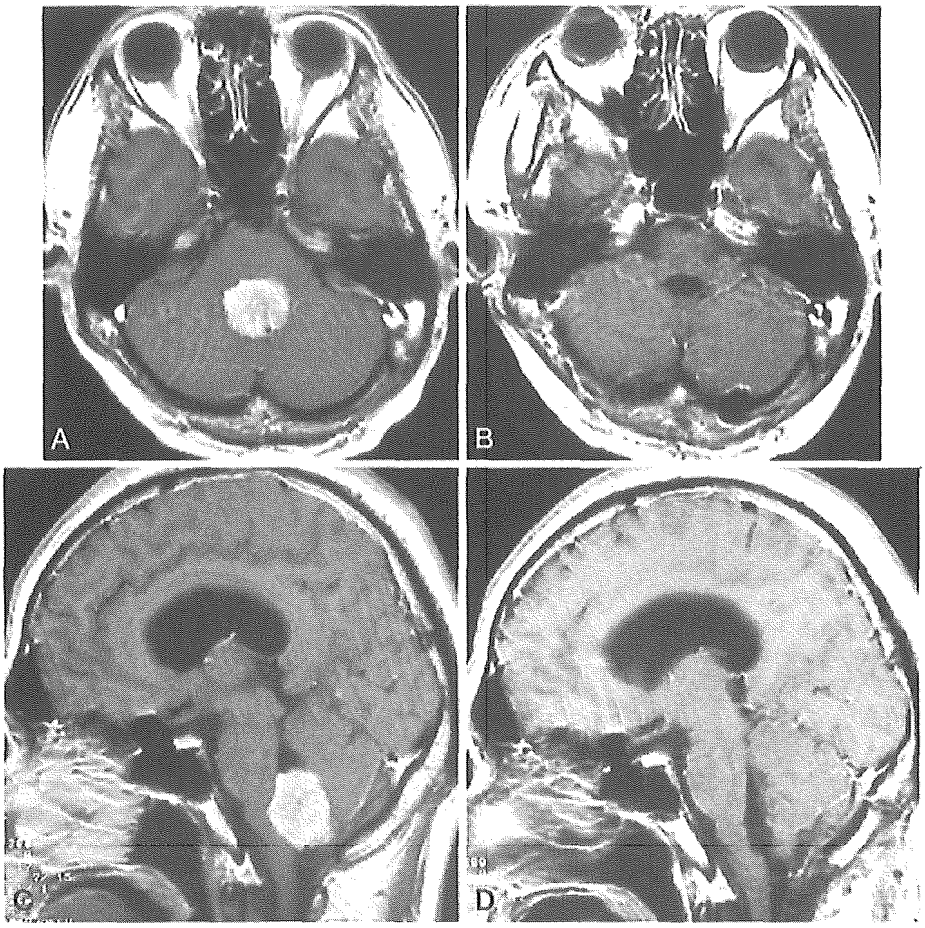


Fig. 4 Case 4, a 37-year-old male with choroid plexus papilloma. Magnetic resonance (MR) imaging with gadolinium (**A**: axial, **C**: sagittal) showed an enhanced mass in the fourth ventricle. The tumor was totally resected (**B**: axial, **D**: sagittal) and he remained in good condition with no deficit.

り初回手術で部分摘出に終わった29歳女性の症例（Case 3）においてのみ，術後に局所60 Gyの照射とACNUによる化学療法を追加した．この症例以外のCPPに対しては補助療法を行っていない．

これら7症例の観察期間は21～140カ月で平均63.0カ月であった．予後については，生存例は7例中6例で，死亡例は1例であった．死亡例は脳幹に浸潤した第4脳室発生のCPPの症例（Case 3）で，初期治療後4年で再発を生じたため2回の追加切除を行ったが，脳幹部病変の増大と頸髄への播種病変により81カ月で窒息死している．後遺障害としては，側脳室発生の2カ月男児のCPC例（Case 5）が発育遅延を来したことと，延髄から上位頸髄に浸潤した領域を全摘出した3歳男児のCPC例（Case 6）が術前からの嚥下障害が残存していることが挙げられる．これら以外の4症例については神経学的脱落症状のない状態で生存中である．

III. 考　察

CPTは全頭蓋内腫瘍の0.4～1.0%程度と稀な腫瘍である[3,15,22,24]．男女比については，一般にCPPでは性差はないとされるが[13,15]，CPCでは89%が男性だったとする報告もある[15]．好発部位は小児では側脳室，成人では第4脳室が多いが

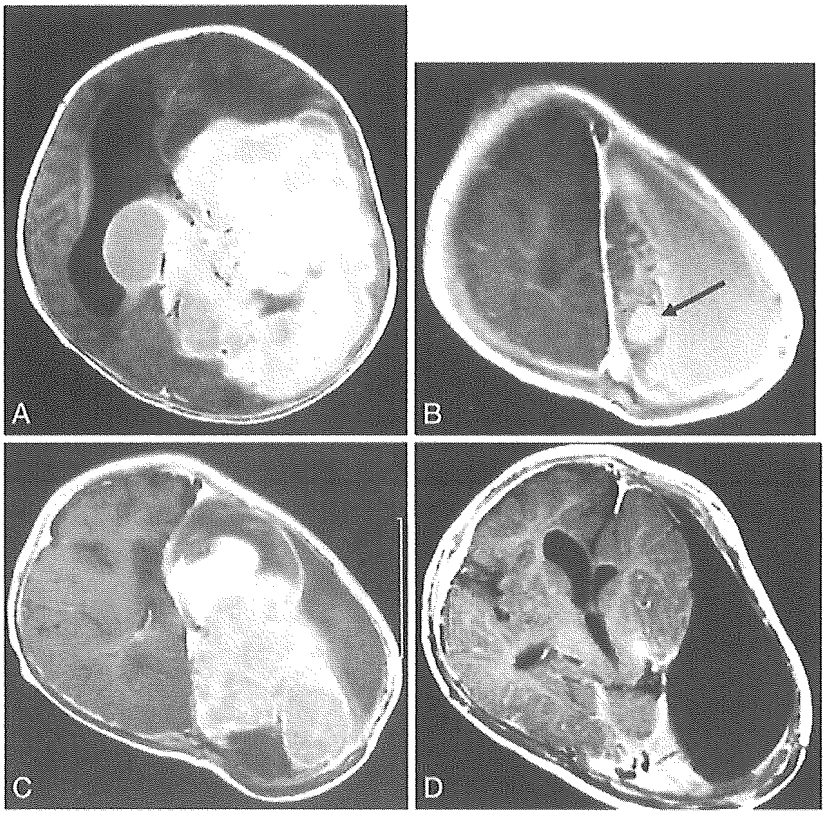


Fig. 5 Case 5, a 2-month-old boy with choroid plexus carcinoma. Magnetic resonance (MR) imaging with gadolinium showed an enhanced mass in the left lateral ventricle (**A**). The tumor was resected subtotally at the first surgery, leaving a small enhanced mass in the parietal region (**arrow**) with clots in the ventricles and the subdural space (**B**). Five months after the first surgery, the residual tumor had enlarged (**C**). The residual tumor was totally removed at the second operation with intraoperative radiation (**D**). Thereafter, ventriculo-peritoneal shunting was necessary for hydrocephalus. Mental retardation and symptomatic epilepsy persisted, but he was in good condition 10 years after the surgery.

