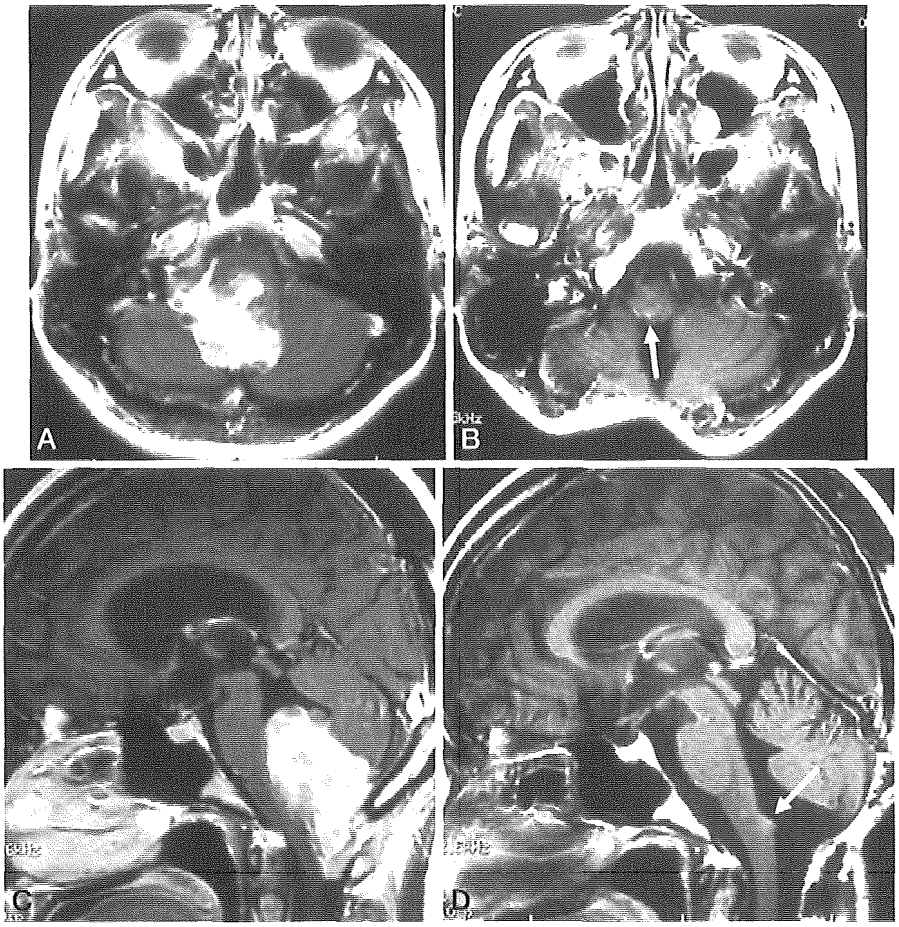

Fig. 7 Case 7, a 25-year-old female with choroid plexus carcinoma. Magnetic resonance (MR) imaging with gadolinium (**A**: axial, **C**: sagittal) showed an enhanced mass in the fourth ventricle. The tumor was subtotally resected (**B**: axial, **D**: sagittal), followed by radiation and chemotherapy to the residual tumor (**arrows**).

が拡大したため再手術により全摘したところ，術中照射と化学療法を追加した効果もあるものの，その後10年間は再発を生じておらず，全摘の重要性が示唆される[14]．

術後の補助療法については確固たるエビデンスはないが，CPPとCPCでは治療方針は異なってくる．CPPの術後照射についての意見は分かれるが，初回手術で全摘，亜全摘いずれの場合でも放射線治療は予後を改善させてはいない[13,16]．しかし再発例については，可及的摘出後の放射線療法は適応だろうとされている[16]．一方，CPCに対しては術後の放射線療法が予後と相関しており，全摘出後でも放射線療法を受けるべきとする意見がある[24,25]．Wolffらによると，全摘出後のCPCの照射群では5年生存率が68%なのに対し，非照射群では16%で[24]，照射が可能な年齢であればCPCに対しては放射線療法を積極的に追加するべきであろう[24]．照射は年長児以上に限られるが，髄液播種などの再発様式などを考慮すると全脳全脊髄照射が推奨されている[2,8,17]．

CPPに対する化学療法については，エビデンスはないとされている．全摘後の治療成績がよいことも考慮すると，CPPの初回手術後は補助療法を行わずにまず経過観察がよいと考えられる

Table Clinical summary of 7 patients with tumors of the choroid plexus

Case	Age	Gender	Location	Surgery	Shunt	Pathology	Radiation	Chemotherapy	Prognosis	Survival period (months)
1	4m	F	3rd ventricle	total	SPS (post-ope)	CPP	none	none	no deficit	21
2	28	M	4th ventricle	subtotal	none	CPP	none	none	no deficit	104
3	29	F	4th ventricle	subtotal, partial (2nd), subtotal (3rd)	VPS (post-ope)	CPP	L60 Gy	ACNU	dead (respiratory disturbance)	81
4	37	M	4th ventricle	total	none	CPP	none	none	no deficit	32
5	2m	M	lateral ventricle	subtotal, total (2nd)	VPS (post-ope)	CPC	IOR10 Gy	VCR, MTX	mental retardation, epilepsy	140
6	3	M	4th ventricle	total	ETV (pre-ope)	CPC	WB&WS24 Gy, L26 Gy	none	dysphagia	34
7	25	F	4th ventricle	subtotal	none	CPC	WB&WS30 Gy, L24 Gy	ACNU	no deficit	29

m: month, **F**: female, **M**: male, **CPP**: choroid plexus papilloma, **CPC**: choroid plexus carcinoma, **L**: local, **IOR**: intraoperative radiation, **WB**: whole brain, **WS**: whole spine **VPS**: ventriculo-peritoneal shunt, **ETV**: endoscopic third ventriculostomy, **SPS**: subdural-peritoneal shunt

[22,25]．しかし，最近の報告ではCPPの再発，脊髄播種後に放射線療法に加えてCCNUを併用したところ腫瘍の消退の効果があったとしており[23]，CPPの再発時におけるCCNU投与は有用かもしれない．

一方，CPCに対する化学療法の効果は不明とする意見もあるが[25]，化学療法を推奨する意見のほうが多い[7]．投与方法については，術前に行う場合と術後に追加する場合のいずれも報告されている．術前の化学療法についての報告では，腫瘍容積を縮小したり腫瘍の栄養血管を減じるため，全摘を目指すうえで効果的としている[1,7]．Souweidaneらは15カ月のCPCの女児に対して，etoposide，cyclophosphamide，vincristine，cisplatinなどを用いて術前に化学療法を行ったところ，腫瘍容積を29.5%減じることができ，全摘を可能にしたと報告している[21]．CPCに対する術後の化学療法については，全摘されていれば必ずしも必要としないとする意見もあるが[10]，全摘後でも術後に放射線療法とともに化学療法を考慮すべきという意見もある[22]．亜全摘後の化学療法では11例中4例でCR（complete recovery）という報告もあり，CPCに対する術後化学療法の有用性を示している[2]．また，部分摘出術後にcarboplatin，doxorubicin，methotrexateによる化学療法を追加したところ完全寛解を得られたという報告もある[9]．これらの結果より，少なくともCPCに対しては術前，術後を問わず積極的な化学療法が有用と考えられる．予後不良という観点からも手術摘出度に関係なく化学療法を行うべきという意見もある[2]．当施設でのCPCの症例では亜全摘に終わった2例で化学療法を追加しているが，全摘例の1例と合わせてすべて生存中である．ただし，化学療法の内容に関しては確立されたものはなく，今後の検討が望まれる．

当院での経験と過去の文献を検討した結果，CPTにおいて最大の予後因子はやはり手術による摘出度であるといえる．CPPは基本的に良性腫瘍なので全摘がなされていれば補助療法は追加せず，亜全摘でも経過観察を行い，再発時（再増大時）に手術による可及的摘出と補助療法を追加する方針がよいと考えられる．また組織学的により悪性度の高いCPCでも可及的摘出は大前提ではあるが，術前化学療法も含めて積極的に補助療法を考慮すべきで，全摘がなされた場合でも術後の放射線療法，化学療法の追加は必要であろう．全摘を妨げる因子としては腫瘍の部位，浸潤度が影響してくるが，特に第4脳室病変では脳幹部への浸潤が全摘を阻むことになるため，症例ごとに機能温存と生命予後との関係を術前に十分に説明

しておく必要があるだろう.

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Brief Report of Special Case

A case of cellular blue naevus with intracranial invasion and malignant transformation

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Introduction

Blue naevus is a congenital benign melanocytic lesion originating from a disorder of the neural crest. Blue naevus generally occurs in the skin, and can affect the eyelids and surrounding tissue. There are two types of blue naevus, common blue naevus and the cellular blue naevus (CBN). Unlike the common blue naevus, CBN can, in rare instances, undergo transformation into malignant melanoma. But contiguous intracranial invasion by CBN is extremely rare [1, 3–5].

Keywords: Blue naevus; intracranial invasion; malignant transformation.

Case report

A 24-year-old man was admitted to our hospital with diplopia due to recurrent intracranial CBN extending from the right eyelids. He had suffered from a naevus around the right eyelid for 20 years, and had undergone dermal transplantation at the age of 4 and 6 years. One year before admission to our hospital, he visited a local hospital with diplopia, where the initial operation was performed and a black pigmented tumor was removed. The histological diagnosis was intracranial CBN without malignancy.

