Particle radiotherapy using protons or carbon ions for unresectable locally advanced head and neck cancers with skull base invasion

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Particle radiotherapy using protons or carbon ions for unresectable locally advanced head and neck cancers with skull base invasion

頭蓋底浸潤した切除不能局所進行頭頸部癌に対する陽子線または炭素線を用いた粒子線治療

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INTRODUCTION

Despite the recent advances in surgical techniques, chemotherapy (CTX) and radiotherapy (RT), treatment of locally advanced head and neck cancers arising in the nasal cavity, paranasal sinuses and temporal bone has been highly challenging in head and neck oncology. Because the advanced lesions often involve the skull base, treatment is technically challenging for both the radiation oncologists and surgeons because of the close proximity and relative radiosensitivity of adjacent critical structures including the orbit, central nervous system and the internal carotid artery. Obtaining sufficient surgical margins in this area of critical functional anatomy is difficult, with a risk of causing great morbidity to the patients. Oncological results of surgical treatment for cancers involving the cavernous sinus (CS) and/or brain tissues are quite poor with significant severe complications (1).

Particle beams, such as proton and heavier ion beams, show an increase in energy deposition with a penetration depth of up to a sharp maximum at the end of their range to form the so-called Bragg peak. Almost no dose is deposited in the normal tissue beyond the Bragg peak with a sharp dose fall-off at the field borders, providing the precise dose localization compared with photon beams. In addition, this precise dose localization facilitates dose escalation without increasing toxicity in the surrounding normal tissues. From a biological aspect, protons have a higher linear energy transfer than photons, but their radiobiologic properties do not differ substantially from those of photons. However, heavier ions such as carbon ions not only have the favorable physical properties of protons but also have a superior biologic advantage in comparison with protons or photons. The biologic advantages of carbon ions over protons are expected to be most pronounced for radioresistant malignant tumors.

On 1 April 2001, the Hyogo Ion Beam Medical Center (HIBMC) was opened as the world's first facility to provide both proton and carbon ion RT. After ministerial approval was granted, regular practice was initiated in April 2003 for proton RT and in March 2005 for carbon ion RT (2 –14). The purpose of this study was to determine the oncological outcomes and complications of patients with unresectable primary head and neck cancers invading the skull base treated with proton or carbon ion RT.

PATIENTS AND METHODS

Between April 2003 and December 2009, 441 patients with head and neck cancers were treated with particle RT at HIBMC. Two hundred and sixty-two patients were treated with proton RT, and 179 patients were treated with carbon ion radiotherapy. Fifty-seven of the 179 patients who had previously untreated locally advanced unresectable primary

head and neck cancers invading the skull base without lymph node metastasis or distant metastasis were retrospectively analyzed in this study. The extent of the tumor was assessed using magnetic resonance imaging (MRI) and computed tomography (CT). Patients were staged according to the 2002 American Joint Committee on Cancer staging system. Unresectability due to skull base invasion was determined as apparent direct invasion to the brain tissue, CS or carotid canal.

Pathologic types were 25 adenoid cystic carcinomas (ACCs), 14 squamous cell carcinomas (SCCs), six olfactory neuroblastomas (ONBs), four adenocarcinomas (ADs), four malignant melanomas (MMs), three undifferentiated carcinomas (UDCs) and one osteosarcoma (OS). Primary sites were paranasal sinus in 39 patients, nasal cavity in six patients, nasopharynx in six patients, parapharyngeal space in two patients, parotid gland in two patients and external and middle ear in two patients. The patients consisted of 29 males and 28 females aged from 24 to 81 years with an average age of 55 years. Performance status was 0 in 11 patients, 1 in 44 patients and 2 in two patients.

Among 47 patients treated with proton RT, 30 received 65.0 gray equivalent (GyE)/26 fraction (fr), one received 70.0 GyE/28 fr and 16 received 70.2 GyE/26 fr. Ten patients were treated with carbon ion RT. Of the 10 patients, six received 57.6 GyE/16 fr, two received 60.8 GyE/16 fr and two received 70.2 GyE/26 fr. Optimal dose fractionation was determined for each patient based on discussion by several radiation oncologists.