[25]，側脳室発生例では悪性は少ないとされる[20]．好発年齢は小児に多く[3,8,11,25]，217文献566例をレビューしたWolffらの論文では，診断時の平均年齢は3.5歳であった[25]．当施設の症例では7例中，成人例が4例とこれまでの報告と比べて成人例が多い．

CPTでは手術摘出度が予後(合併症率，死亡率)に相関しており，全摘出こそが最重要とされている[3,10,15,16,25]．特にCPCにおいて手術の役割が大きいとする意見もあり[17]，CPCでは全摘例では亜全摘例と比較して予後が明らかに良好である[2,8,10]．手術摘出度については，当施設の症例では組織型の違いによる差は認めなかった．組織の悪性度と手術摘出度ついては，われわれ同様に相関しなかったという意見もあるが[16]，栄養血管の豊富さや腫瘍の大きさ，浸潤傾向などからCPCのほうがCPPよりも全摘が困難とする報告もある[8,18]．

予後を考えると可及的摘出がまず第一だが，病変が第4脳室に存在する場合は，腫瘍の脳幹部への浸潤が全摘を困難なものにしている．実際，当施設での症例を検討すると，病変が側脳室あるいは第3脳室に存在する症例では最終的には全摘出が可能だったが，第4脳室に存在する症例では5例中3例が亜全摘にとどまっている．これら3例のうち1例では再発を繰り返し，最終的に脳幹病変の増大と頸髄への播種により死亡している(Case 3)．一方，全摘した2例のうちの1例(Case 6)では，術前から認められていた嚥下障害が術後も残存している．脳幹部病変に対する術後の後遺症としては，橋に発生したCPPで術後に片麻痺が残った症例[19]や，第4脳室発生のCPPの摘出術後に構音障害，嚥下障害が残存したという報告がある[4]．この領域の病変では手術による全摘出を目指す一方で，機能温存のためには摘出操作をどこでとどめるべきかというジレンマがあるた

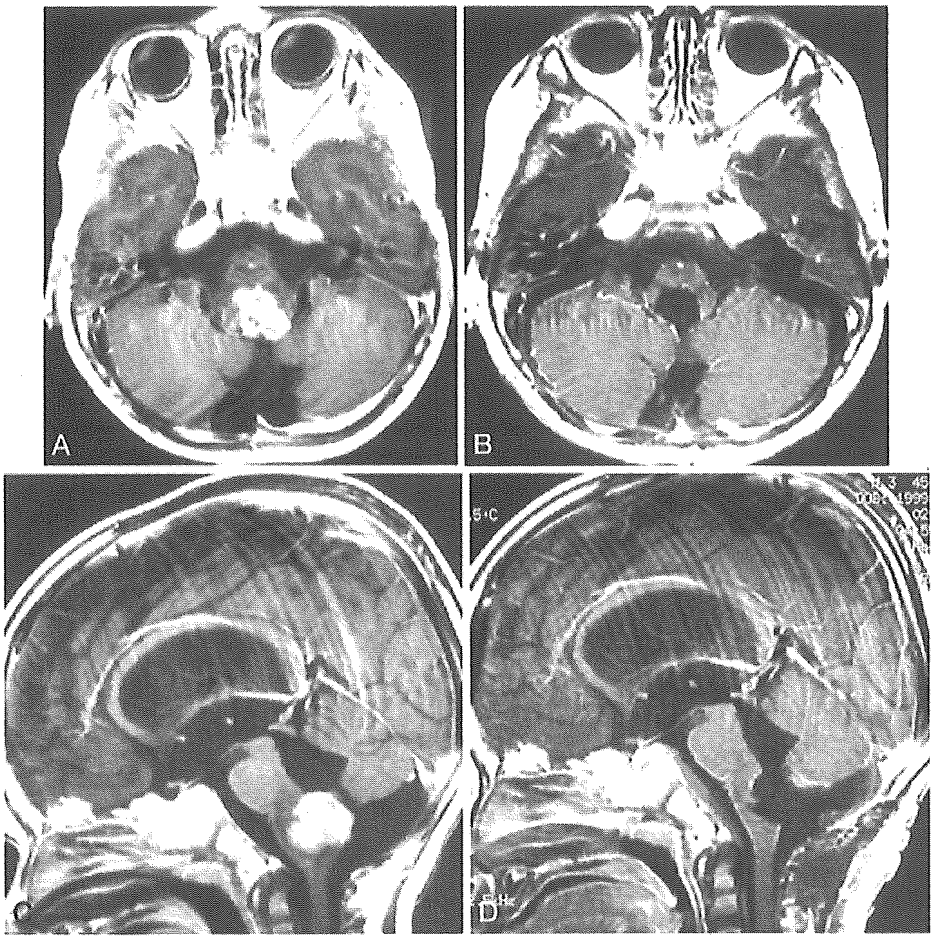


Fig. 6 Case 6, a 3-year-old boy with choroid plexus carcinoma. The patient had dysphagia at the first visit to our hospital. Magnetic resonance (MR) imaging with gadolinium (**A**: axial, **C**: sagittal) showed an enhanced mass in the fourth ventricle. Endoscopic third ventriculostomy was performed for hydrocephalus before resection of the tumor. The tumor was resected totally at surgery (**B**: axial, **D**: sagittal). He received radiation as adjuvant therapy.

め，治療戦略を立てるのが難しい．

組織学的悪性度の高いCPCはCPTの10～25%を占めるといわれており[2,20]，予後はCPPよりも不良とされる[24]．特に小児例では予後が不良である[3,5]．5年生存率についてもさまざまな報告があるが，CPPでは81～100%であるのに対し，CPCでは26～50%と明らかに成績が悪い[2,6,8,13,18,25]．過去にCPCの長期生存例の報告もなされているものの[11]，CPCは一般には予後不良である．しかしながら，以前はCPCの平均生存期間が9カ月程度だったのに対し[5]，最近の報告では平均生存期間が48カ月にまで延長している[17]．診断技術，手術，補助療法のいずれの進歩が理由かは不明だが，手術の占める要素が大きいのは確かである．CPCの5年生存率は26%だったとするBergerらの報告でも，全摘例に限っていえば5年生存率は86%にまで上昇している[2]．この報告ではCPCは手術による摘出度こそが予後因子であり，年齢，性別，初発症状から診断までの期間，場所，大きさ，補助療法などと予後は相関しないとしている[2]．当科の症例をみても2カ月男児の症例は初回亜全摘後に急速に残存腫瘍

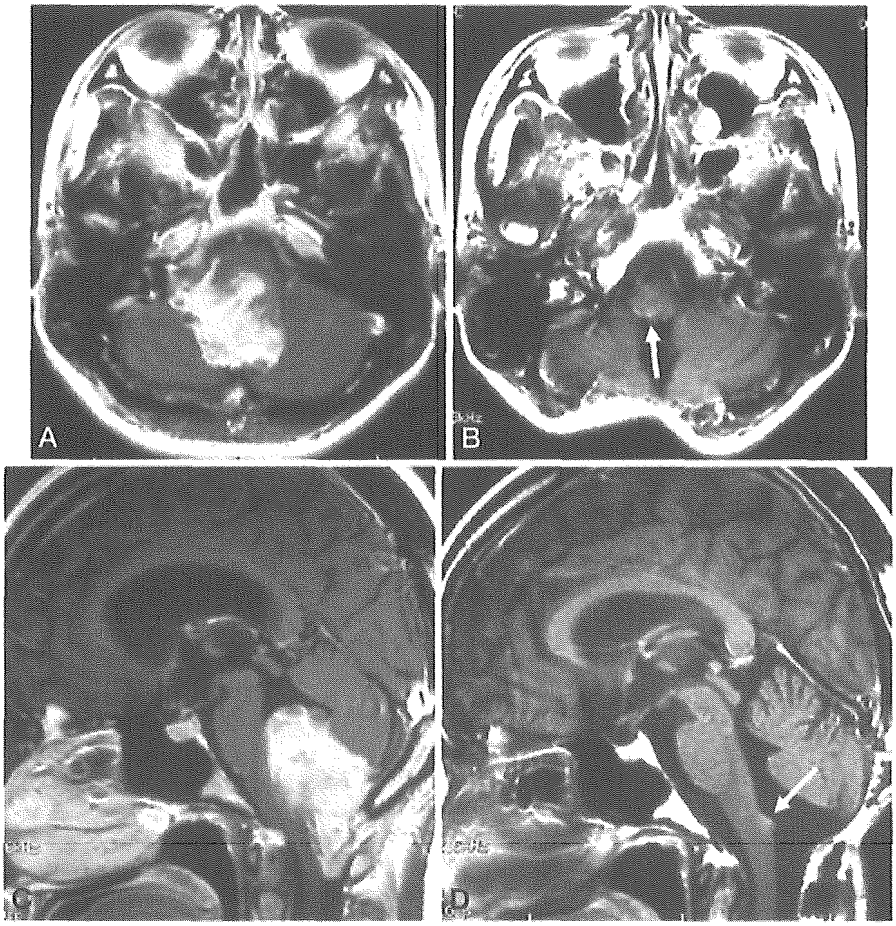


Fig. 7 Case 7, a 25-year-old female with chorcid plexus carcinoma. Magnetic resonance (MR) imaging with gadolinium (**A**: axial, **C**: sagittal) showed an enhanced mass in the fourth ventricle. The tumor was subtotally resected (**B**: axial, **D**: sagittal), followed by radiation and chemotherapy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