On admission to our hospital, pigmentation in the skin graft to the right eyelids was found (Fig. 1a). Magnetic resonance imaging demonstrated an intracranial mass lesion extending from the right superior orbital fissure to the medial sphenoidal ridge (b, c). Surgery by Dolenc's approach revealed direct extension from the pigmented skin lesion to the intracranial lesion (d). Histological examination showed the intracranial lesion was an intermediate grade melanocytic neoplasm, which was graded between melanocytoma and malignant melanoma (e). Immunohistochemical studies showed significant expression of S-100 protein, HMB45, and melan-A. The MIB-1 labelling index was 15%. Unlike the intracranial lesion, the dural lesion was less malignant. Furthermore, the specimen of the first operation did not show any malignancy. Histological examination of a biopsy sample taken from the pigmented peri-ocular lesion was consistent with benign CBN (f). The postoperative course was uneventful, and the patient showed no deterioration of his neurological condition. There was no re-growth of the tumor by magnetic resonance imaging 5 months after surgery.

Discussion

Intracranial invasion of CBN from the skin is extremely rare [1, 3–5], and such a condition with malignant transformation is even rarer [3, 4]. The following are features that, alone or in combination, should raise the index of suspicion when evaluating the possible malignant potential of a cellular blue naevus: a solitary lesion with a diameter greater than 2 cm; presence of multiple lesions in a multinodular or plaque form; and a history of rapid or progressive growth or sudden change [2].

The present case of blue naevus with intracranial invasion and malignant transformation shows that although CBN is considered benign, scalp or periorbital CBN has the potential for intracranial invasion and malignant transformation. Early surgical exploration to prevent the intracranial invasion of CBN is recommended.

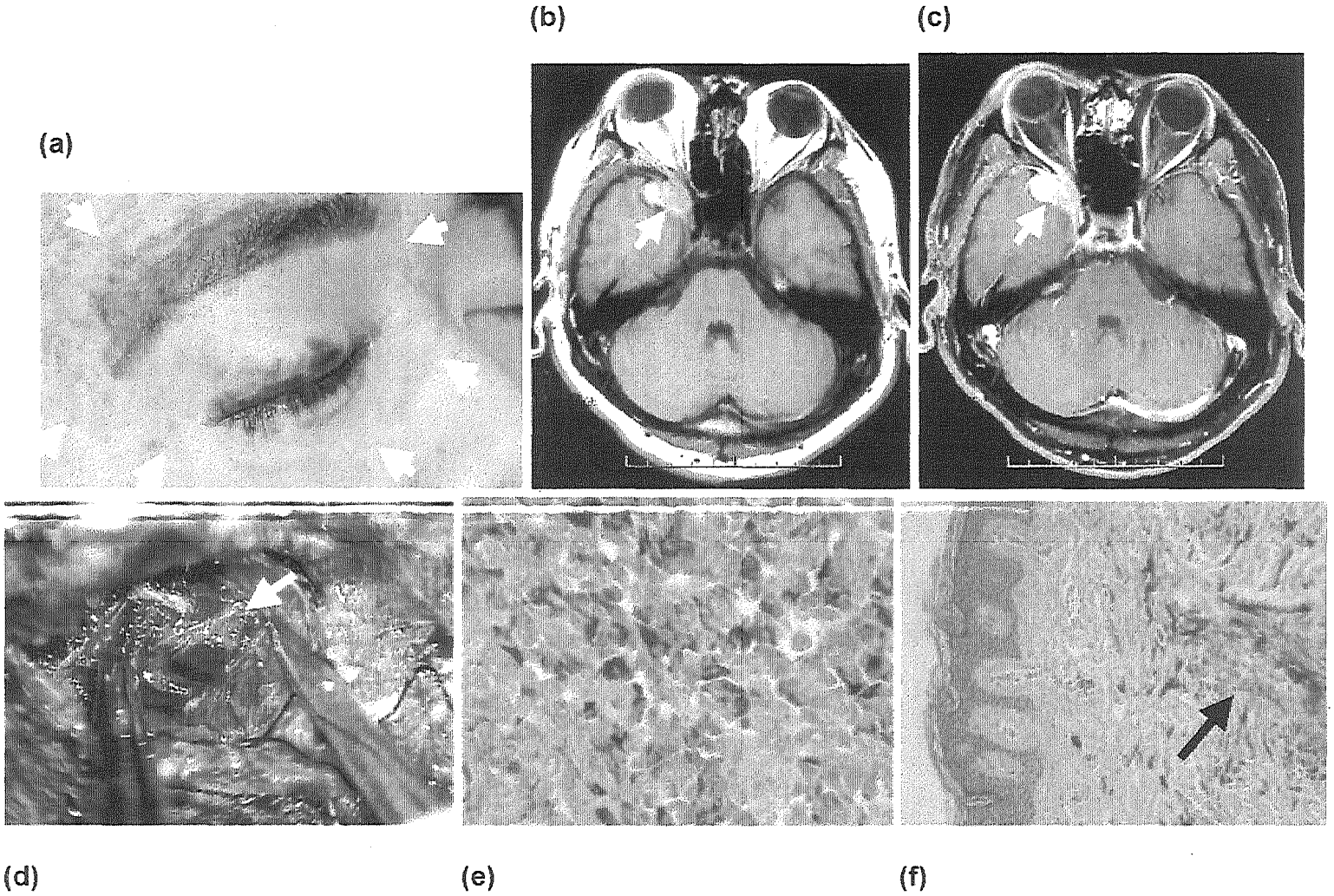

Fig. 1. (a) Bluish discoloration on the right upper and lower eyelids, multiple peri-orbital pigmented lesions, and the scar of dermal transplantation (arrows). (b, c) Magnetic resonance images on admission revealing an irregular mass lesion at the medial side of the right sphenoidal ridge extending to the right superior orbital fissure and the optic canal (arrows). (b) T_1-weighted image. (c) T_1-weighted image with gadolinium. (d) Photographs taken after dural incision showing encapsulated tumor (white arrow) occupying the cavernous sinus. (e, f) Photomicrographs of the surgical specimens from the intracranial lesion (e, H-E, original magnification ×400) showing the tumor cells consisted of variably pigmented spindle cells with abundant brown granules of melanin arranged in loose nests or sheets indicating increased malignancy, and from a naevus around the right eyelid (f, original magnification ×100) showing the lesion (arrow) consisted of well-differentiated, spindle-shaped, variably pigmented melanocytes

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Comment

In this case report Noshita *et al.* describe a rare case of a cellular blue naevus originally confined to the eyelid with subsequent intracranial and dural expansion.

The patient had been suffering from a naevus of Ota for 20 years and undergone several operations. Radical removal of the recurrent intracranial mass resulted in an uneventful postoperative period and follow up of five months, despite of the ample malignant transformation of the intracranial mass. Histology revealed three different parts of the tumor: the one at the peri-orbital region proved benign, the intracranial part was diagnosed to be an intermediate grate melanocytic neoplasm while the dural infiltration appeared "less malignant".

Naevus of Ota is a congenital hyperpigmentation in the territory of the trigeminal nerve, purportedly caused by accumulation of melanocytes which have not migrated completely from the neural crest to the epidermis during the embryonic stage.

Histologically it can appear as a typical blue naevus.

According to Balmaceda CM *et al.* (Neurology, 1993 43(2): 381–386) it has a tendency for being associated with malignant intracranial tumors. Nevertheless, cellular blue naevus/naevus of Ota is more frequently associated with relatively benign intracranial lesions (Piercecchi-Marti MD *et al.*/J Neurosurg, 2002 Mar; 96(3): 619–623./) thereby in the majority of cases considerable long-term survival can be achieved with radical surgical resection and careful follow-up alone.

Andras Buki
Pecs

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High-dose conformal radiotherapy for supratentorial malignant glioma: a historical comparison

Minoru Tanaka, Yasushi Ino, Keiichi Nakagawa, Masao Tago, Tomoki Todo

Summary

Background Although radiotherapy remains the main postoperative treatment for patients with malignant glioma, modifications to regimens have not improved the poor outlook of patients with this disease. We aimed to investigate whether high-dose conformal radiotherapy improves the survival of patients with supratentorial malignant glioma compared with conventional radiotherapy.

Methods 29 patients with anaplastic astrocytoma and 61 patients with glioblastoma who received high-dose conformal radiotherapy during 1990–2002 were compared with 34 patients with anaplastic astrocytoma and 60 patients with glioblastoma who received conventional 60 Gy radiotherapy during 1979–89. 77 of the 90 patients receiving high-dose radiotherapy were given 80 Gy; the remaining 13 patients, all with glioblastoma, received 90 Gy. Radiotherapy was planned on the basis of images taken before surgery, and doses were delivered in 2 Gy per fraction per day for 5 days a week. Hazard ratios for death were calculated with a Cox model, and were adjusted for age, Karnofsky performance scale, tumour size, and extent of resection.

Findings Patients who received high-dose radiotherapy had significantly longer overall survival compared with those who received conventional radiotherapy (adjusted hazard ratio 0·30 [95% CI 0·12–0·76], p=0·011 for anaplastic astrocytoma and 0·49 [0·28–0·87], p=0·014 for glioblastoma). Patients with anaplastic astrocytoma in the high-dose group have not yet reached median survival; median survival in the conventional radiotherapy group was 22·3 months (95% CI 20·6–24·0). 5-year survival was 51·3% (29·2–73·4) for the high-dose group and 14·7% (0·0–30·0) for the conventional group. Median survival in patients with glioblastoma was 16·2 months (12·8–19·6) for the high-dose group and 12·4 months (10·0–14·8) for the conventional group. 2-year survival was 38·4% (23·5–53·3) for the high-dose group and 11·4% (0·0–25·3) for the conventional group. Survival did not differ between those that received 80 Gy radiotherapy and those that received 90 Gy (hazard ratio 0·94 [95% CI 0·42–2·12]). The higher frequency of radiation-induced white matter abnormality in the high-dose group compared with the conventional radiotherapy group did not lead to increased disability.