Particle RT was delivered daily at five per week, to the isodose encompassing the planning target volume (PTV). To protect the optic nerve, optic chiasm and spinal cord, doses were limited to 52, 52 and 48 GyE, respectively. The tumors were treated with a 5 mm field margin as the clinical target volume and 3 mm (carbon ion beams) or 5 mm (proton beams) field margins as the PTV. Choices of beam were determined to obtain the optimal dose distribution to the targeted lesion and maximum reduction of dose deposition in non-targeted critical tissues, such as optic nerves, optic chiasm, eye balls, brain, brain stem and spinal cord.

All patients were followed up at least 12 months or until death. The median follow-up period was 32.1 months, ranging from 6.4 to 80.4 months. Response was classified according to Response Evaluation Criteria in Solid Tumor. Acute and late toxicities were scored according to the National Cancer Institute Common Terminology Criteria for Adverse Event v4.0. Survival rates and local progression-free rates were calculated using the Kaplan–Meier method.

RESULTS

Characteristics of the patients treated with proton ions are summarized in Table 1. In

the patients treated with proton RT, a complete response (CR) and partial response (PR) were achieved in two patients and 21 patients, respectively. In 24 patients, the response was judged as stable disease (SD). Progression of disease (PD) was not observed. During the follow-up periods, local recurrence or progression of local disease was observed in one patient (50%) in the CR group, nine patients (43%) in the PR group and 12 patients (50%) in the SD group. Regional lymph node metastasis was observed in two patients (100%) in the CR group and three patients (13%) in the SD group. No regional lymph node metastasis was observed in the PR group. Distant metastasis was observed in two patients (100%) in the CR group, eight patients (38%) in the PR group and 10 patients (42%) in the SD group. Representative pretreatment and posttreatment imagings and dose distribution of proton radiotherapy are shown in Fig. 1. Mucositis and dermatitis are seen as acute toxicity, but none of the patients developed Grade 4 or 5 acute toxicity. In terms of late toxicity, the most common toxicity was visual disorder. Grades 2, 3 and 4 visual disorders were observed in three, four and two patients, respectively. Grades 3 and 4 nervous system disorders were observed in one patient each. Details are seen in Table 2. No other severe late complication was observed.

In the patients treated with carbon ion RT, CR and PR were achieved in one and four patients, respectively. In five patients, the response was judged as SD, and PD was not observed. During the follow-up periods, local recurrence or progression of local disease was observed in three patients. Regional lymph node metastasis and distant metastasis were observed in two and four patients, respectively. Patient characteristics are listed in Table 3, and representative pretreatment and posttreatment imagings and dose distribution of carbon ion RT are shown in Fig. 2. Grade 3 mucositis and dermatitis are seen as acute toxicity, but none of the patients developed Grade 4 or 5 acute toxicity. The most common late toxicity was visual disorder. Grades 2 and 3 visual disorder was observed in four patients (three optic nerve disorders and one retinal vascular disorder) and one patient (optic nerve disorder), respectively. Grade 3 central nervous system necrosis was observed in one patient. Grade 2 osteonecrosis of the jaw and Grade 2 middle ear inflammation were observed in one and two patients, respectively. Details are seen in Table 4.

The actual 3-year overall survival rate and local progression-free rate of all the patients were 60 and 55%, respectively (Fig. 3). According to the pathologic types, the actual 3-year overall survival rates were 80% for ACC, 44% for SCC, 75% for ONB, 0% for AD and 38% for MM. Actual 3-year local progression-free rate was 63% for ACC, 28% for SCC, 83% for ONB, 50% for AD (2-year) and 0% for MM(Table 5).

According to primary site, the actual 3-year survival rate was 100% for nasopharynx, 57% for maxillary sinus, 38% for ethmoid sinus, 63% for sphenoid sinus, 50% for frontal

sinus, 100% for nasal cavity, 0% for external and middle ear, 100% for parapharyngeal space and 50% for parotid gland (Fig. 3). The 3-year local progression-free rate was 83% for nasopharynx, 53% for maxillary sinus, 42% for ethmoid sinus, 63% for sphenoid sinus, 50% for frontal sinus (2-year), 83% for nasal cavity, 0% for external and middle ear, 50% for parapharyngeal space and 0% for parotid gland (Table 6).