文 献

1) 荒木加寿美, 青木友和, 高橋 潤, 野崎和彦, 永田泉, 菊池晴彦, 横山瑞香, 服部春夫, 秋山祐一, 久保田優, 横溝 大：Choroid plexus carcinoma の1例. No Shinkei Geka **25**：853-857, 1997
2) Berger C, Thiesse P, Lellouch-Tubiana A, Kalifa C, Pierre-Kahn A, Bouffet E：Choroid plexus carcinomas in childhood：clinical features and prognostic factors. Neurosurgery **42**：470-475, 1998
3) Boyd MC, Steinbok P：Choroid plexus tumors：problems in diagnosis and management. J Neurosurg **66**：800-805, 1987
4) Cornwell PL, Murdoch BE, Ward EC, Morgan A：Dysarthria and dysphagia following treatment for a fourth ventricle choroid plexus papilloma. J Clin Neurosci **10**：506-512, 2003
5) Dohrmann GJ, Collias JC：Choroid plexus carcinoma. Case report. J Neurosurg **43**：225-232, 1975
6) Due-Tonnessen B, Helseth E, Skullerud K, Lundar T：Choroid plexus tumors in children and young adults：report of 16 consecutive cases. Childs Nerv Syst **17**：252-256, 2001
7) Duffner PK, Kun LE, Burger PC, Horowitz ME, Cohen ME, Sanford RA, Krischer JP, Mulhern RK, James HE, Rekate HL, et al：Postoperative chemotherapy and delayed radiation in infants and very young children with choroid plexus carcinomas. The Pediatric Oncology Group. Pediatr Neurosurg **22**：189-196, 1995
8) Ellenbogen RG, Winston KR, Kupsky WJ：Tumors of the choroid plexus in children. Neurosurgery **25**：327-335, 1989
9) Fiorillo A, Maggi G, Cirillo S, Migliorati R, Buffardi F, Alfieri E, Sabbatino MS, D'Amico A, Del Basso De Caro ML：Efficacy of sequential chemotherapy including methotrexate and doxorubicin in an infant with partially resected choroid plexus carcinoma. Pediatr Neurosurg **38**：21-26, 2003
10) Fitzpatrick LK, Aronson LJ, Cohen KJ：Is there a requirement for adjuvant therapy for choroid plexus carcinoma that has been completely resected? J Neurooncol **57**：123-126, 2002
11) Hawkins JC 3rd：Treatment of choroid plexus papillomas in children：a brief analysis of twenty years' experience. Neurosurgery **6**：380-384, 1980
12) Kimura M, Takayasu M, Suzuki Y, Negoro M, Nagasaka T, Nakashima N, Sugita K：Primary choroid plexus papilloma located in the suprasellar region：case report. Neurosurgery **31**：563-566, 1992
13) Krishnan S, Brown PD, Scheithauer BW, Ebersold MJ, Hammack JE, Buckner JC：Choroid plexus papillomas：a single institutional experience. J Neurooncol **68**：49-55, 2004
14) Kumabe T, Tominaga T, Kondo T, Yoshimoto T, Kayama T：Intraoperative radiation therapy and chemotherapy for huge choroid plexus carcinoma in an infant. Neurol Med Chir (Tokyo) **36**：179-184, 1996
15) McEvoy AW, Harding BN, Phipps KP, Ellison DW, Elsmore AJ, Thompson D, Harkness W, Hayward RD：Management of choroid plexus tumors in children：20 years experience at a single neurosurgical centre. Pediatr Neurosurg **32**：192-199, 2000
16) McGirr SJ, Ebersold MJ, Scheithauer BW, Quast LM, Shaw EG：Choroid plexus papillomas：long-term follow-up results in a surgically treated series. J Neurosurg **69**：843-849, 1988
17) Packer RJ, Perilongo G, Johnson D, Sutton LN, Vezina G, Zimmermann RA, Ryan J, Reaman G, Schut L：Choroid plexus carcinoma of childhood. Cancer **69**：580-585, 1992
18) Pencalet P, Sainte-Rose C, Lellouch-Tubiana A, Kalifa C, Brunelle F, Sgouros S, Meyer P, Cinalli G, Zerah M, Pierre-Kahn A, Renier D：Papillomas and carcinomas of the choroid plexus in children. J Neurosurg **88**：521-528, 1998
19) Pillai A, Rajeev K, Chandi S, Unnikrishnan M：Intrinsic brainstem choroid plexus papilloma. Case report. J Neurosurg **100**：1076-1078, 2004
20) Raimondi AJ, Gutierrez FA：Diagnosis and surgical treatment of choroid plexus papillomas. Childs Brain **1**：81-115, 1975
21) Souweidane MM, Johnson JH Jr, Lis E：Volumetric reduction of a choroid plexus carcinoma using preoperative chemotherapy. J Neurooncol **43**：167-171, 1999
22) Strojan P, Popovic M, Surlan K, Jereb B：Choroid plexus tumors：a review of 28-year experience. Neoplasma **51**：306-312, 2004
23) Valencak J, Dietrich W, Raderer M, Dieckmann K, Prayer D, Hainfellner JA, Marosi C：Evidence of therapeutic efficacy of CCNU in recurrent choroid plexus papilloma. J Neurooncol **49**：263-268, 2000
24) Wolff JE, Sajedi M, Coppes MJ, Anderson RA, Egeler RM：Radiation therapy and survival in choroid plexus carcinoma. Lancet **353**：2126, 1999
25) Wolff JE, Sajedi M, Brant R, Coppes MJ, Egeler RM：Choroid plexus tumours. Br J Cancer **87**：1086-1091, 2002

Int. J. Radiation Oncology Biol. Phys., Vol. 56, No. 3, pp. 793–800, 2003

0360-3016/03/$–see front matter

ELSEVIER

doi:10.1016/S0360-3016(03)00014-2

CLINICAL INVESTIGATION **Brain**

HYPOFRACTIONATED STEREOTACTIC RADIOTHERAPY ALONE WITHOUT WHOLE-BRAIN IRRADIATION FOR PATIENTS WITH SOLITARY AND OLIGO BRAIN METASTASIS USING NONINVASIVE FIXATION OF THE SKULL

HIDEFUMI AOYAMA, M.D.,* HIROKI SHIRATO, M.D.,* RIKIYA ONIMARU, M.D.,* KENJI KAGEI, M.D.,* JUN IKEDA, M.D.,† NOBUAKI ISHII, M.D.,† YUTAKA SAWAMURA, M.D.,† AND KAZUO MIYASAKA, M.D.*

Departments of *Radiology and †Neurosurgery, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Purpose: To evaluate the efficacy and toxicity of hypofractionated stereotactic radiotherapy (HSRT) using noninvasive fixation of the skull on solitary or oligo brain metastatic patients as an alternative to stereotactic radiosurgery (SRS) using invasive fixation.

Patients and Methods: The subjects were 87 patients who had 4 or fewer brain metastases (50 solitary, 37 oligometastases). Treatment was conducted on 159 metastases by using a linac-based stereotactic system. The median isocentric dose was 35 Gy in 4 fractions. Whole-brain irradiation was not applied as an initial treatment. For the salvage treatment of metachronous brain metastases, repeat HSRT or whole-brain irradiation was applied.

Results: The actuarial 1-year local tumor control rate was 81%. Treatment-related complications were observed in 4 patients in the early period (<3 months) and in 2 patients in the late period. The median survival period was 8.7 months. Metachronous brain metastases occurred in 30 patients, and none of the 18 patients who were eligible for salvage HSRT refused to receive it again.

Conclusions: Hypofractionated stereotactic radiotherapy achieved tumor control and survival equivalent to those of SRS reported in the literature. The results suggested that HSRT could be an alternative for solitary or oligo brain metastatic patients with less toxicity and less invasiveness compared to SRS. © **2003 Elsevier Inc.**

Brain, Metastasis, Radiosurgery, Radiation, Stereotactic.