Interpretation High-dose, standard-fractionated radiotherapy shows potential as the main postoperative treatment for patients with supratentorial malignant glioma.

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Introduction

Common treatment for newly diagnosed malignant glioma is resection to the maximum extent possible, followed by chemoradiotherapy.[1,2] Temozolomide has become a standard chemotherapeutic agent in Europe, Canada, and the USA,[3,4] whereas use of nimustine has been standard practice in Japan, despite the lack of definitive evidence.[5]

Malignant glioma cells are somewhat resistant to radiation and are highly invasive to surrounding healthy tissue.[6,7] Recurrence after initial radiotherapy is inevitable; the most common pattern of recurrence is regrowth at the primary location.[8,9] Undoubtedly, local tumour control is important for improving the survival of patients with malignant glioma.

Several reports[2,10,11] have suggested that survival of patients with malignant glioma depends on the total dose of the initial radiotherapy. An early report[10] showed that patients who received a median of 75 Gy (range 70–80) had significantly longer survival than did those who received a median of 50 Gy (50–55). A randomised control study[11] showed that 60 Gy lengthened survival by about 3 months compared with 45 Gy. However, a total dose of 60 Gy is regarded the limiting dose for the brain when delivered by the standard fractionation of 2 Gy per day.[12] Attempts to safely increase the total dose to beyond 70 Gy by use of hyperfractionation have not improved survival.[13–16]

Use of stereotactic radiosurgery before conventional radiotherapy did not improve the outcome of patients with glioblastoma,[17] and accelerated radiotherapy, in which 2-Gy fractions are given three times a day to a total dose of 30–60 Gy, or 1·5-Gy fractions are given twice a day to a total of 60 Gy, did not improve the outcome of patients with malignant glioma compared with those given conventionally fractionated radiotherapy.[18–20] These results, and the assumption that radiotherapy doses of higher than 60 Gy with standard fractionation would significantly increase morbidity, have prevented neuro-oncologists from using high-dose radiotherapy for patients with glioma in large-scale studies.[21]

Technological advances such as three-dimensional conformal radiotherapy have allowed minimum involvement of surrounding healthy tissue. Results of several

	Conventional radiotherapy		High-dose radiotherapy	
	Glioblastoma (n=60)	Anaplastic astrocytoma (n=34)	Glioblastoma (n=61)	Anaplastic astrocytoma (n=29)
Age				
Median (range), years	47 (15–77)	41 (15–71)	55 (15–76)	46 (15–73)
<50 years	32	25	25	19
≥50 years	28	9	36	10
Sex				
Women	24	13	21	7
Men	36	21	40	22
Karnofsky performance scale				
60–70	22	15	20	8
80–100	38	19	41	21
Tumour diameter				
Mean (SD), cm	4·3 (1·3)	4·4 (1·2)	4·6 (1·6)	4·5 (1·2)
<4 cm	36	19	29	14
≥4 cm	24	15	32	15
Tumour location				
Frontal	22	16	21	15
Temporal	16	10	24	7
Parietal	14	2	8	3
Occipital	5	1	7	3
Thalamus	3	5	1	1
Extent of resection				
<95%	39	17	35	14
≥95%	21	17	26	15
Chemotherapy				
Nimustine and vincristine	34	21	57	27
Nimustine	18	8	3	2
Carmustine	7	0	0	0
None	1	5	1	0
Repeat resection				
Yes	4	3	6	6
No	56	31	55	23
Salvage chemotherapy				
Interferon beta	1	5	3	0
Cisplatin and interferon beta	1	0	1	0
Intrathecal methotrexate	1	0	0	1
None	57	29	57	28

Data are number of patients unless otherwise indicated.

Table 1: Patient and tumour characteristics

small-scale studies[22–24] have suggested that high-dose radiotherapy (70–90 Gy) is tolerated well in patients with malignant glioma, and the frequency of cognitive impairment or necrosis was not notably raised in long-term survivors. Since 1990, we have been using radiotherapy with a total dose of 80–90 Gy, given with standard fractionation of 2 Gy per day, for all patients with supratentorial malignant glioma. We aimed to compare the outcomes of these patients with those who received the conventional 60 Gy radiotherapy given before 1990 at our institution.

Methods

Patients

We investigated 240 consecutive patients who had been newly diagnosed with glioblastoma or anaplastic astrocytoma according to WHO classification at University of Tokyo Hospital from 1979 to 2002, who met the inclusion criteria. Patients were included if they had histopathologically confirmed glioblastoma or anaplastic astrocytoma, were at least 15 years old, and had a Karnofsky performance scale of 60% or higher at the start of radiotherapy. Patients were excluded if they had secondary glioblastoma, chronic renal failure, restrictive pulmonary disease, or infratentorial or brainstem glioma (n=55), or chronic heart failure (n=1; died 2 months after surgery). All patients had maximum possible resection that avoided neurological worsening. Of 94 patients that received 60 Gy radiotherapy (conventional radiotherapy), 87 had craniotomy and seven had a biopsy; of the 90 patients that received high-dose radiotherapy, 87 underwent craniotomy and three had a biopsy before radiotherapy. The proportion of tumour volume resected was calculated from postoperative CT or MRI scan. With the exception of seven patients who refused chemotherapy, all patients received intravenous nimustine (Nidran®; Sankyo, Tokyo, Japan) or carmustine (BiCNU®; Bristol-Myers Squibb, New York, NY, USA) with or without vincristine (Oncovin®; Nippon Kayaku, Tokyo, Japan) during radiotherapy. All patients were assessed for the presence of radiation-induced toxic effects at follow-up examination by neurosurgeons. Written informed consent was obtained from all patients and from a member of their family before radiotherapy.

Radiotherapy

All treatments were planned on the basis of preoperative images, and done with a standard fractionation of 2 Gy per fraction per day for 5 days a week. Conventional radiotherapy started 7–21 days after surgery, and high-dose radiotherapy started 11–21 days after surgery. No patient died before the start of radiotherapy.

From 1979 to 1989, 60 patients with glioblastoma and 34 patients with anaplastic astrocytoma received conventional 60 Gy radiotherapy. Until 1984, patients received external-beam radiotherapy of 40 Gy to the whole brain followed by a local boost of 20 Gy (48 patients with glioblastoma and 18 patients with anaplastic astrocytoma). In 1984, a three-step cone-down technique was introduced, which was used in the remaining 12 patients with glioblastoma and 16 patients with anaplastic astrocytoma. Gross tumour volume was defined as the contrast-enhanced lesion depicted by contrast-enhancing CT scan or T1-weighted MRI (contrast-enhancing materials manufactured by Schering AG, Berlin, Germany, or Daiichi Pharmaceutical, Tokyo, Japan). Clinical target volume I was defined as the tumour, II as the tumour and surrounding oedema (high-intensity area on T2-weighted MRI) plus a 2-cm margin, and III as the whole brain. Planning target volume was defined as clinical target volume plus 0·5 cm for setup errors; thus, the margin with a setup error for planning target volume II was 2·5 cm. Planning target volume III was the whole brain plus 0·5 cm. The doses for planning target volumes I, II, and III were 60 Gy, 40 Gy, and 26 Gy, respectively.

From 1990 to 2002, 90 patients received high-dose radiotherapy with a total dose of 80 Gy or 90 Gy. Clinical target

volumes were modified and defined as tumour (I), tumour plus a 2-cm margin (II), and tumour and surrounding oedema plus a 2-cm margin (III). Planning target volume was defined as the clinical target volume plus 0·5 cm for setup errors. All 29 patients with anaplastic astrocytoma received 80 Gy radiotherapy: the doses of planning target volumes were 80 Gy, 60 Gy, and 40 Gy. Initially, patients with glioblastoma received a total of 90 Gy with planning target volumes of 90 Gy, 70 Gy, and 50 Gy (n=13). Because one patient showed grade-4 memory impairment, the total dose was reduced to 80 Gy for the subsequent 48 patients with glioblastoma, with planning target volumes similar to those for anaplastic astrocytoma. High-dose radiotherapy was done with the rotational conformal method, which uses a combination of coplanar gantry rotation and movement of a multileaf collimator.[25–27] The leaves were focused in two dimensions to avoid penumbra and moved independently from each other according to the gantry angles to create a dose distribution confined to the target volume. The area surrounding the target volume had a uniform gradient of dose fall-off.

Treatment lasted for 6 weeks in the 60-Gy group, 8 weeks in the 80-Gy group, and 9 weeks in the 90-Gy group. However, three patients in the 60-Gy group and two patients in the 80-Gy group had a 1-week interruption, and one patient in the 60-Gy group had an interruption of 2 weeks during treatment.

Follow-up

Follow-up CT or MRI scans were obtained at least every 4 months after radiotherapy; tumour progression and white-matter abnormalities were diagnosed on the basis of reports by neuroradiologists. Tumour progression was defined in accordance with MacDonald criteria.[28] Karnofsky performance scale was assessed for all patients. White-matter abnormality was defined as radiation necrosis, leucoencephalopathy, or brain atrophy. A contrast-enhanced lesion that appeared after radiotherapy on contrast-enhancing CT scan or T1-weighted MRI was diagnosed as radiation necrosis if a biopsy or resection sample showed a pathological diagnosis of radiation necrosis or if no uptake of fluorine-18 fluorodeoxyglucose or L-methyl-carbon-11 methionine could be seen on PET images.[29] PET has been done routinely on patients who developed contrast-enhanced lesions since 1990 at our institution.