Distant metastasis developed in 13 of 25 patients (52%) with ACC, two of 14 patients (14%) with SCC, one of six patients (17%) with ONB, two of four patients (50%) with AD, three of four patients (75%) with MM, one of three patients (33%) with UDC and one of one patient (100%) with OS. Regional lymph node metastasis developed in one patient with ACC and one with ONB, respectively, and one patient with both SCC and UDC.

In terms of extent of the tumor, the actual 3-year overall survival rate was 45% in the patients with anterior skull base invasion (n = 23), 64% in the patients with middle skull base invasion (n = 11), 83% in the patients with CS invasion (n = 12) and 58% in the patients with CS and middle skull base invasion (n = 11). The 3-year local progression-free rate was 52% in the patients with anterior skull base invasion, 50% in the patients with middle skull base invasion, 62% in the patients with CS invasion, and 61% in the patients with CS and middle skull base invasion.

From the point of initial response to the particle therapy, the actual 3-year overall survival rate was 50% for the CR group, 70% for the PR group and 55% for the SD group. There was no statistical difference in the 3-year local progression-free rate between the CR (33%) and the PR groups (49%). The 3-year local progression-free rate was 33% for the CR group, 49% for the PR group and 61% for the SD group. There was no statistical significance in the actual 3-year survival rates or local progression-free survival rates in terms of the initial response.

DISCUSSION

According to the international collaborative study, craniofacial resection for malignant tumors of the skull base has 4.7% of the overall mortality rate and 36.3% of the complication rate, with 56% of the 5-year overall survival rate (1). Although malignant lesions involving CS, internal carotid artery or brain tissue can be technically resectable, this surgical procedure leads to disappointing oncological outcomes with great morbidity and mortality rates as well as poor functional results (15). Thus, cancers involving these lesions have been considered as unresectable from a practical standpoint. However, the reported oncological outcomes of conventional RT are also poor even in combination with CTX (16, 17) (Table 7).

Particle RT offers physical advantages over the conventional photon RT, which means

that improved dose distribution permits dose escalation within the target and optimal sparing of normal tissue (18). As expected, Zenda et al. (19) reported favorable outcome for patients with unresectable malignancies of the nasal cavity and paranasal sinuses treated with definitive proton RT. The 3-year overall survival rate was 58.0%. In this series, we obtained similar or better oncological results. The patients with far advanced tumors completed proton or carbon ion RT without fatal adverse events. Most frequent late toxicities were related to visual impairment. However, these were mainly observed in the diseased side, where exenteration of the orbital content cannot be avoided if surgical treatment is adopted. These results are substantially better than those reported previously for photon RT, suggesting that definitive proton RT may be a promising treatment option for patients who are not candidates for surgery.

Moreover, favorable local control and survival rates of the patients with ACC (17), SCC (20) and ONB (21) invading the skull base were reported, suggesting the potential advantage of proton RT over conventional RT, especially for locally advanced disease with intracranial invasion (21). Because these oncological outcomes are not inferior to those of surgical treatment involving the craniofacial approach (22–24), definitive proton RT may be a promising treatment option for patients with not only unresectable but also resectable head and neck cancers invading the skull base (Table 7).

In conventional RT with or without CTX, initial response was considered as a significant factor to predict therapeutic effect. However, interestingly, in the present study, there was no significant difference in the local progression-free and survival rates according to the initial response, in accordance with the report of Zenda et al. CR or PR was not necessarily required to obtain long-term local progression-free survival. Patients with long survival often show the persistence of the tumor on CT or MRI after proton RT (19).

From the pathological oncological point of view, in this series, local progression-free rates and actual survival rates of the patients with ACC (14) and ONB (21) are favorable in comparison with other pathologies, in accordance with previous reports. Because these pathologies are relatively slow-growing, long-term follow-up is required to determine the significance. However, these results further support that ion beam therapy has its role in the treatment of ACC and ONB invading the skull base. However, slow-growing malignancies, such as ACC and ONB, most likely have microscopic metastases, as shown in our series. Hence, local treatment alone is insufficient for radical cure. Treatment strategies such as CTX and targeted therapy, for distant metastasis, should be considered for complete cure.

