034
Diabetes mellitus (yes vs no) 0.0001	
Hypertension (yes vs no)	0.5172
Beam (carbon ion vs proton)	0.4230
D_{max} to ON (GyE_3: ≤100 vs >100)	0.1537
D_{max} to ON (GyE_3: ≤110 vs >110)	**0.0435**
D_{max} to ON (GyE_3: ≤120 vs >120)	0.3889

Abbreviations: D_{max}, maximum dose; ON, optic nerve.

Multivariate Analysis for Visual Loss (Cox Proportional Hazards Model)



Covariate	P-value	95% CI
Age (year: ≤65 vs >65)	**0.04711.033-156.340**	
Gender (male vs female)	**0.0124**	**2.208-695.198**
Previous treatment (yes vs no)	0.30270.027-3.076	
Diabetes mellitus (yes vs no)	**0.0177**	**1.859-689.725**
Hypertension (yes vs no)	0.23120.014-2.809	
Beam (carbon ion vs proton)	0.80290.082-25.449	
D_{max} to ON (GyE_3: ≤110 vs >110)	0.25960.481-15.073	

Abbreviations: CI, confidence interval; D_{max}, maximum dose; ON, optic nerve.

Discussion (1)

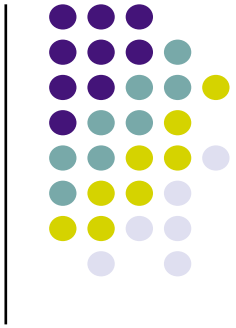
- Tolerance dose of 50 Gy for ON with 5% probability of complication is widely used for photon radiotherapy.[1)]
- Urie et al. reported that 5% complication rate occurred at 70 GyE ($\approx$ 112 GyE_3) for proton irradiation to cranial nerves.[2)]
- According to the analysis by Hasegawa et al., VL after carbon ion therapy did not occur in ONs irradiated with <57 GyE and seems to be correlated with a delivery of >60 GyE to 20% of ON (D_{20}).[3)]

1) Emami B, et al. *IJROBP.* 1991;21:109-122.

2) Urie MM, et al. *IJROBP.* 1992;23:27-39.

3) Hasegawa A, et al. *IJROBP.* 2006;64:396-401.

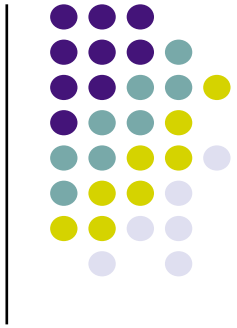
Discussion (2)



- In this study, carbon-ion-treated cases showed later onsets of VL compared to proton-treated ones. It is probably because of small number of carbon-ion-treated cases, however, may be because of the biologic difference between carbon ion and proton.
- D_{max} to ON of >110 GyE_3* was a significant factor on VL in univariate analysis. Although it was not significant in multivariate analysis, the value of 110 GyE_3 was very close to the one reported by Urie et al. It is possible that approximately 110 GyE_3 is a threshold for occurrence of RION for particle therapy.

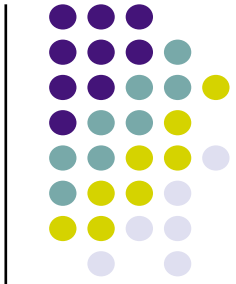
*110 GyE_3 is approximately equivalent to 52 GyE/16 fr or 61GyE/26 fr.

Discussion (3)



- The number of patient assessed in this study was relatively small, especially the number of ON with VL, and accumulation of cases would be needed to obtain more reliable results.
- Some patients whose follow-up periods are relatively short, especially less than 2 years, may develop VL later.
- From the results of this study, we may not have to allow the D_{max} to ON to excess 110 GyE_3 especially in female patients with DM or advanced age to prevent VL.

Conclusions



- The time to the onset of VL ranged widely (1.5-6 years).
- There was no significant difference between carbon ion and proton in the occurrence of VL; however, carbon-ion-treated ONs showed later onset compared to proton-treated ones.
- According to the multivariate analysis, age, gender, and DM seemed to be correlated with the occurrence of VL.
- D_{max} to ON of >110 GyE_3 showed a tendency to cause VL due to radiation-induced optic neuropathy.