Radiation-induced toxic effects were scored according to the common terminology criteria for adverse events (version 3.0).[30] Neurological symptoms that could not be explained by tumours were regarded as radiation-induced neurological deterioration.

Four independent neuropathologists reviewed the tumour histopathology of patients who survived for more than 20 months after radiotherapy to confirm the original diagnoses of glioblastoma or anaplastic astrocytoma. After tumour recurrence, patients were given further treatment at the discretion of treating doctors.

	Conventional (n=94)	High-dose (n=90)
Follow-up		
Median (range), months	7·7 (1·0–297·0)	15·5 (1·5–183·0)
Anaplastic astrocytoma		
Overall survival, months (median [95% CI])	22·3 (20·6–24·0)	Not reached
Progression-free survival, months (median [95% CI])	17·0 (12·8–21·2)	37·5 (NC)
5-year overall survival, % (95% CI)	14·7 (0·0–30·0)	51·3 (29·2–73·4)
2-year overall survival, % (95% CI)	44·1 (23·3–64·9)	78·1 (61·0–95·2)
Glioblastoma		
Overall survival, months (median [95% CI])	12·4 (10·0–14·8)	16·2 (12·8–19·6)
90-Gy group	NA	19·6 (13·3–25·9)
80-Gy group	NA	16·2 (12·6–19·8)
Progression-free survival, months (median [95% CI])	7·2 (4·0–10·4)	7·0 (5·0–9·8)
90-Gy group	NA	11·1 (3·0–19·2)
80-Gy group	NA	6·9 (5·5–8·3)
2-year survival, % (95% CI)	11·4 (0·0–25·3)	38·4 (23·5–53·3)
90-Gy group	NA	38·9 (8·5–69·3)
80-Gy group	NA	37·6 (20·4–54·8)

NC=not calculable. NA=not applicable.

Table 2: **Patient outcomes**

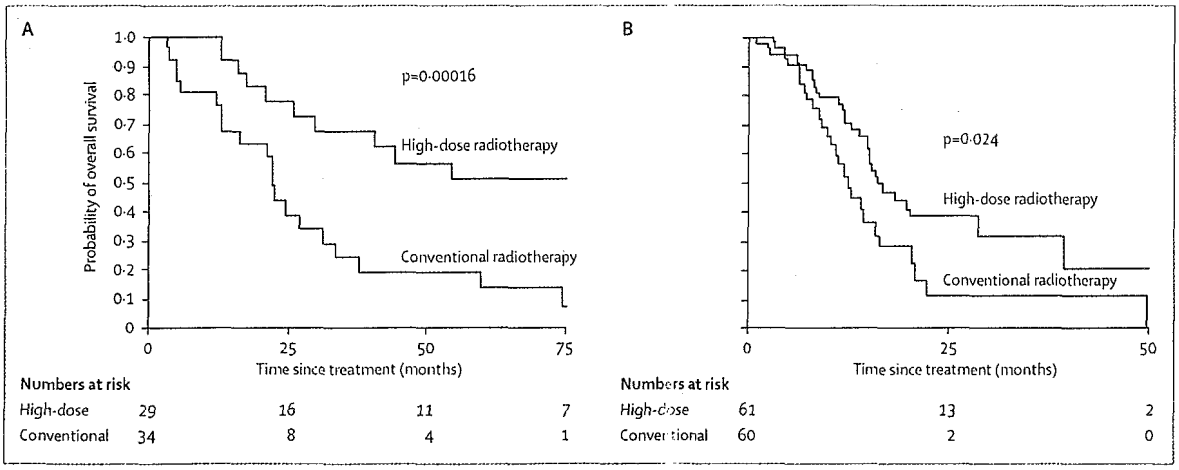

Figure 1: Kaplan-Meier estimates of overall survival according to radiation dose in patients with anaplastic astrocytoma (A) and glioblastoma (B)

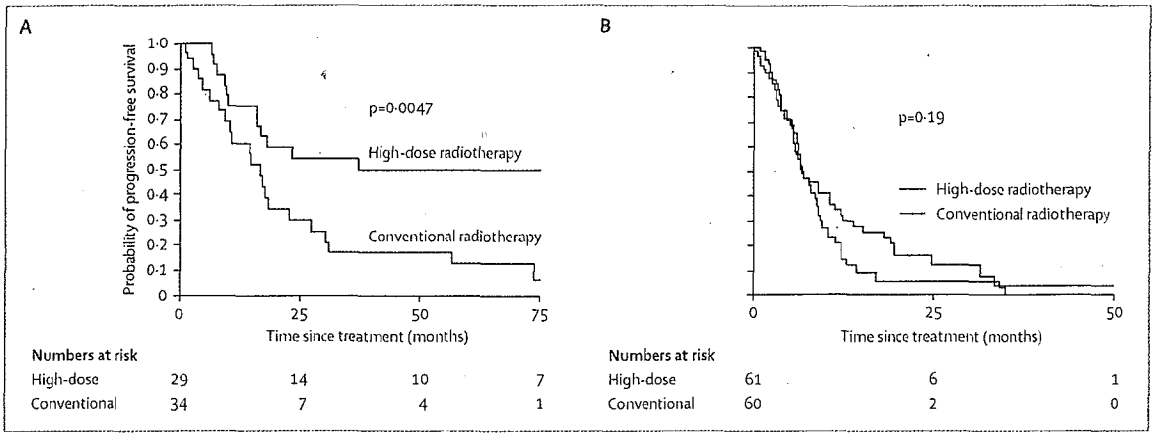

Figure 2: Kaplan-Meier estimates of progression-free survival according to radiation dose in patients with anaplastic astrocytoma (A) and glioblastoma (B)

Statistical analysis

Frequency distributions and summary statistics were calculated for all clinical and histological variables. χ^2 or Fisher's exact test were used for categorical variables, and the Kruskal-Wallis test for categorical continuous variables. Overall survival was calculated from the date of operation until the date of death or last follow-up, and progression-free survival until the date when recurrence was seen or until last follow-up. The Kaplan-Meier method was applied for survival analyses, and significance was calculated by the log-rank test. Cox's proportional hazard model was used to analyse prognostic variables and to ascertain the risk factors associated with time of onset of white-matter abnormality. Adjusted hazard ratios for death were calculated by adjustment for age, Karnofsky performance scale, tumour size, and extent of resection. Univariate and multivariate Cox regression analysis (with the entry cutoff level of p=0·05 and the stay cutoff of p=0·1) were used to assess the association of variables with survival or time to onset of white-matter abnormality. All data analyses were done with Dr SPSS II version 11.01 for Windows.

Role of the funding source

The funding sources had no role in study design; in collection, analysis, and interpretation of data; or in writing of the report. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Results

Table 1 shows the patient and tumour characteristics. The conventional group did not differ from the high-dose group in any of the characteristics listed. Median follow-up was 12·0 months overall (range 1·0–297·0; table 2).

Overall survival (figure 1), and 2-year and 5-year survival (table 2) were significantly improved in patients with anaplastic astrocytoma who received high-dose radiotherapy compared with those who received conventional radiotherapy. Median survival has not yet been reached in patients with anaplastic astrocytoma in the high-dose group. The adjusted hazard ratio for death in the high-dose group compared with the conventional group for patients with anaplastic astrocytoma was 0·30 (95% CI 0·12–0·76, p=0·011). These results were confirmed by sensitivity analysis that adjusted for the follow-up ranges.

In patients with glioblastoma, overall survival (figure 1), median survival, and 2-year survival (table 2) were significantly higher in the high-dose group than in the conventional group. The adjusted hazard ratio for death in the high-dose group versus the conventional group for patients with glioblastoma was 0·49 (95% CI 0·28–0·87, p=0·014).

However, the extra 10 Gy given to 13 of the 61 patients with glioblastoma who received high-dose radiotherapy did not result in a significant survival benefit compared with patients who received 80 Gy

	60 Gy		80 Gy		90 Gy
	Glioblastoma (n=60)	Anaplastic astrocytoma (n=34)	Glioblastoma (n=48)	Anaplastic astrocytoma (n=29)	Glioblastoma (n=13)
Any recurrence	39	22	37	12	10
Local recurrence only	32	16	26	5	4
Local recurrence and dissemination	7	6	11	6	0
Dissemination only	0	0	0	1	6

Data are number of patients.

Table 3: Recurrence by radiotherapy dose

	60 Gy (n=94)	80 Gy (n=77)	90 Gy (n=13)
Toxic effects			
Any	4	17	6
Cognitive dysfunction			
Grade 3	1	1	1
Grade 4	0	0	1
Memory impairment			
Grade 2	0	4	1
Grade 3	1	5	1
Grade 4	0	0	1
White-matter abnormality			
Radiation necrosis	0	7	2
Leucoencephalopathy	1	5	1
Brain atrophy	1	2	0
Time to onset (median [95% CI], months)	136·9 (NC)	32·5 (29·7–35·3)	24·8 (7·9–41·7)

Data are number of patients unless otherwise indicated. NC=not calculable. Some patients had more than one toxic effect.

Table 4: Radiation-induced toxic effects

(p=0·89, table 2). The unadjusted hazard ratio for death in patients with glioblastoma in the 90-Gy group relative to the 80-Gy group was 0·94 (95% CI 0·42–2·12, p=0·89) and the adjusted ratio was 0·70 (0·31–1·61, p=0·70).