On the other hand, local progression-free rates of the patients with SCC, MM and AD are unsatisfactory. Because most of the patients (82%) in the present series were treated

with proton RT, these results suggest that proton RT alone is not enough for such aggressive cancers. Combination with induction or concomitant CTX might be considered if proton RT is applied. The other option is carbon ion RT, which can be administered at our facility. Ramaekers et al. (25) reported from a systemic review and meta-analysis that carbon ion RT resulted in a statistically significant increase in the 5-year overall survival compared with conventional photon therapy for mucosal MM. Mizoe et al. reported that the outcome of carbon ion RT showed a specific effectiveness in local control of non-SCC, such as ACC (n = 9) and MM (n = 5). Five-year local control rates were 50 and 100%, respectively (26). In the beginning, considering the high relative biological effectiveness of carbon ions, we hesitated to use carbon ion RT for cases with invasion of the skull base, which was exposed extensively in the brain. However, with experience, we found that late adverse events of carbon ion RT are acceptable with respect to such a far advanced malignant tumor invading the skull base, as shown in this study. Ever since ministerial approval was granted in 2005, we have made both proton and carbon ion treatment plans, and have selected the modality with better dose distribution at our daily conference. Thus, recently, we have been preferably using carbon ion RT for head and neck malignancies. Although the number of patients is limited, the oncological results are promising.

CONCLUSIONS

Particle RT is highly effective in the local control of unresectable locally advanced head and neck cancers with skull base invasion. Satisfactory oncological results were obtained for ONB and ACC. Although the follow-up period is still limited, acute and late toxicities were at acceptable levels except for optic disturbance. On the other hand, particle RT alone might be insufficient as a curative treatment against high-grade malignant tumors such as SCC, UDC and MM invading the skull base. Currently, we are planning a randomized clinical trial to compare the effects of proton RT and carbon ion RT for head and neck cancers. Concurrent or sequential CTX or/and molecular-targeted drugs in combination with particle RT also should be considered to develop an optimal strategy using particle RT for head and neck cancers.

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Conflict of interest statement

None declared.

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Table 1. Patient characteristics (proton)

Item	No. of patients	Item	No. of patients
Age	26	Primary site	
<60 years old	21	Paranasal sinus	33
>60 years old		Nasopharynx	5
Gender		Nasal cavity	4
M	25	Parotid gland	2
F	22	External/middle ear	2
Pathological types		Parapharyngeal space	1
ACC	22	Extent of tumor	
SCC	13	Anterior skull base	19
ONB	4	Middle skull base	11
AD	3	Cavernous sinus	10
MM	2	Middle skull base + cavernous sinus	7
UDC	3		

ACC, adenoid cystic carcinoma; SCC, squamous cell carcinoma; ONB, olfactory neuroblastoma; AD, adenocarcinoma; MM, malignant melanoma; UDC, undifferentiated carcinoma

Table 2. Late toxicities (proton)

Toxicity	No. of patients			
	Grade 2	Grade 3	Grade 4	Grade 5
Optic nerve disorder	2	3	2	-
Cataract	-	1	-	-
Extraocular muscle paralysis	1	-	-	-
Edema cerebral	-	-	1	-
Meningismus	-	1	-	-
Pharyngeal mucositis	-	1	-	-
Hearing impaired	-	1	-	-

Table 4. Late toxicities (carbon)

Toxicity	No. of patients			
	Grade 2	Grade 3	Grade 4	Grade 5
Optic nerve disorder	3	1	-	-
Retinal vascular disorder	1	-	-	-
Central nervous system necrosis	-	1	-	-
Osteonecrosis of jaw	1	-	-	-
Middle ear inflammation	2	-	-	-

Table 5. Survival and local progression-free rates according to the pathological types

Pathological types	No. of patients	Three-year survival rate (%)	Three-year local progression-free rate (%)
ACC	25	80	63
SCC	14	44	28
ONB	6	75	83
AD	4	0	50
MM	4	38	0
UDC	3	0	67
OS	1	0	0

Table 6. Survival and local progression-free rates according to the primary site

Primary site	No. of patients	Three-year survival rate (%)	Three-year local progression-free rate (%)
Nasopharynx	6	100	83
Maxillary sinus	12	57	53
Ethmoid sinus	17	38	42
Sphenoid sinus	8	63	63
Frontal sinus	2	50	50
Nasal cavity	6	100	83
External/middle ear	2	0	0
Parapharyngeal space	2	100	50
Parotid gland	2	50	0