INTRODUCTION

Treatment for patients with brain metastases has been evolving over the past several decades since stereotactic radiosurgery (SRS) emerged. Whole-brain irradiation (WBI) is a standard treatment for brain metastases, but some authors have recently advocated using SRS alone for solitary or oligo metastatic (i.e., 2–4 metastases) patients, because it is a 1-day therapy only, and it has a short-term toxicity compared to WBI. The long-term effect on neurocognitive function after WBI has been of great concern, even though these effects have been poorly defined (1–3). It is known that the omission of up-front WBI for newly diagnosed brain metastases doubles the risk of metachronous brain metastases in comparison with using SRS and WBI in combination (3, 4). Repeating SRS is one of the treatment options for metachronous brain metastases (3–6). However, it is sometimes difficult to get patients to agree to repeat SRS, because they do not want to undergo the painful frame fixation again (6). The limitations of the single-fraction, high-dose radiation of SRS have also been recognized. The local tumor control rate for tumors larger than 10 cc (or more than 3 cm in diameter) is usually unsatisfactory (7, 8). In addition, acute and very early complications after SRS, such as seizures or the worsening of neurologic symptoms, have been recognized in the recent literature (9–13). Although these are not long-lasting adverse effects, they are not trivial for patients with a poor prognosis.

Stereotactic radiotherapy using a noninvasive fixation system and dose fractionation schedule has been suggested to increase the treatable size of the tumor and to reduce the complications of SRS for vestibular schwannoma (14). From a biologic point of view, the additional advantage of dose fractionation over a short treatment time has been suggested for malignant tumors (15).

We report here on the results of hypofractionated stereotactic radiotherapy (HSRT) over a short period with a non-

Reprint requests to: Hiroki Shirato, M.D., Department of Radiology, Hokkaido University Graduate School of Medicine, North-15 West-7, Kita-ku, Sapporo, Japan, 060-8638. Tel: 81-11-716-1161; Fax: 81-11-706-7876; E-mail: hshirato@radi.med.hokudai.ac.jp

Presented in part at the American Society for Therapeutic Radiology and Oncology (ASTRO) Annual Meeting, San Francisco, CA, November 2001.

Received Aug 29, 2002, and in revised form Dec 30, 2002. Accepted for publication Jan 3, 2003.

invasive fixation system as an alternative to SRS for solitary or oligo brain metastatic patients in this study. The local control rate, risk of adverse radiation effect, and functional preservation of the patients were evaluated.

METHODS AND MATERIALS

Patient characteristics

The subjects for this study were 87 patients who had 4 or fewer brain metastases and had been treated with HSRT between March 1995 and November 2000. Fifty patients had solitary brain metastasis, and 37 had oligometastases (2–4 metastases). A total of 159 metastases were treated. The patient characteristics are listed in Table 1. Patients' distribution according to a Radiation Therapy Oncology Group (RTOG) Recursive Partition Analysis (RPA) is shown in the table (16). There were only 5 (6%) patients with RPA Class I (age <65, Karnofsky performance status [KPS] ≥70%, controlled primary tumor, and absence of extracranial metastases). Twenty-two (25%) patients were RPA Class III (KPS <70%). Therefore, the majority of patients (60 patients [69%]) in this study had RPA Class II (other than Class I and III). No patients had clinical and/or radiologic evidence of meningeal carcinomatosis, and none had previously received brain irradiation. The primary tumor status was considered inactive if the tumor had been controlled for at least 6 months before the brain metastases were diagnosed. Thirty-nine patients had an inactive primary tumor, and 48 patients had an active one.

Treatment

Treatment was conducted on an outpatient basis. The patients were treated with 6- or 10-MV photons using a linac-based stereotactic system, and were immobilized by a thermo-shell and custom-made headrest (Moldcare, Alcare, Tokyo) that were made exclusively for each patient. The setup accuracy was measured to be ±2 mm (17). Whole-brain irradiation was not applied as an initial treatment. The clinical target volume was defined to be identical to the gross tumor volume, which is the contrast-enhanced area with CT and/or MRI. For gross tumor volume/clinical target volume delineation, an MRI fusion program was used after 1998 (18). The planning target volume provided an additional margin of 2 mm in all directions, to account for fixation inaccuracy. The fractionation schedule of HSRT was calculated using a linear quadratic formula as described by Brenner *et al.* for an early radiation effect (15). The basic fractionation schedule was determined to be 35 Gy in 4 fractions over a 4–6-day period at the isocenter (D_{iso}) and 28 Gy at the periphery of the planning target volume (D_{min}) in this study. This schedule was used for 74% (118/159) of the lesions. The total dose was modified to be 10–20% lower for tumors at the brainstem, and 10–20% higher for tumors smaller than 1 cc in the noneloquent area. The median D_{iso} was 35 Gy (range: 20–40 Gy), covering the planning target volume with an 80–90% isodose line. The median dose of D_{min} was 32 Gy (range: 18–36 Gy).

If a patient had metachronous brain metastases during follow-up and was in fairly good general condition, that patient received salvage HSRT again. If the number of new lesions was 5 or more at that time, WBI was used instead of HSRT. The patients were informed about the possibility of receiving salvage HSRT or WBI before receiving treatment. Patients and/or their guardians were informed that WBI is the standard treatment for brain metastasis and that they could choose WBI instead of HSRT.

Table 1. Characteristics of patients (87 patients)

	Patients	
	No.	%
Male/female	54/33	62/38
Age*		
<65	34	39
≥65	53	61
KPS, %		
50–60	22	25
70–90	65	75
Status of primary tumor		
Active	48	55
Inactive	39	45
Extracranial metastases		
Exist	53	61
None	34	39
RTOG-RPA classification†		
RPA Class I	5	6
RPA Class II	60	69
RPA Class III	22	25
Posterior fossa tumors		
Exist	26	30
None	61	70
No. of metastases		
1	50	57
2	21	24
3	10	12
4	6	7
Prior resection of brain metastases		
Yes	9	10
No	78	90
Primary site		
Lung	52	60
Colon	7	8
Breast	6	7
Others	22	25
Pathology		
Radioresistant		
Thyroid carcinoma	5	6
Renal cell carcinoma	5	6
Others		
Adenocarcinoma	48	55
Squamous cell carcinoma	12	14
Small cell carcinoma	7	8
Others	10	11

* Median age = 65; range: 36–87.

† Radiation Therapy Oncology Group = Recursive Partition Analysis, defined by Gasper *et al.* (16).

Abbreviations: KPS = Karnofsky performance status.

Follow-up and statistics

The end points for evaluation were the local tumor control rate, toxicities, the survival rate, the metachronous brain metastases rate, the functional preservation rate, and the neurologic functional preservation rate. Principally, follow-up images were obtained at a 1–3-month interval and were used to assess tumor control and freedom from metachronous brain metastases. Local tumor control was defined as the lack of any significant sustained increase in tumor volume (≥25%) on follow-up MRI and/or CT, except for lesions that were surgically resected because of subsequent regrowth, which were considered to be local failure, even if the increase in volume was less than 25%. If the MRI showed a central or heterogeneous low density, and the lesion size decreased with further follow-up, the lesion was diagnosed as radiation necrosis. The radiation necrosis was not counted as an event in the response analysis, and the response of the tumor was judged using the images taken before the occurrence of the necrosis. If regrowth of the tumor after the necrosis occurred, the tumor was judged to be progressing.

The patients were periodically monitored by neurologic and radiologic examinations at Hokkaido University Hospital and/or at referred hospitals during and after treatment. The functional preservation of the patients was scored for systemic and neurologic status. Neurologic and systemic functional preservation was defined as follows. If the KPS was maintained to be 70% or more, systematic function was defined as being preserved. If the KPS was 70% or more, or if the KPS was less than 70% but without major neurologic deficit, the neurologic function was defined as being preserved. The neurologic major deficit was defined as the neurologic deficit that results in the patient's being less than fully active at home/work and requiring assistance (16). The actuarial systemic and neurologic functional preservation rates were estimated in patients with initial KPS >70% (RPA Class I–II). Death was considered to be non–central nervous system related only when it was attributable to extracranial lesions of the cancer.

All statistical analyses were performed with a commercial statistical software package (StatView5.0J, SAS Institute Inc., Cary, NC, USA). The actuarial curves were calculated based on the interval from the first date of the treatment using the Kaplan-Meier method. Univariate analyses of the categorical variables were performed using the log–rank test. A stepwise Cox proportional hazard model was used for the multivariate analysis.