Kaplan-Meier analyses based on the type of chemotherapy received showed that median survival for patients with anaplastic astrocytoma who received high-dose radiotherapy was not yet reached for those that received nimustine and vincristine, and was 40·6 months (95% CI not calculable because of small number of patients) for those who received nimustine alone (p=0·92). For the conventional radiotherapy group, median survival was 21·9 months (95% CI 14·2–29·6) for those on nimustine and vincristine, and 27·1 months (19·4–34·8) for those on nimustine alone (p=0·78). For patients with glioblastoma, median survival in the high-dose group was 15·8 months (13·4–18·2) for those on nimustine and vincristine, and median survival has not yet been reached in those receiving nimustine alone (p=0·29). In the conventional radiotherapy group, median survival was 15·9 months (8·3–23·5) and 12·1 months (7·5–16·7), respectively (p=0·24).

Progression-free survival was significantly lengthened by high-dose radiotherapy compared with conventional radiotherapy in patients with anaplastic astrocytoma, but not in those with glioblastoma (figure 2, table 2).

Most recurrences occurred at the primary site in both the conventional and 80-Gy groups (table 3). More local recurrences accompanied dissemination in the cerebrospinal fluid space in the 80-Gy group than in the 60-Gy group (p=0·14), and this trend was most notable in patients with anaplastic astrocytoma, although the numbers are small (table 3). Only one of 12 patients with anaplastic astrocytoma and none of 37 patients with glioblastoma who had recurrent disease after receiving 80-Gy radiotherapy had tumour dissemination in the cerebrospinal fluid space without local recurrence. By contrast, dissemination without recurrence was more frequent in patients with glioblastoma who received 90-Gy radiotherapy than in those who received 80 Gy (p<0·0001) or 60 Gy (table 3).

Table 4 shows the frequency and types of radiation-induced toxic effects recorded. The radiation-induced toxic effects that resulted from high-dose radiotherapy were generally tolerable. One patient who received 90-Gy radiotherapy developed grade-4 cognitive dysfunction and memory impairment, which led to reduction of the total dose to 80 Gy for patients with glioblastoma thereafter. None of these patients that received 80-Gy radiotherapy showed grade-4 toxic effects. White-matter abnormalities were significantly more frequent in the high-dose group than in the conventional group (p=0·0002, table 4). Nine patients in the high-dose group developed radiation necroses, compared with none in the 60-Gy group: five necroses were confirmed pathologically from surgical samples and four were diagnosed by PET. Four of these nine patients showed no neurological deterioration and maintained their active daily life after the diagnoses of radiation necrosis. One patient showed tumour recurrence 12 months after development of radiation necrosis. Kaplan-Meier analyses showed that, compared with the 60-Gy group, the median time to onset of white matter abnormality was significantly shorter for both the 80-Gy group (p=0·011) and the 90-Gy group (p=0·0043). Cox analyses showed that lower radiation dose was the only pretreatment clinical variable analysed that lengthened time to onset of white-matter abnormality (p=0·028).

	Hazard ratio (95% CI)	p
Univariate analyses		
Sex (women vs men)	1·51 (0·97–2·33)	0·067
Age (<50 years vs ≥50 years)	0·51 (0·32–0·80)	0·003
Histology (anaplastic astrocytoma vs glioblastoma)	0·43 (0·27–0·70)	0·001
Karnofsky performance scale (80–100 vs 60–70)	0·28 (0·18–0·44)	<0·0001
Tumour diameter (<4 cm vs ≥4 cm)	0·64 (0·42–0·98)	0·038
Tumour location		
Temporal vs frontal	1·14 (0·68–1·91)	0·61
Parietal vs frontal	1·22 (0·65–2·31)	0·52
Occipital vs frontal	0·96 (0·46–2·02)	0·92
Thalamus vs frontal	2·06 (0·85–5·00)	0·11
Extent of resection (≥95% vs <95%)	0·34 (0·21–0·55)	<0·0001
Chemotherapy (yes vs no)	0·81 (0·33–1·99)	0·64
Radiation dose (high dose vs 60 Gy)	0·49 (0·33–0·76)	0·001
Repeat resection (yes vs no)	0·39 (0·16–0·69)	0·003
Salvage chemotherapy (yes vs no)	0·72 (0·35–1·49)	0·38
Multivariate analyses		
Histology (anaplastic astrocytoma vs glioblastoma)	0·41 (0·25–0·67)	<0·0001
Karnofsky performance scale (80–100 vs 60–70)	0·39 (0·23–0·66)	<0·0001
Extent of resection (≥95% vs <95%)	0·41 (0·24–0·72)	0·002
Radiation dose (high dose vs 60 Gy)	0·42 (0·26–0·68)	<0·0001
Age (<50 years vs ≥50 years)	0·72 (0·43–1·23)	0·23
Tumour diameter (<4 cm vs ≥4 cm)	0·95 (0·56–1·62)	0·86
Repeat resection (yes vs no)	0·48 (0·22–1·02)	0·055

Table 5: Univariate and multivariate analyses for favourable prognostic factors

Univariate Cox analyses showed that seven of 11 clinical factors analysed were associated with favourable prognosis: age younger than 50 years, anaplastic astrocytoma histology, Karnofsky performance scale of at least 80%, tumour diameter of less than 4 cm, tumour removal of at least 95%, radiation dose of 80 Gy or higher, and repeat resection (table 5). Stepwise multivariate analyses showed that independent factors associated with favourable prognosis were histology of anaplastic astrocytoma, Karnofsky performance scale of at least 80%, tumour resection of at least 95%, and radiation dose of 80 Gy or more (table 5). Age of younger than 50 years was found to be an independent favourable prognostic factor only for the 60-Gy group (hazard ratio 0·32 [95% CI 0·14–0·73], p=0·007) when the 60-Gy and high-dose groups were analysed separately.

Discussion

Our results show that high-dose radiotherapy of 80–90 Gy delivered by a standard fractionation provides a significant survival benefit over standard 60-Gy radiotherapy for patients with supratentorial malignant glioma, without notable increases in radiation-induced disability. The efficacy of conventional radiotherapy of more than 70 Gy for malignant glioma has never been investigated in a multi-institutional randomised-controlled study, because of the general assumption that toxic effects to the brain induced by the radiation dose would outweigh the advantages.[21] The two groups compared in our study, both of which consisted of consecutive eligible patients, did not vary significantly from each other, with the exception of the radiotherapy approaches, since radiotherapeutic techniques have become more sophisticated over time. The survival benefit was most evident in patients with anaplastic astrocytoma. The survival results we recorded for high-dose radiotherapy are comparable with the best treatment outcomes reported to date for anaplastic astrocytoma.[31,32]

Furthermore, median survival and 2-year survival were higher for patients with glioblastoma who were given high-dose radiotherapy than for those given conventional radiotherapy. As expected,[33,34] we noted that radiation-induced white-matter abnormality was significantly more frequent, and the time to onset shorter, with high-dose radiotherapy than with conventional radiotherapy; however, radiation necroses were controllable by steroid administration or surgery. The frequency of impairment to cognition or memory was not significantly increased by the raised dose, and high-dose radiotherapy was generally tolerated well by patients with malignant glioma, which is in agreement with others' findings.[22–24] In support of our findings, Shrieve and colleagues[35] showed that a radiosurgical boost after conventional radiotherapy in 78 patients with glioblastoma resulted in median survival of 19·9 months (95% CI 18·2–23·0) in patients with glioblastoma, even though 39 (50%) patients needed reoperation and 20 (51%) patients who had a reresection had radiation necrosis without evidence of tumour. A concern remains that intensified radiotherapy treatment could lead to long-term effects on cognitive functions that seriously affect quality of life, although this concern is yet to be investigated through careful follow-up of long-term survivors. A randomised trial[4] in patients newly diagnosed with glioblastoma showed that use of temozolomide during and after conventional radiotherapy improved median survival from 12·1 months (11·2–13·0) in those given radiotherapy alone to 14·6 months (13·2–16·8) in those receiving radiotherapy with temozolomide. In our study, use of nimustine-based chemotherapy did not significantly affect prognosis. Potentially, concomitant chemotherapy with temozolomide could further improve the survival benefit obtained by the high-dose radiotherapy.

As to the mechanism of the favourable outcome with high-dose radiotherapy: more patients in the high-dose group than in the conventional group showed dissemination in the cerebrospinal-fluid space, with six of ten patients with glioblastoma who recurred after 90 Gy radiotherapy showing dissemination without local failure, suggesting that tumour regrowth at the primary site is suppressed more efficiently by high-dose radiotherapy than by 60-Gy radiotherapy. Furthermore, in support of our findings, Nakagawa and colleagues[25] showed that 90 Gy radiotherapy in patients with glioblastoma resulted in significantly fewer local failures at the time of recurrence compared with the low-dose radiotherapy group. The high rate of dissemination at recurrence in the high-dose group seems paradoxical, but it should be noted that time to recurrence was significantly longer for patients with anaplastic astrocytoma who received high-dose radiotherapy than for those who received conventional radiotherapy. However, because this finding was from a small number of patients, it could be an artifact. Although many of the patients in our study had extensive removal of the tumour (≥95%), the survival benefit from high-dose radiotherapy was also seen in patients that had less than 95% of the tumour removed when Kaplan-Meier analyses were done separately for subtotal and partial resection (data not shown). This finding suggests that extensive tumour reduction is not needed for patients to benefit from high-dose radiotherapy, whereas it is an independent predictor of good prognosis. Patients with glioblastoma who received high-dose radiotherapy had longer overall survival but similar progression-free survival as did those who received conventional radiotherapy, suggesting that recurrent lesions detected by radiological images after high-dose radiotherapy require longer to cause death than do those seen after 60 Gy radiotherapy.