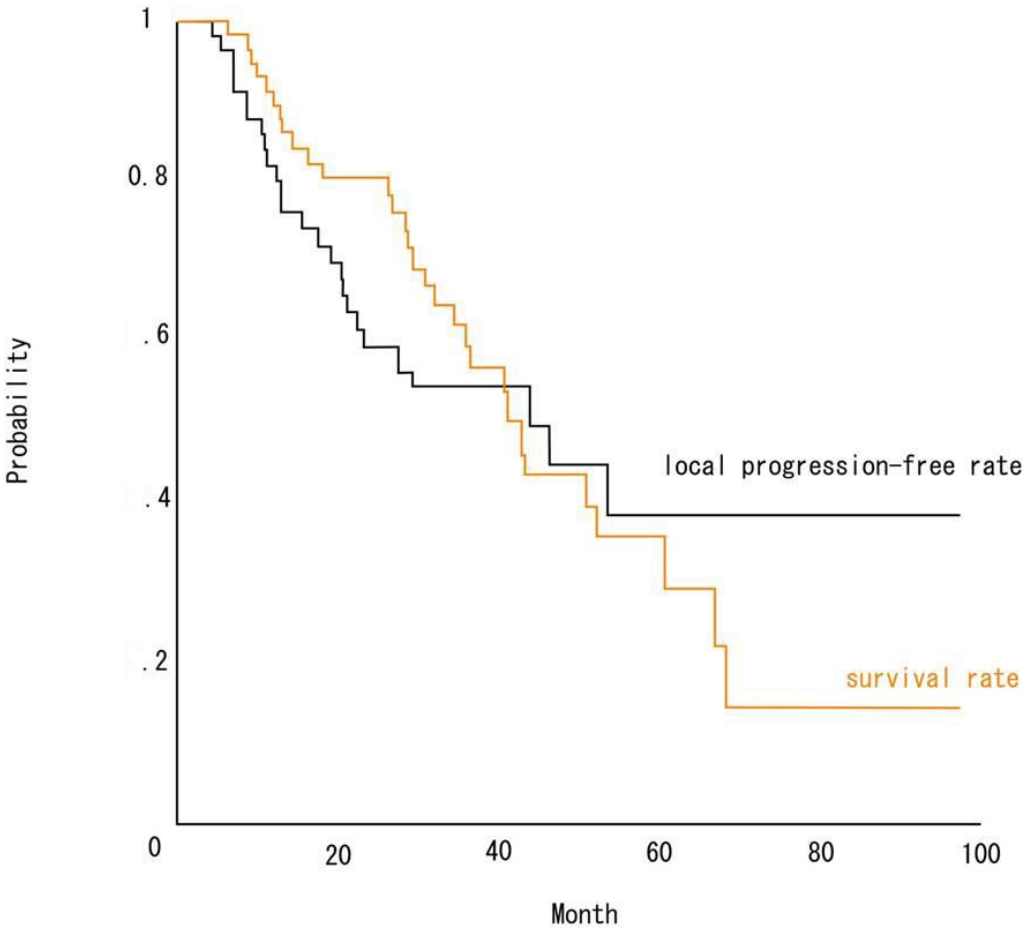

Figure 3. Overall survival and local progression-free rates of all cases.

Table 3. Paiente characteristic (carbon)

Age/Sex	Histology	Primary Site	Site of skull base invasion	Dose	Response	Time to reecurrence	Recurrence site	Prognosis
37/F	OS	Sphenoid sinus	CS+MF	57.6GyE/16fr	SD	7mo	Local/Dist	DWD 12mo
24/F	ACC	Sphenoid sinus	CS	57.6GyE/16fr	SD	-	-	NED 39mo
64/M	ACC	Parapharyngeal Sjpace	CS	57.6GyE/16fr	PR	20mo	Local/Dist	AWD 24mo
59/F	ACC	Nasopharynx	CS+MF	57.6GyE/16fr	PR	-		NED 31mo
57/F	ONB	Sphenoid S	CS+MF	57.6GyE/16fr	SD	-		NED 30mo
41/F	MM	Maxillary S	AF	57.6GyE/16fr	SD	10mo	Dist	DWD 10mo
51/M	SCC	Ethmoid S	CS+MF	60.8GyE/16fr	PR	-		NED 22mo
48/F	AD	Nasal cavity	AF	60.8GyE/16fr	SD	-		NED 25mo
48/F	ONB	Nasal cavity	AF	70.2GyE/26fr	CR	7mo	Local	AWD 17mo
62/M	MM	Ethmoid S	AF	70.2GyE/26fr	PR	13mo	Dist	AWD 13mo