RESULTS

Local tumor control

Ten patients died of systematic progression of the cancer after HSRT but before their follow-up scans were performed. Seventy-seven patients with 140 lesions (88% of all lesions) had follow-up scans available and were therefore eligible for local tumor control analysis. The median tumor volume, which was calculated as a product of three perpendicular diameters, was 3.3 cc (mean: 6.7 cc, range: 0.006–48.3 cc). The progression of the tumor was observed in 19 lesions at the last follow-up. The actuarial local tumor control rates at 6 months, 1 year, and 2 years were 85% (95% confidence interval [CI]: 77–93%), 81% (95% CI: 71–90%), and 69% (95% CI: 54–84%), respectively (Fig. 1). The univariate analyses were conducted for the potential variables listed in Table 2. Three factors were identified as poor prognostic factors for tumor control: tumors >3 cc (p = 0.0003), D_{iso} <35 Gy (p = 0.001), and D_{min} <32 Gy (p = 0.015). Neither so-called radioresistance (p = 0.58) nor the enhancement pattern (p = 0.43) showed statistical significance. The actuarial local tumor control rate of lesions ≤3 cc and >3 cc at 1 year was 96% (95% CI: 90–100%) and 59% (95% CI: 39–79%), respectively (Fig. 2). In the multivariate analysts, which included 3 factors (tumor volume, D_{iso}, D_{min}), only the tumor volume remained a significant prognostic factor (p = 0.023).

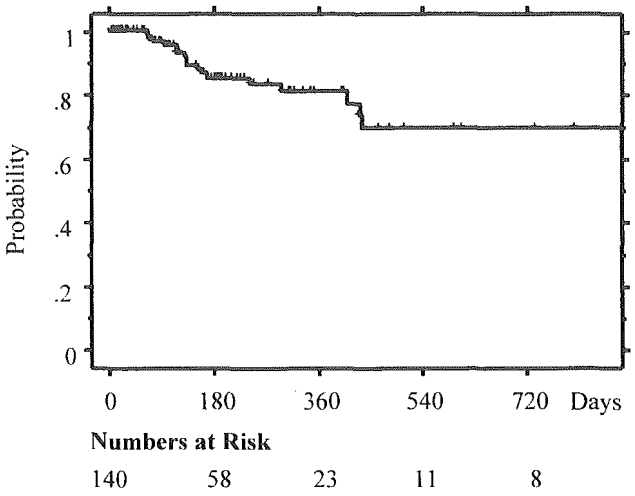


Fig. 1. Kaplan-Meier curve of local control rates for the 140 lesions evaluated.

Toxicity

In the very early phase, that is, during the course of HSRT or 0–72 h after the last treatment delivery, 2 patients with posterior fossa tumors complained of transient severe nausea that required steroid intake. No patient experienced a seizure during this phase. During the first day of treatment to 3 months after the last treatment day, 2 other patients experienced radiation-induced severe adverse reactions. One of them experienced hypomnesia a week after the completion of radiation. He died as a result of systemic disease at 83 days without improvement after steroid intake. Another patient, who received the highest dose in the whole group (D_{iso} 40 Gy, D_{min} 35 Gy), experienced a seizure 2 weeks after the completion of radiation, and suffered from hemiparesis due to brain edema. The brain edema did not respond to steroid intake, and the patient died from systemic disease 160 days after the treatment. Therefore, the crude

Table 2. Actuarial local tumor control rate according to potential factors and the results of univariate and multivariate analyses

			Actuarial rate (%)		p value	
	No.	%	6 months	1 year	Univariate	Multivariate
Radioresistant tumor						
Yes	19	14	100	89	0.99	–
No	121	86	83	80		
Enhance pattern						
Homogeneous	104	74	85	83	0.43	–
Inhomogeneous	36	26	84	73		
Tumor volume						
≤3 cc	72	51	96	96	0.0003	0.0023
3 cc	68	49	71	59		
D_{iso}*						
<35 Gy	22	16	62	52	0.001	0.118
≥35 Gy	118	84	89	86		
D_{min}†						
<32 Gy	42	30	71	64	0.015	0.968
≥32 Gy	98	70	91	88		

* Dose to the isocenter.
† Dose to the periphery of planning target volume.

rate of very early and early adverse reaction was 4.6% (4/87).

Symptomatic late complications, occurring ≥3 months after treatment, were observed in 2 patients among the 75 patients who were followed for over 3 months (2.7%). One patient complained of hemiparesis and another of severe nausea. Both lesions showed radiation necrosis based on pathologic examination, one after surgical resection, and the other after autopsy. The D_{iso} of these lesions was 35 Gy, and the D_{min} was 35 Gy and 32 Gy, respectively.

Survival

The median follow-up time of the whole study population and of the surviving patients was 6.3 months (range: 0.2–60.3 months) and 7.6 months (range: 1.7–58.3 months), respectively. The median survival was 8.7 months. Sixty of the 87 patients had died at the last follow-up. Death was attributed to neurologic causes in 9 patients (15%), progression of brain tumors in 8 patients, and cerebrospinal fluid dissemination in 1 patient. None of the 5 patients in RPA Class I had died by the median follow-up time of 17 months (range: 12–58 months). The median survival of the patients in RPA Class II, Class III, and Class II–III were 9.0 months, 4.6 months, and 8.2 months, respectively.

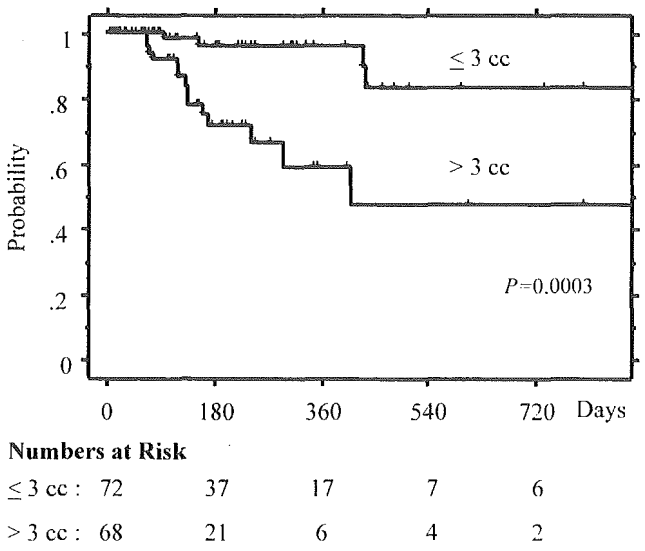


Fig. 2. Kaplan-Meier curves of local control rates of tumors ≤3 cc and tumors >3 cc.

Actuarial survival rates at 6 months and 1 year were 65% (95% CI: 54–75%) and 39% (95% CI: 27–50%), respectively. Univariate analyses were conducted for the following potential prognostic variables: age (<65 years vs. ≥65 years), KPS (<70% vs. ≥70%), primary tumor status (active vs. inactive), extracranial metastases (existent vs. absent), number of brain metastases (solitary vs. oligo), primary tumor sites (lung vs. others), existence of posterior fossa tumor (exist vs. absent), and the history of surgical resection of brain metastases (yes vs. no). Only the primary tumor status was a statistically significant variable among these, and patients with an active primary tumor had a poorer prognosis than those without an active primary tumor (p = 0.0004) (Table 3). A multivariate analysis was conducted including the above variables, except for primary tumor sites, existence of posterior fossa tumor, and history of surgical resection of brain metastases, because of the negligible influence of these variables in univariate analyses. The primary tumor status was the only significant factor (p = 0.0003) in the multivariate analysis (Table 3).

Metachronous brain metastasis and salvage treatment

Metachronous brain metastases were observed in 30 patients. The actuarial rate of occurrence of metachronous brain metastasis was 34% (95% CI: 21–46%) and 60%

Table 3. Actuarial survival rate according to potential factors and the results of univariate and multivariate analyses

		Actuarial rate (%)		*p* value	
	No.	6 months	1 year	Univariate	Multivariate
Age					
<65	34	79	43	0.12	0.37
≥65	53	55	35		
KPS					
<70%	22	39	27	0.15	0.14
≥70%	65	73	43		
Primary tumor status					
Active	48	49	27	0.0004	0.0003
Inactive	39	84	52		
Extracranial metastases					
Exist	53	60	29	0.30	0.08
Absent	34	72	52		
Number of brain mets					
Solitary	50	64	39	0.86	0.84
Oligo	37	66	38		
Primary tumor site					
Lung	52	65	38	0.38	–
Others	35	64	41		
Posterior fossa tumors					
Exist	26	77	50	0.29	–
Absent	61	59	33		
History of resection					
Yes	9	64	51	0.47	–
No	78	65	37		
RPA class*					
I	5	100	100	–	–
II	59	71	36	–	–
III	22	39	27	–	–

* Radiation Therapy Oncology Group-Recursive Partition Analysis, defined by Gasper *et al.* (16).
Abbreviations: KPS = Karnofsky performance status.