By contrast with our findings, Chan and co-workers[22] reported that a dose-escalation from 70–80 Gy to 90 Gy did not change survival or patterns of local failure in 34 patients with malignant glioma. An important feature of our high-dose conformal radiotherapy technique that might have affected outcome was that treatments were planned with preoperative CT or MRI scans, and treatments therefore did not take account of the extent of tumour resection. Furthermore, the initial planning target volume included the surrounding oedema plus a 2-cm margin. Many radiotherapy trials for malignant glioma have restricted their planning target volumes to the contrast-enhanced lesion plus a margin, because most patients who receive treatment have local failure, and to lessen radiation-induced toxic effects.[20,22,23,36–38] However, glioma cells are known to migrate along myelinated fibre tracts of the white matter and penetrate to the so-called surrounding oedema depicted on CT or MRI scans,[9] and proton magnetic-resonance spectroscopy has shown that malignant glioma can extend beyond the areas of T2-weighted signal changes on MRI.[40] For these reasons and because high-dose radiotherapy is tolerated well by patients with malignant glioma, inclusion of the regions of surrounding oedema plus a margin in the planning target volume could be important to obtain good local control.

Although new therapeutic approaches are being developed, radiotherapy remains the main postoperative treatment for malignant glioma. Our findings suggest that high-dose conformal radiotherapy with standard fractionation results in a significant lengthening of survival of patients with malignant glioma compared with conventional 60 Gy radiotherapy, without significantly increasing radiation-induced disabilities. If confirmed in correctly powered phase III trials with appropriate integration of systemic antitumour agents, 80 Gy conformal radiotherapy should be regarded as a standard postoperative treatment for supratentorial malignant glioma.

Contributors

M Tanaka analysed data and wrote the initial draft. Y Ino, K Nakagawa, and M Tago contributed to data collection. T Todo analysed and interpreted data, and wrote the article.

Conflict of interest

We declare no conflicts of interest.

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Clinical Study

Pathological changes after radiotherapy for primary pituitary carcinoma: a case report

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Key words: MIB-1 LI, pituitary carcinoma, PRL-producing, radiotherapy, tunnel stain

Summary

Pituitary carcinomas are extremely rare. The definition, diagnosis, therapy, and prognosis are controversial. So far, to our knowledge, there has been no report regarding pathological changes after radiotherapy for primary pituitary carcinoma. We reported a single case of a presumed prolactin staining pituitary carcinoma. We defined carcinoma by premorbid intracranial dissemination of the tumor. There were no proven extracranial metastases. The tumor was silent on PET scanning. The patient received external beam radiotherapy alone as primary therapy. Post-irradiation histology revealed that necrotic tissue made up approximately more than half. Tumor had viable cells. Probably approximately three-fifth of tumor cells were without alteration and approximately two-fifth were with degeneration. We confirmed that necrosis but no apoptosis were coexistent in the cells post irradiation for pituitary carcinoma.

Introduction

Malignant pituitary tumors (carcinomas), currently defined as primary adenohypophyseal neoplasms with evidence of metastatic spread, are quite uncommon and exceptionally rare. Silent corticotroph carcinomas of the pituitary gland represent 0.05% of adenohypophyseal tumors surgically treated at Mayo Clinic during a 20-year period and about 5% of all reported pituitary carcinomas [1]. Defined as tumors having metastasized, primary carcinomas of the pituitary gland represent 0.2% of all surgically treated adenohypophysial neoplasms [2, 3].

As part of initial treatment for pituitary carcinoma, X-ray radiotherapy (RT) was often selected. But so far there has been no report concerning pathological changes after RT. A PRL-secreting pituitary carcinoma is reported with emphasis on pathological changes after RT.

Case report

Presentation and treatment

The patient was a 30-year-old woman. She had noticed irregular menstruation (amenorrhea) in September 2002. She rushed to the Hospital on 20 August 2003, with a severe headache, right eye pain, and a narrow visual field.

Preoperative blood examination

Serum levels were sodium (Na): 132 mEq/l (low, 132–148 mEq/l), PRL: 55.9 ng/ml (high, 0–30 ng/ml), Cortisol (CS): 3.4 μg/dl (low, 4.0–23.3 μg/dl), and free triiodothyronine (FT3): 1.87 pg/ml (low, 2.8–4.5 pg/ml), TSH: 0.01 μU/ml (low, 0.49–3.83 μU/ml), thyroxine (T4): 7.94 μg/dl (normal, 5.71–10.11 μg/ml), triiodothyronine (T3): 0.90 ng/ml (low, 0.92–1.54 ng/ml), free thyroxine (FT4): 1.55 ng/dl (normal, 0.8–1.72 ng/dl), FSH: 1.0 mIU/ml (low, 1–17 mIU/ml), LH: 0.2 mIU/ml (low, 1–22 mIU/ml), GH: 1.29 ng/ml (normal, 0.28–8.7 ng/ml), aldosterone (ALDS): 5.6 ng/dl (normal, 2–13 ng/dl), somatomedin C (SM-C): 288 ng/ml (normal, 121–436 ng/ml), antidiuretic hormone (ADH): 0.15 pg/ml (low, 0.3–4.2 pg/ml), ACTH: 5 pg/ml (low, 7.0–56.0 pg/ml), and glucagon (IRG): 81 pg/ml. Then adrenocortical steroid drug (hydrocortisone, Cortril®: 20 mg/day), thyroid hormone drug (levothyroxine sodium, T4, Thyradin S®: 50 μg/day), potassium chloride drug (Slow-K®: 600 mg/day), and anti-epilepsy drug (sodium valproate, Depakene R®: 400 mg/day) were administered through mouth.

Preoperative radiological examination

Computed tomography (CT) and magnetic resonance imaging (MRI) revealed a large cystic tumor located from sella turcica to suprasella. First of all, craniopharyngioma was suspected, and the treatment method of surgical mass reduction followed by RT was planned. On September 1, tumor resection was tried by interhemispheric approach.

Intraoperative finding

The tumor appearance was pinkish and it looked like vascular tumor. The tumor was soft like rubber and easy to bleed. So it was hard to resect widely and was resected just only to the extent of biopsy, hence postoperative CT and MRI in August 22nd revealed no remarkable change. A state of mania, disorientation and a lowering of encoding efficiency had appeared since then. CT of

the brain in August 29 revealed the pituitary tumor was enlarged rapidly (although we might possibly see the bleeding within tumor). She had disorientation of time and place. Her visual field was normal and her eye movement was full.

Serum levels of such tumor markers as α-fetoprotein, carcinoembryonic antigen, carbohydrate antigen (CA) 15–3, CA125, squamous cell carcinoma, neuron specific enolase, and CYFRA (CK 19 fragment) were all within normal limits. Urine analysis revealed that 17-KS was 1.3 mg/day (low, 2.4–11.0 mg/day), and 17OHCS, U-CS, U-ALDS, and U-TAT were within normal limits.

Postoperative and preradiation radiological examination
MRI of the brain in 1 September 2003 revealed there was a well enhanced mass (30 × 27 × 29 mm) in supresellar region containing a necrotic structure (Figure 1). CT of the chest in September 3, 2003 revealed there was no obviously abnormal finding in the bilateral lung. F-18 fluoro-deoxy-glucose (FDG) positron emission tomography (PET) in 18 September 2003 revealed there was hardly uptake in her pituitary and this result indicated this disease was a typical pituitary adenoma rather than carcinoma. Additionally there was no highly uptake region in her whole body. We searched metastatic lesion and primary lesion to suspect this pituitary tumor was a metastatic tumor, but CT of the abdomen and pelvis, ultrasonography (US) of the mammary gland, US of the thyroid gland, and F-18 FDG PET indicated no evidence of systemic disease. Since the outcome of F-18 FDG PET was negative and hemoccult test was negative in addition to her own bad compliance, we didn't perform fiberscope of the upper and lower digestive tract. We carried forward the treatment regarding as solitary pituitary tumor.

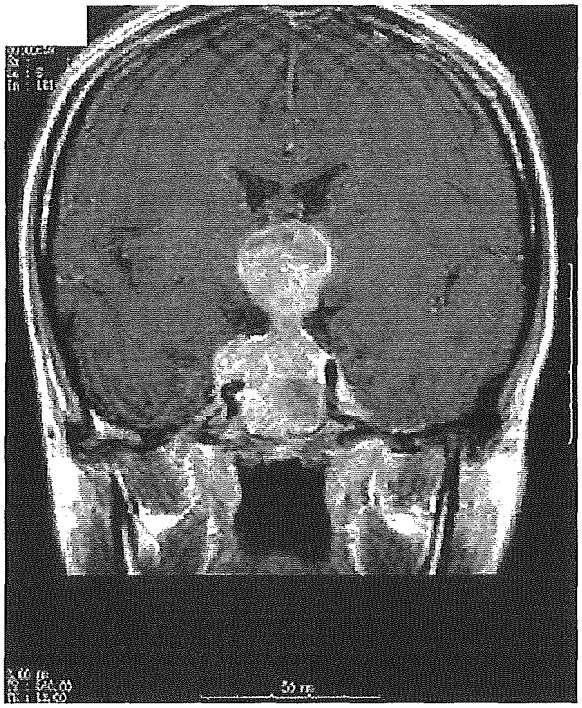

Figure 1. MRI of the brain (coronal, T1-weighted), with gadolinium enhancement before RT. There was a tumor from clivus to sella turcic and suprasellar region with internal necrosis or cystic component. was a slight segmented tumor. Its diameter was 3.5 × 3 × 6.5 cm. Th solid component was enhanced highly. In the right side, it also invade cavernous sinus and encased right distal internal carotid artery. The was an epidural hematoma just under frontal craniotomy region. Th postoperative change along with dura was remarkable too. There w no hydrocephalus.