ACC, adenoid cystic carcinoma; ONB, olfactory neuroblastoma; MM, malignant melanoma; SCC, squamous cell carcinoma; AD, adenocarcinoma; S, sinus; CS, cavernous sinus; MF, middle fossa; AF, anterior fossa; fr, fraction; PR, partical response; SD, stable disease; CR, complete response; mo, months; Dist, distant recurrence; DWD, died with disease; NED, no evidence of disease; AWD, alive with disease

Table 7. Survival rates of published cases

Authors	Year	Primary Site	Main modality	No. of patients	Survival Rate (%)
Nibu et a. (15)	1998	Head and neck	Skull base surgery	29	54% (5 years)
Schulz-Ertner et al. (17)	2003	Head and neck (ACC)	Proton + carbon	16	83% (3 years)
Diaz et al. (22)	2005	Nasal cavity (ONB)	Skull base surgery	30	89% (5 years)
Ganly et al. (1)	2006	Head and neck	Skull base surgery	53	28% (3 years)
Nishimura et al. (21)	2007	Nasal cavity (ONB)	Proton	14	93% (5 years)
Hoppe et al. (16)	2008	Paranasal sinus (unresectable)	RT w/wo CTX	38	15% (5 years)
Zenda et al. (19)	2010	Paranasal sinus	Proton	14	58% (3 years)
Present study	2014	Head and neck	Proton/carbon	58	61% (3 years)

RT, radiotherapy; CTX, chemotherapy; w/wo, with or without.