(95% CI: 44–77%) at 6 months and 1 year, respectively (Fig. 3). If we exclude 10 patients who did not receive any follow-up scans until their death, the actuarial rate of occurrence of metachronous brain metastasis was 37% (95% CI: 23–50%) and 63% (95% CI: 50–83%) at 6 months and 1 year, respectively. Univariate and multivariate analyses were conducted regarding the incidence of metachronous brain metastasis relative to the following factors: the primary tumor site (lung vs. others), the status of the primary tumor (active vs. inactive), the existence of extracranial metastases (existent vs. nonexistent), and the number of brain metastases (solitary vs. oligo). The number of initial brain metastases was the only significant factor in both the univariate analyses ($p = 0.02$) (Fig. 4) and multivariate analysis ($p = 0.02$) (Table 4).

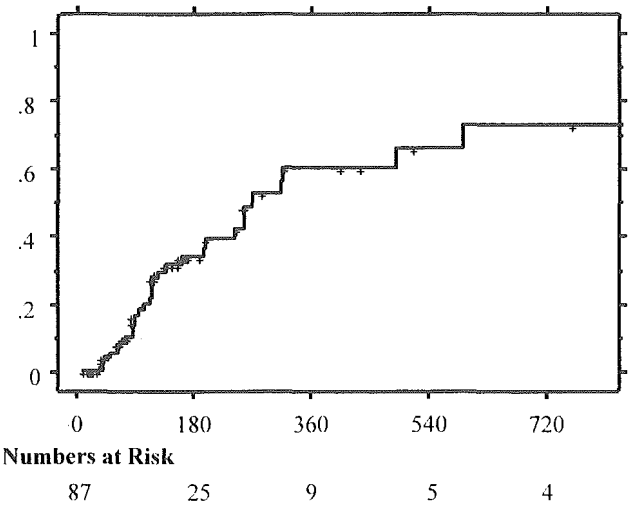
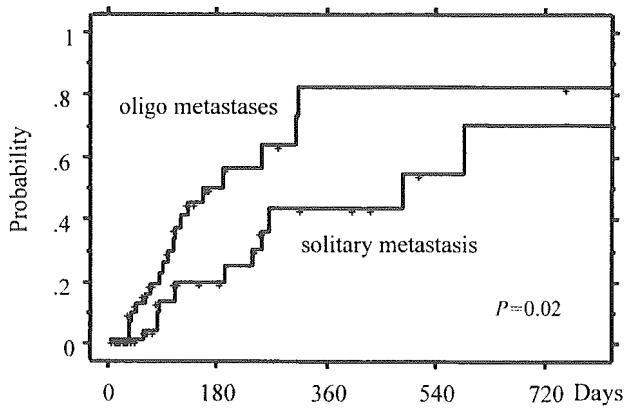


Fig. 3. Cumulative Kaplan-Meier curves of metachronous brain metastases.

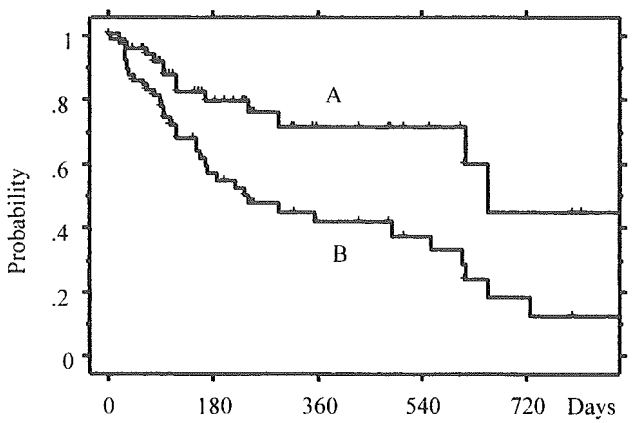
Eight of those 30 patients who were found to have metachronous brain metastases received only symptomatic treatment, because of significant systemic deterioration. Twenty-two patients were in sufficiently good general condition to receive retreatment of the initial metachronous brain metastasis. Whole-brain irradiation was necessary in 4 patients who had 5 or more new lesions at the first manifestation of relapse. Eighteen patients with 4 or fewer new lesions were candidates for retreatment with HSRT, and none refused to receive it again. Twelve received salvage HSRT once, 5 received it twice, and 1 received it 3 times. There were 23 patients who survived more than 1 year, and none of them received WBI.



Numbers at Risk

Oligo:	37	8	2	2	2
Solitary:	50	17	7	3	2

Fig. 4. Cumulative Kaplan-Meier curves of metachronous brain metastases in patients with solitary and oligo metastases.



Numbers at Risk

A:	65	27	13	8	3
B:	65	25	13	8	3

Fig. 5. Kaplan-Meier curves of neurologic and systemic functional preservation rates for the 65 patients who had initial KPS ≥70%: (A) neurologic functional preservation rate, (B) systemic functional preservation rate.

The deterioration of the patients' function was attributable to systemic causes in the majority of cases. The actuarial systemic functional preservation rates for the 65 patients who had initial KPS ≥70% (RPA Class I and II) were 57% (95% CI: 43–70%) and 41% (95% CI: 26–56%) at 6 months and 1 year, respectively, whereas the actuarial neurologic functional preservation rates for the same population were 79% (95% CI: 68–91%) and 71% (95% CI: 56–86%) at 6 months and 1 year, respectively (Fig. 5). In the remaining 22 patients whose KPS was <70% before HSRT, 7 patients showed neurologic functional improvement and obtained KPS ≥70% at least once after the treatment.

DISCUSSION

The results of this report suggest that HSRT using noninvasive fixation can be a good alternative to SRS using invasive fixation with regard to local tumor control and toxicities. The actuarial 1-year local tumor control rate of 81% after HSRT was equivalent to the control rates from the SRS series that are listed as 70–90% in the reports (3–12). HSRT also did not compromise the local tumor control for large metastases and radioresistant tumors, such as thyroid carcinomas and renal cell carcinomas, compared with the results of SRS in the literature (7, 8). In the report from the University of California at San Francisco, 1-year local control rates of tumors ≤3 cc, 3–10 cc, and >10 cc were 87%, 63%, and 25%, respectively (7). In the series of Chen *et al.*, 1-year local control rates of tumors <3 cc and >3 cc were 90% and 75%, respectively (8). In our series, the local control rate at 1 year was 96% in tumors ≤3 cc and 59% in tumors >3 cc. So-called radioresistant tumors to conventional fractionated radiotherapy, such as thyroid cell carcinoma, melanoma, and renal cell carcinoma, were not

Table 4. Actuarial rate of occurrence of metachronous brain metastases according to potential factors and the results of univariate and multivariate analyses

		Actuarial rate (%)		*p* value	
	No.	6 months	1 year	Univariate	Multivariate
Primary tumor site					
Lung	52	35	55	0.74	0.66
Others	35	30	63		
Primary tumor status					
Active	48	37	66	0.23	0.21
Inactive	39	30	55		
Extracranial metastases					
Exist	53	36	55	0.92	0.88
Absent	34	31	66		
Number of brain metastases					
Solitary	50	19	42	0.02	0.02
Oligo	37	49	81		

resistant to HSRT. These results are consistent with the results of SRS (7, 12), suggesting that the short treatment period (4 days) and relatively high daily dose in HSRT were both advantageous for these tumors. A relatively high incidence of acute/early complications after SRS has been revealed in the recent literature (8–13). Seizures were reported to occur at a mean frequency of 6% (range: 2.3–15%) in the SRS series, whereas in our series we observed only a 1.1% incidence of seizure. Manning *et al.* (19) and Laing *et al.* (20) also reported a low incidence of seizure after HSRT. In the series conducted by Manning *et al.* (19), 32 patients were treated by HSRT combined with WBI, and a seizure was observed in only 1 patient 3 weeks after the treatment. In the series conducted by Laing *et al.* (20), none of the 24 patients given 10–20 Gy in 2 fractions experienced seizure. Although the lower acute/early complication rate with the equivalent tumor control rate may not have been predicted by radiobiologic methods, these results suggest that there is a threshold dose between about 8 Gy and 20 Gy for symptomatic seizures. Changes in cell membrane permeability by irradiation may be the cause of these seizures (21–23).