Pathological finding of surgical specimen
Tissue sections were stained with hematoxylin and eosin (H & E) (Figure 2). The diagnosis was the specimen which had tumor tissue with severe heterotype originated in pituitary anterior lobe gland and these histological features were consistent with pituitary carcinoma. Histologically, relatively small tumor cells with atypical nucleus whose body was clear were proliferous solidly . Cellularity was high. Bizarre nucleus and the image of nuclear fission were also outstanding. Additionally, bleeding was accompanied. Hemosiderin deposition was seen in places. In the region where the atypical was relatively weak, reticular structure, which was origin from pituitary, was also seen.

Immunohistochemically, tumor cell was epithelial membrane antigen (EMA): negative, keratin: infinitesimally partially positive, Vimentin: partially positive, LCA: negative, aynaptophysin: positive, chromogranin A: negative, glia fibrillary acidic protein (GFAP): negative (positive in cerebral tissue), MIB-1 (antigen Ki-67) labeling index (LI): 24.1% (proliferation indices were calculated as the percentage of labeled tumor nuclei per total tumor nuclei counted, in the area of greatest tumor labeling) (Figure 3), p53 expression: negative, p21 expression: negative, tunnel: negative, PRL: weakly positive in part, and mitoses (mitotic activity was evaluated at 400× magnification and expressed as number of mitoses per 10 high power fields): 3 × 10 HPF. The stain pattern of epithelial marker was slightly atypical but the findings indicated the tumor was carcinoma originated in neuroendocrine.

Radiation therapy
The patient then underwent dynamic conical conformal radiotherapy (total: 60 Gy, 2 Gy/fraction) using a c-arm-mounted for the sellar and parasellar area in order to control the tumor from 19 September 2003 to 11 November 2003 (Figure 4). At the beginning, we examined combined chemotherapy, but gave it up because of her bad compliance.

Tumor reaction during RT
In 23 September 2003, right palpebra drooping, right miosis, and right external ophthalmoplegia began to worsen. We thought due to direct compression by the tumor in right cavernous sinus, palsy of right oculomotor nerve and trochlear nerve developed. However as the treatment goes on, in mid-October the symptoms improved slowly.

CT in 3 October (at 20 Gy) revealed the tumor became larger slightly compared with CT in 17 September. CT in 17 October (at 38 Gy) and 31 October (at 58 Gy) revealed the cystic component expanded and the tumor had a tendency to become larger slightly.

Acute adverse reaction by RT to become an issue didn't occur.

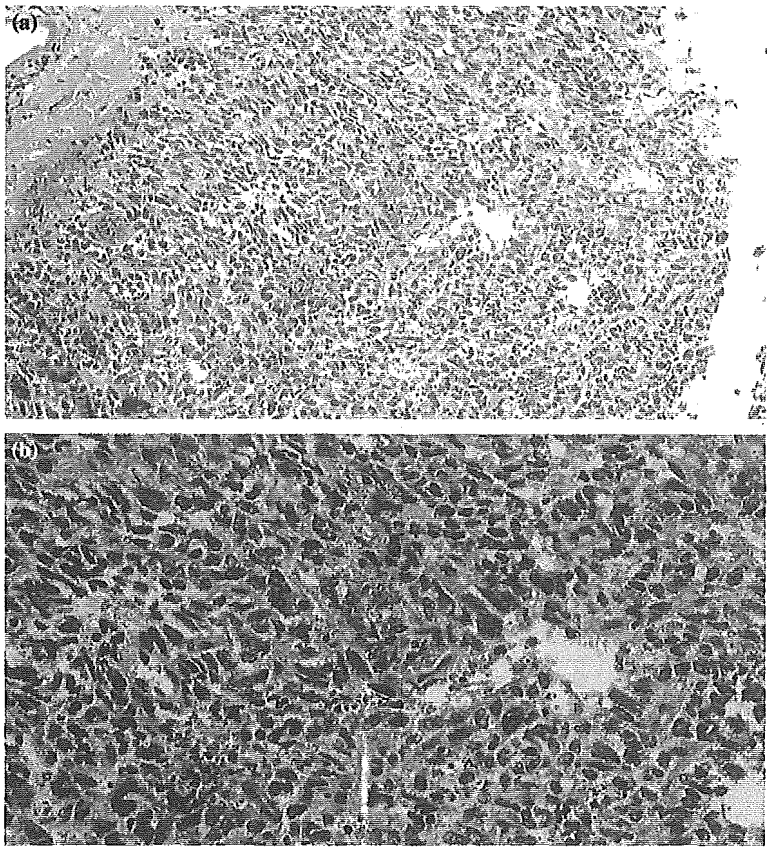

Figure 2. Pathological findings of pituitary biopsy specimen before RT. The primary tumor is composed of monomorphic cells showing mild to moderate nuclear pleomorphism [hematoxylin and eosin, (a) 20×; (b) 40×].

Easy fatigability and hypotension continue from hospitalization day due to lowering of the adrenal cortex function following lowering of the pituitary function. So in October 20, we increased the dose of adrenocortical steroid drug (hydrocortisone, Cortril®) from 20 to 30 mg/m^2. After that, systolic pressure increased up to the normal level. Easy fatigability improved too. The state of mania and disorientation, which appearing after surgery, also became better slightly during her admission.

Postradiation radiological finding

According to MRI in 6 November (on the 2nd day after the completion of RT), regarding the tumor with internal necrosis or cystic component located from clivus to sella turcica and suprasellar region, cystic lesion enlarged slightly but solid lesion itself tended to become smaller, and the enhanced lesion paralleled with left cerebral falx also tended to become better slightly, and hydrocephalus could not be seen.

Reoperation

In 30 March (on the approximately 5th month after the completion of RT), she received transnasal tumor resection to depress intracranial pressure. Its histology revealed that necrotic tissue made up approximately more than half. Tumor had viable cells. Probably

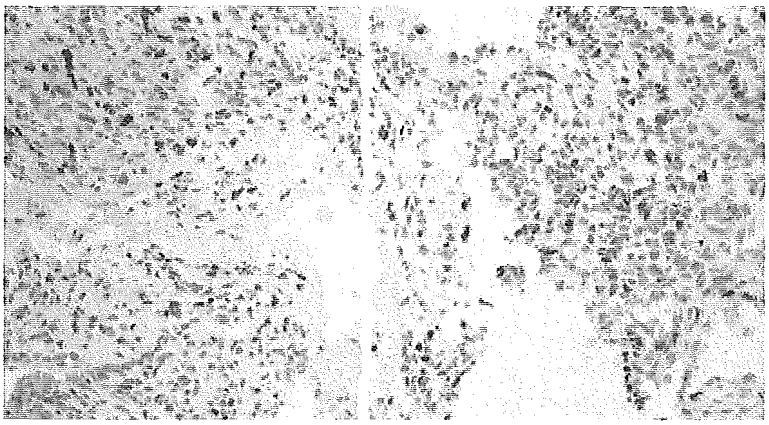

Figure 3. MIB-1 immunostaining of pituitary biopsy specimen before RT, 20×. MIB-1 LI = 24.1%. Proliferation indices were calculated as the percentage of labeled tumor nuclei per total tumor nuclei counted, in the area of greatest tumor labeling.

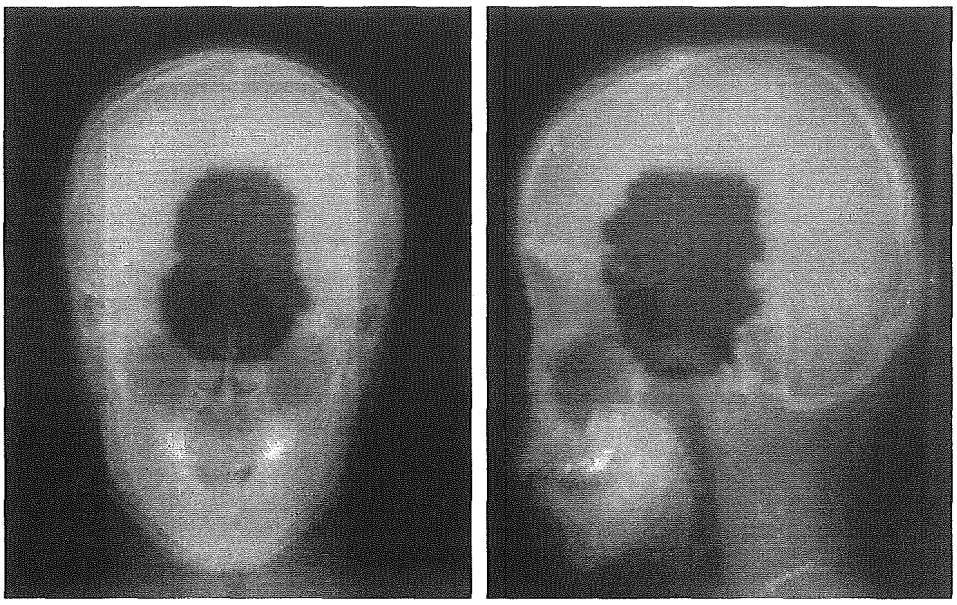

Figure 4. Linacgram (one monitor unit irradiation) in dynamic conical conformal radiotherapy using a c-arm-mounted for the sellar and parasellar area. [(1) anterior-posterior direction; (2) lateral direction.]

approximately three-fifth of tumor cells were without alteration and approximately two-fifth were with degeneration (Figure 5). Immunohistochemically, there was no remarkable change in p53, p21, chromogranin A, PRL, MIB1-LI, and tunnel.