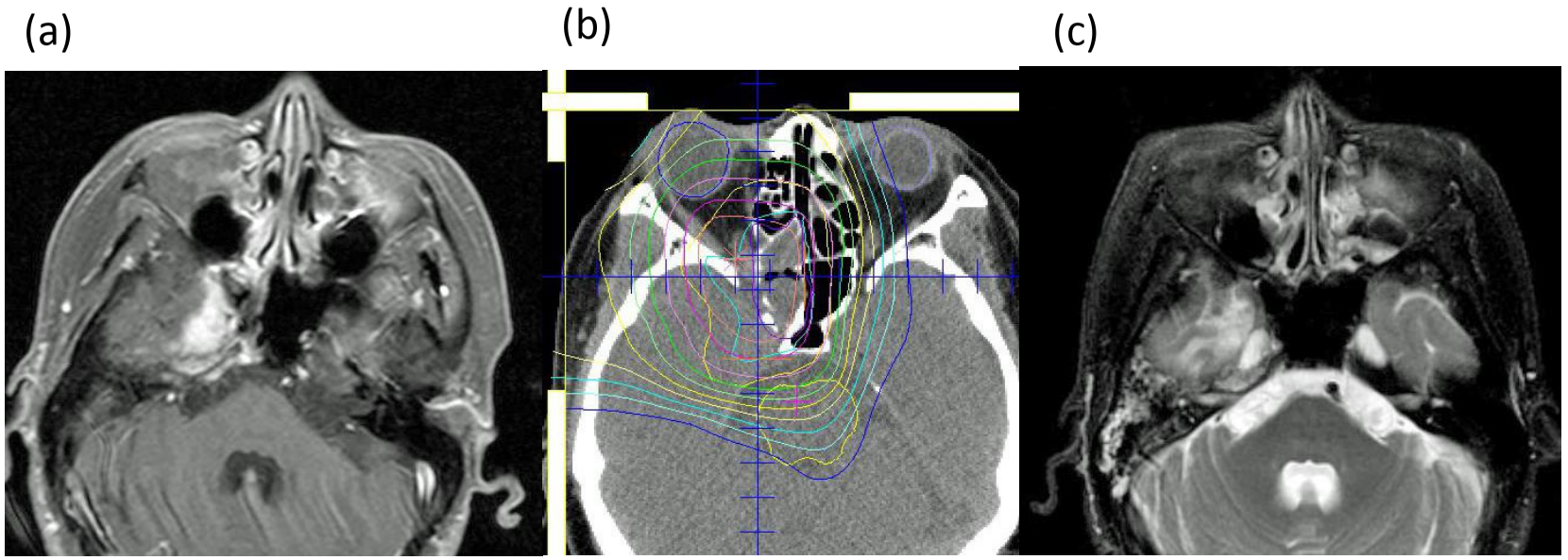

Figure 1. Proton radiotherapy (RT). A 55-year-old female patient with adenoid cystic carcinoma (ACC) invading the cavernous sinus (CS). PR was obtained by proton RT. She has been alive without disease for >80 months. (a) Pretreatment Gd-enhanced T1-weighted magnetic resonance imaging (MRI), (b) beam arrangement and (c) T2-weighted MRI 36 months after proton RT.

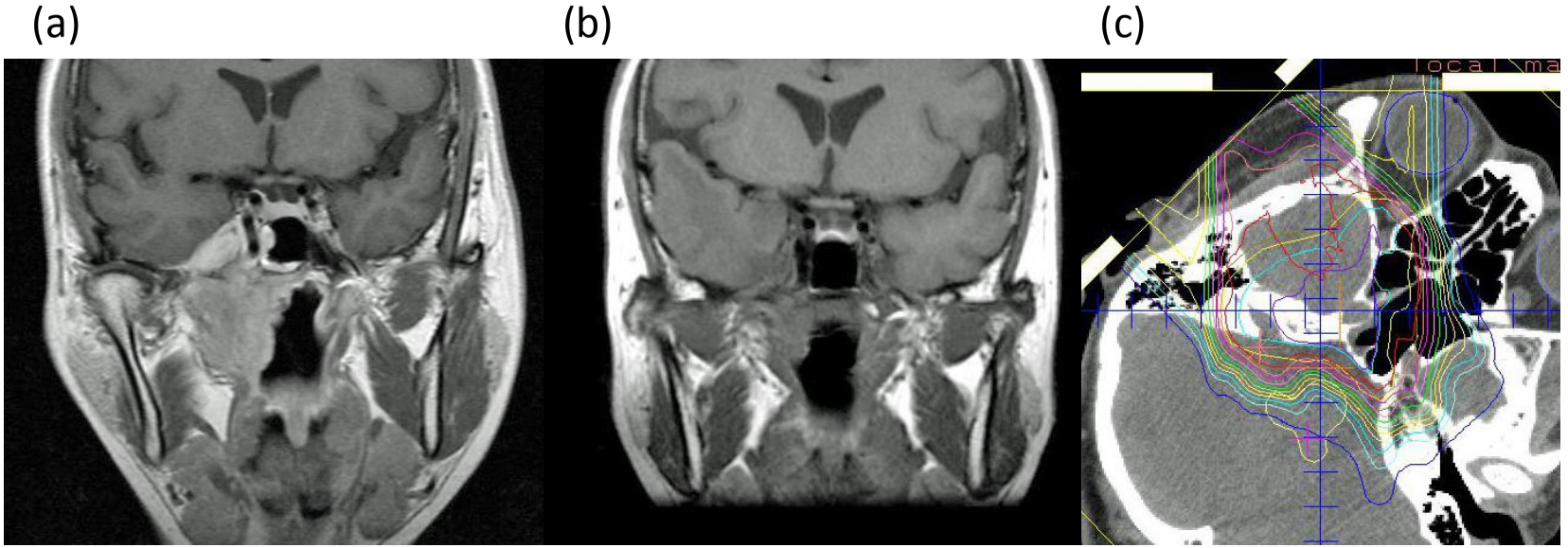

Figure 2. Carbon ion RT. A 59-year-old female with nasopharyngeal ACC invading the CS and middle carnial fossa. PR was obtained By carbon ion RT. She has been alive without disease for >36 months. (a) Pretreatment Gd-enhanced T1-weighted MRI, (b) T2-weighted MRI 36 months after carbon ion RT and (c) beam arrangement.