Effective doses of HSRT in combination with WBI have been reported. Manning *et al.* used 27 Gy in 3 fractions after WBI (19), and Laing *et al.* used 10 Gy in 2 fractions and 20 Gy in 3 fractions with or without WBI (20). However, an optimal fractionation schedule of HSRT alone has not yet been established. Brenner *et al.* provided an *in vitro* model of an equivalent fractionation schedule to SRS, and 33 Gy in 4 fractions was found to be equivalent to 20 Gy in a single fraction for an early effect and for lower toxicity of a late effect (15). In the present series, we administered a median D_{iso} of 35 Gy and D_{min} of 32 Gy in 4 fractions; this schedule was estimated to be equivalent to SRS using a D_{iso} of 25 Gy and a D_{min} of 18 Gy (15). We have already documented that the same dose schedule is effective and safe for brain arteriovenous malformation with a mean follow-up period of 35 months (24). In the arteriovenous malformation series, we also experienced a lower incidence of acute/early and late complications with a similar obliteration rate compared to SRS. Thus, we recommend the dose schedule used in the present study for HSRT.

The question of whether the omission of up-front WBI compromises the survival of patients treated with SRS has not been fully investigated (3, 5). Gasper *et al.* (16) analyzed factors influencing the survival of patients who were enrolled in 3 RTOG brain metastases trials with different WBI schedules and classified the patients into 3 prognostic groups: RPA Class I, II, and III. In this series, patients with RPA Class I had a median survival of 7.1 months, Class II had 4.2 months, and Class III had 2.3 months. Chidel *et al.* analyzed patients who were treated with SRS with or without WBI and found that the median survival of patients in RPA Class I was 11.2 months and in RPA Class II–III was 6.9 months (5). In our series, the patients in Class I were all alive at the median follow-up of 17 months, and we were therefore not able to calculate the median survival time. The median survival of patients in RPA Class II, Class III, and Classes II–III were 9.0 months, 4.7 months, and 8.2 months, respectively. As far as survival is concerned, HSRT was suggested to be not worse than SRS with or without WBI or WBI alone according to RPA, although it is invalid to conclude anything from this comparison.

Sneed *et al.* recently investigated this question in a retrospective multi-institutional analysis (3). The results suggested that the omission of WBI from the initial treatment was not detrimental in terms of survival. However, other studies showed a worse survival trend after SRS alone compared to SRS with WBI among patients with no known extracranial disease (4, 5). A randomized comparison between stereotactic irradiation alone and stereotactic irradiation with WBI is under way for patients with solitary and oligo brain metastasis in Japan, the findings of which will hopefully confirm this statement. Provided that the omission of an up-front WBI does not compromise survival, the largest problem of SRS or HSRT alone is the high frequency of metachronous brain metastasis. Metachronous brain metastasis was observed in 30–50% of the total patients during the follow-up period, and retreatment was required in 20–30% of the total patients in previous reports, including ours, on SRS alone or HSRT alone (3–8). The high frequency of salvage treatment after SRS or HSRT alone for solitary and oligo metastases must be further examined on the basis of the physical and psychological invasiveness to patients caused by these treatments. The use of a noninvasive fixation allowed us to obtain good compliance from patients when salvage HSRT was necessary, and none of the 18 patients who were well suited to salvage HSRT refused to receive the treatment again. Although the fixation involved in retreatment is not painful, and HSRT provides good compliance for retreatment, it would be inappropriate to use HSRT alone if neurologic deterioration due to the new brain lesion is severe. We were not able to find neurologic functional preservation rates after WBI for brain metastasis in the current literature. It is unclear whether the neurologic functional preservation rate among patients who had an initial KPS $\geq$70% (79% at 6 months and 71% at 1 year) in our series is higher or lower than that of a similar population of patients receiving WBI. Sporadic but definite long-term survival after treatment for brain metastasis has been reported (25, 26). Considering that 23 patients in our series who survived for more than 1 year after treatment had not received WBI, SRS, or HSRT without WBI would reduce the possible risk of long-term effects on neurocognitive function in long-term survivors.

In conclusion, HSRT without WBI showed local control rates and survival rates equivalent to those with SRS in the literature and showed a possibly lower incidence of acute/early adverse effects compared with SRS. Although metachronous brain metastasis after HSRT alone occurred at a high incidence in this study, as it did after SRS alone in the literature, the willingness of patients to undergo retreatment with HSRT using noninvasive fixation was sufficiently high to consider this treatment as an alternative to local treatment with WBI. Further investi-

gation in a prospective randomized study is required to compare the overall survival and neurologic functional preservation rates of HSRT found in this study to those of other treatment options.

REFERENCES

1. Murray KJ, Scott C, Zachariah B, *et al.* Importance of the mini-mental status examination in the treatment of patients with brain metastases: A report from the Radiation Therapy Oncology Group protocol 91-04. *Int J Radiat Oncol Biol Phys* 2000;48:59–64.
2. Asai A, Matsutani M, Kohno T, *et al.* Subacute brain atrophy after radiation therapy for malignant brain tumor. *Cancer* 1989;63:1962–1974.
3. Sneed PK, Suh JH, Goetsch SJ, *et al.* A multi-institutional review of radiosurgery alone vs. radiosurgery with whole brain radiotherapy as the initial management of brain metastases. *Int J Radiat Oncol Biol Phys* 2002;53:519–526.
4. Pirzkall A, Bebus J, Lohr F, *et al.* Radiosurgery alone or in combination with whole-brain radiotherapy for brain metastases. *J Clin Oncol* 1998;16:3563–3569.
5. Chidel MA, Suh JH, Reddy CA, *et al.* Application of recursive partition analysis and evaluation of the use of whole brain radiation among patients treated with stereotactic radiosurgery for newly diagnosed brain metastases. *Int J Radiat Oncol Biol Phys* 2000;47:993–999.
6. Shirato H, Takamura A, Tomita M, *et al.* Stereotactic irradiation without whole-brain irradiation for single brain metastasis. *Int J Radiat Oncol Biol Phys* 1997;37:385–391.
7. Shiau CY, Sneed KP, Shu HKG, *et al.* Radiosurgery for brain metastases: Relationship of dose and pattern of enhancement to local control. *Int J Radiat Oncol Biol Phys* 1997;37:375–383.
8. Chen JCT, Petrovich Z, O'Day S, *et al.* Stereotactic radiosurgery in the treatment of metastatic disease to the brain. *Neurosurgery* 2000;47:268–281.
9. Simonova G, Liscak R, Novotny Jr J, Novotny J. Solitary brain metastases with the Leksell gamma knife: Prognostic factors for patients. *Radiother Oncol* 2000;57:207–213.
10. Alexander E III, Moriarity TM, Davis RB, *et al.* Stereotactic radiosurgery for the definitive noninvasive treatment of brain metastases. *J Natl Cancer Inst* 1995;87:34–40.
11. Joseph J, Adler JR, Cox RS, *et al.* Linear accelerator-based stereotactic radiosurgery for brain metastases: The influence of number of lesions on survival. *J Clin Oncol* 1996;14:1085–1092.
12. Breneman JC, Warnick RE, Albright RE, *et al.* Stereotactic radiosurgery for the treatment of brain metastases: Results of a single institution series. *Cancer* 1996;79:551–557.
13. Gelblum DY, Lee H, Bilsky M, *et al.* Radiographic findings and morbidity in patients treated with stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys* 1998;42:391–395.
14. Shirato H, Sakamoto T, Takeichi N, *et al.* Fractionated stereotactic radiotherapy for vestibular schwannoma (VS): Comparison between cystic-type and solid-type VS. *Int J Radiat Oncol Biol Phys* 2000;48:1395–1401.
15. Brenner DJ, Martel MK, Hall EJ. Fractionated regimens for stereotactic radiotherapy of recurrent tumors in the brain. *Int J Radiat Oncol Biol Phys* 1991;21:819–824.
16. Gasper L, Scott C, Rotman M, *et al.* Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys* 1997;37:745–751.
17. Shirato H, Isu T, Abe S, *et al.* Daily intermittent multiportal therapy followed by stereotactic boost (DIMT-SB) for treatment of small intracranial lesions—technical aspects and preliminary results. *J Jpn Soc Ther Radiol Oncol* 1992;4:149–162.
18. Aoyama H, Shirato H, Nishioka T, *et al.* Magnetic resonance imaging (MRI) system for three-dimensional conformal radiotherapy (3D-CRT) and its impact on gross tumor volume (GTV) delineation of central nervous system (CNS) tumors. *Int J Radiat Oncol Biol Phys* 2001;50:821–827.
19. Manning MA, Cardinale RM, Benedict SH, *et al.* Hypofractionated stereotactic radiotherapy as an alternative to radiosurgery for the treatment of patients with brain metastases. *Int J Radiat Oncol Biol Phys* 2000;47:603–608.
20. Laing RW, Warrington AP, Hines F, Graham JD, Brada M. Fractionated stereotactic extracranial beam radiotherapy in the management of brain metastases. *Eur J Cancer* 1993;29:1387–1391.
21. Loeffler JS, Siddon RL, Wen PY, Nedzi LA, Alexander E III. Stereotactic radiosurgery of the brain using a standard linear accelerator: A study of early and late effects. *Radiother Oncol* 1990;17:311–321.
22. Fike JR, Cann CE, Turowski K, *et al.* Radiation dose response to normal brain. *Int J Radiat Oncol Biol Phys* 1988;14:63–70.
23. Sheline GE, Wara WM, Smith V. Therapeutic irradiation and brain injury. *Int J Radiat Oncol Biol Phys* 1980;6:1215–1228.
24. Aoyama H, Shirato H, Nishioka T, *et al.* Treatment outcome of single or hypofractionated single-isocentric stereotactic irradiation (STI) using a linear accelerator for intracranial arteriovenous malformation. *Radiother Oncol* 2001;59:323–328.
25. Nozaki M, Higuchi K, Kohno N, Yoshida K, Niibe H. A case report of long-term survival after radiotherapy for a solitary brain metastasis from breast cancer. *Breast Cancer* 1997;31:179–182.
26. Salvati M, Artico M, Carloia S, Orlando ER, Gagliardi FM. Solitary cerebral metastasis from lung cancer with very long survival: Report of two cases of the literature. *Surg Neurol* 1991;36:458–461.