On the sixth month after RT, tumor around cavernous sinus grew bigger and she became completely blind. In May 24, she received transnasal ventriculo-peritoneal shunt surgery for hydrocephalia. Its histology revealed that it was a fibro-fatty tissue accompanied with bleeding. The tumor cell was hyperchromatic and short of cellularity. Such tumor cell was proliferating with remarkable bleeding necrosis. Although there were many cells that had changed into degeneration and necrosis, viable tumor tissues remained to be seen. The morphology was similar to the previous findings.

Dissemination and death

MRI in 11 June (Figure 6) revealed that band of enhanced lesions in midbrain, pons, medulla, and the surface of bilateral temporal lobe were recognized, which was thought of as meningeal seeding. Enhanced nodule was recognized at the bottom of the left temporal lobe too, which was thought of as metastasis.

At June 22, she died of brain symptom. Survival time from present to death was approximately 10 months.

Discussion

Pituitary carcinomas are rare neoplasms distinguished from invasive adenomas by the presence of craniospinal and/or systemic metastases. Also in our case, intracranial metastases were recognized at 10 months after the onset of symptoms.

In this case, the histological change after RT was thought of as an influence from RT not surgery nor natural course of the tumor. On the approximately 5th month after completing RT, its histology revealed that necrotic tissue made up approximately more than half.

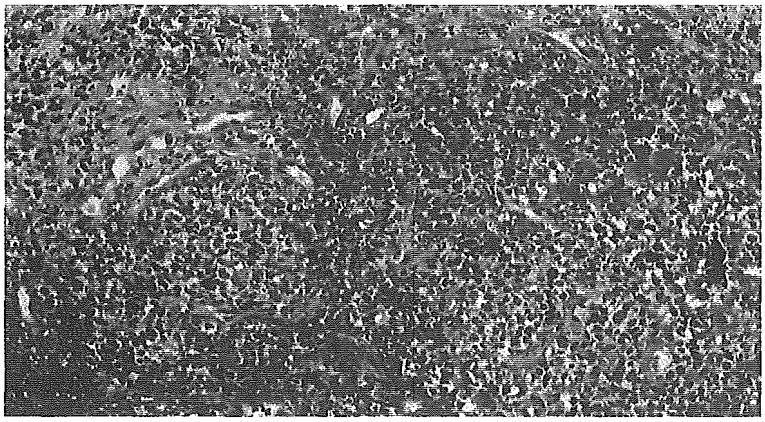

Figure 5. Pathological findings of pituitary biopsy specimen after RT. Necrotic tissue made up approximately more than half. Tumor had viable cells. Probably approximately three-fifth of tumor cells were without alteration and approximately two-fifth were with denaturalization (hematoxylin and eosin).

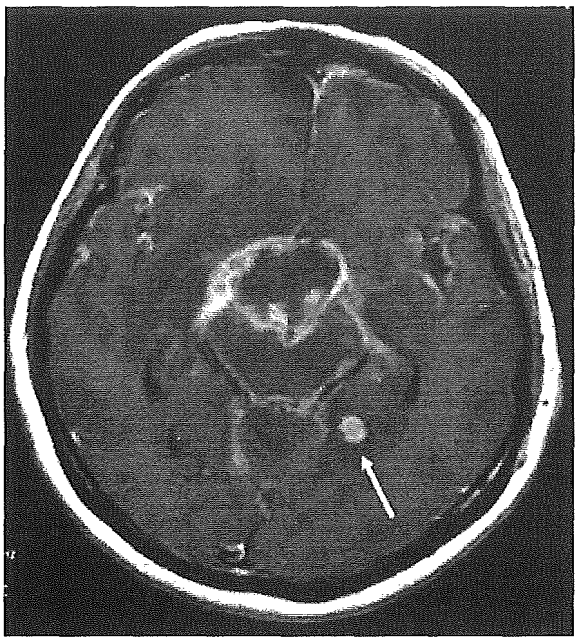

Figure 6. MRI (axial, T1-weighted), with gadolinium enhancement on the 10th month after completing RT. Band of enhanced lesions in midbrain, pons, medulla, and the surface of bilateral temporal lobe were recognized, which was thought of as meningeal seeding. Enhanced nodule was recognized at the bottom of the left temporal lobe too, which was thought of as metastasis (*arrowhead*).

But viable cells were also residual in two-fifth of tumor cells. Additionally we performed tunnel stain in order to detect the presence of plasmotomy and injury of nuclear DNA. In the nucleus of postirradiated cells, tunnel stain remained to be negative. It was confirmed by using tunnel stain that the cells lapsing into apoptosis didn't increase and in other words this state of post irradiation cell wasn't a cell death caused by apoptosis. Necrosis post irradiation occurred but it wasn't confirmed that the phenomenon of apoptosis happen actually.

In our case, serum PRL level before treatment was slightly high. Additionally immunohistochemically, PRL was weakly positive in part of the tumor. Our tumor may be a PRL-producing pituitary carcinoma. Fifty-two cases, which have been reported in the literature published in English to date, include 30% PRL-producing tumors [2]. Pernicone et al. [2] reported that patients with PRL cell tumors presented most commonly with headache and visual field deficits and amenorrhea and galactorrhea were noted in one each out of 7 patients. Our case also presented with amenorrhea, a severe headache, and a narrow visual field.

Expression of the Ki-67 antigen, which occurs during the S, M, and G1 phases of the cell cycle and is demonstrated with the MIB-1 antibody (which detects a nuclear antigen expressed by proliferating cells during the entire cell cycle), was quantified in the primary tumors. Indices of MIB-1 were often high (< 1–40%) in carcinomas [1, 2, 4–7]. The values obtained for our patient indicate above-average labeling for the primary tumor, which correlates well with the rapid growth of the metastasis.

Because such labeling indices do not account for ongoing apoptosis in tumors and are subject to variations in technical interpretation and to sampling errors, they are better used as predictors of tumor behavior for populations of patients, rather than predictors of the behavior of any particular tumor.

In a large series of pituitary tumors, including non-invasive and invasive adenomas as well as carcinomas, Thapar et al. [4] reported significant differences in MIB-1 mean LI. Aside from considerable case-to-case variations, these authors established a cutoff value of 3% to separate indolent adenomas from ones exhibiting more aggressive behavior. This threshold is generally viewed as a reliable indicator of clinical outcome [4].

Abnormal accumulation of p53 protein was not observed in our case. The p53 tumor suppressor gene is thought to play a role in the development or evolution of adenohypophysial neoplasms. Deletion of one gene copy and/or mutation of the remaining copy interferes with its normal suppressive activity and has been found to occur in a variety of neoplasms, including colorectal, brain, breast, lung, bone, soft tissue, testis, and bladder tumors [8, 9]. A recent study from a laboratory demonstrated p53 overexpression in most pituitary carcinomas [10]. Pituitary carcinoma lacking accumulation of p53 protein is very rare, only three such cases being previously reported, but may occur in the absence of p53 accumulation [11].

Pituitary carcinomas are associated with a poor prognosis. They often undergo extensive dissemination, exhibit a poor response to radiation and chemotherapy, and result in death within 1 year of diagnosis. The literature further suggests that patients with systemic disease have poorer survival than those with craniospinal spread. Clinically non-functionally pituitary carcinomas occasionally demonstrated synchronous presentation [12, 13] but otherwise exhibited intervals to metastasis ranging from 2 months [14] to 148 months [15]. The survival times after initial presentation also varied widely. The longest surviving patient reported was still alive 72 months after diagnosis of the metastasis [16], but several patients survived 6 months or less after the onset of metastasis [17, 18]. Once metastases occurred, the new carcinomas were rapidly fatal; the mean survival period was 2.6 years in patients with craniospinal metastases, usually to the subarachnoid space or dura, and 1 year in those with extraneural spread, usually to liver, bone, and lung [3]. In our case, survival time from present to death was approximately 10 months and survival from the onset of dissemination to death was a few weeks, which was shorter than most of previous reports.

The only pituitary carcinomas previously demonstrated in radionuclide scans included one GH-secreting tumor and two prolactin-secreting tumors [19–21]. In our case, the PET study before treatment revealed that no uptake was detected in the pituitary carcinoma. We surmise that because in our case the tumor had a lot of liquid and interstitial component, that is, necrotic and cystic component and little material part according to histopathology, in the PET the uptake of the tumor was remarkably lower than that of surrounding normal brain tissue.

Pituitary carcinomas can follow unpredictably indolent or fulminant courses. Tailoring appropriate therapy

for individual patients can therefore be difficult. Cytotoxic chemotherapy in setting has been reported by others but has demonstrated limited success in controlling tumor growth or hormonal hypersecretion. Because no standard regimen exists, a number of drugs have been tested, in a variety of combinations. No objective response was achieved in the majority of cases. RT generally provides only palliation. In our case, because the lesion was confined to the pituitary without systemic metastasis and the patient compliance was poor, the patients did not receive chemotherapy.

In our pituitary carcinoma, MIB-1 LI was relatively high (24.1%), pathologically approximately 2/5 of tumor cells were viable cells even after RT (60 Gy in 30 fractions) and survival time was very short (approximately 10 months). Probably this was not independent.

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