J Neurosurg 99:685–692, 2003

Management of vestibular schwannoma by fractionated stereotactic radiotherapy and associated cerebrospinal fluid malabsorption

YUTAKA SAWAMURA, M.D., PH.D., HIROKI SHIRATO, M.D., PH.D., TOURU SAKAMOTO, M.D., PH.D., HIDEFUMI AOYAMA, M.D., PH.D., KEISHIRO SUZUKI, M.D., RIKIYA ONIMARU, M.D., PH.D., TOYOHIKO ISU, M.D., PH.D., SATOSHI FUKUDA, M.D., PH.D., AND KAZUO MIYASAKA, M.D., PH.D.

Departments of Neurosurgery, Radiology, and Otolaryngology, Hokkaido University School of Medicine, Sapporo; Department of Radiology, Obihiro Kousei Hospital, Obihiro; and Department of Neurosurgery, Kushiro Rosai Hospital, Kushiro, Japan

Object. The goal of this study was to investigate outcomes in patients with vestibular schwannoma (VS) who were treated with fractionated stereotactic radiotherapy (SRT).

Methods. One hundred one patients with VS were treated with fractionated SRT at a radiation level of 40 to 50 Gy administered in 20 to 25 fractions over a 5- to 6-week period. The median tumor size in these patients was 19 mm (range 3–40 mm), and 27 tumors were larger than 25 mm. Patients were consistently followed up using magnetic resonance imaging every 6 months for 5 years in principle. The median follow-up period was 45 months. The actuarial 5-year rate of tumor control (no growth > 2 mm and no requirement for salvage surgery) was 91.4% (95% confidence interval 85.2–97.6%). Three patients with progressive tumors underwent salvage tumor resection. The actuarial 5-year rate of useful hearing preservation (Gardner–Robertson Class I or II) was 71%. The observed complications of fractionated SRT included transient facial nerve palsy (4% of patients), trigeminal neuropathy (14% of patients), and balance disturbance (17% of patients). No new permanent facial weakness occurred after fractionated SRT. Eleven patients (11%) who had progressive communicating hydrocephalus (cerebrospinal fluid malabsorption) and no evidence of tumor growth after fractionated SRT required a shunt. The symptoms of this type of hydrocephalus were similar to those of normal-pressure hydrocephalus and occurred 4 to 20 months (median 12 months) after fractionated SRT. The mean size (± standard deviation) of tumors causing symptomatic hydrocephalus (25.5 ± 7.8 mm) was significantly larger than that of other tumors (18.2 ± 8.7 mm) ($p = 0.011$). Only four of the 72 patients with tumors smaller than 25 mm in maximum diameter received a shunt.

Conclusions. Fractionated SRT resulted in an excellent tumor control rate, even for relatively large tumors, and produced a high rate of hearing preservation that was comparable to the best results of single-fraction radiosurgery. The progression of communicating hydrocephalus should be monitored closely, particularly in patients harboring a large VS.

KEY WORDS • **fractionated radiotherapy** • **hydrocephalus** • **radiosurgery** • **stereotactic irradiation** • **vestibular schwannoma**

SINGLE high-dose radiation administered via SRS has proved useful in the treatment of VS,[2,5,6,11,18,19,21,22,24,27–31,38,39] whereas conventional fractionated radiotherapy has not been used extensively for the treatment of this tumor. Nevertheless, there is some evidence for the efficacy of radiotherapy when the biological benefit of fractionation is provided.[6,15,41] Between 1986 and 1992, Maire and associates[15] treated 24 patients with Stage III or IV VS by using only conventional fractionated external-beam radiotherapy. The mean total radiation dose was 51 Gy (1.8 Gy/fraction administered 5 days/week) and the mean follow-up period was 60 months. In that study the 6-year actuarial rate for local tumor control was 82%.

Abbreviations used in this paper: CI = confidence interval; CSF = cerebrospinal fluid; GKS = gamma knife surgery; MR = magnetic resonance; NPH = normal-pressure hydrocephalus; PTA = pure tone average; SRS = stereotactic radiosurgery; SRT = stereotactic radiotherapy; VP = ventriculoperitoneal; VS = vestibular schwannoma.

The radiobiology of SRS requires lower, potentially less effective doses for larger target volumes to avoid complications.[6] The radiation dose used in SRS correlates significantly to the incidence of cranial neuropathy, particularly in large tumors (> 4 cm^3).[38] This may limit the use of SRS to the treatment of smaller VSs. Because radiation in SRS is given in a single fraction, this treatment modality may lack the anticipated biological benefit of fractionation; historically, radiation has been given in divided doses to minimize damage to normal tissues suppressing the growth of neoplasms.[13,17] Fractionated stereotactic radiotherapy may be able to treat tumors of larger volumes better than SRS without causing serious neurotoxicity.

Recently, fractionated SRT administered with a linear accelerator has been shown to be effective in controlling tumor growth.[7,10,14,17,35,36,43] A similar tumor control rate of approximately 90% can be achieved with low toxicity for cochlear, facial, and trigeminal nerves with the use of either SRS or fractionated SRT. Nevertheless, in reports on frac-

tionated SRT the numbers of patients assessed have been small, the observation periods have been short, and few treatment details have been described, compared with reports on SRS.[7,10,14,17,26,32,33,35,36,43]

Although SRT may offer a good rate of tumor control (growth cessation or no tumor enlargement), the rate of shrinkage of the treated tumor during the early period after irradiation is not high. Symptoms caused by the remaining tumor and complications induced by irradiation must be treated in outpatient clinics for a certain period after radiotherapy. For example, symptomatic communicating hydrocephalus resulting from VS is not rare and often requires a shunt placement operation.[25] To our knowledge, however, there have been few studies in which the necessity for the shunt placement operations and the incidence of communicating hydrocephalus after radiotherapy for VS have been described.[18,20,23,40,41]

In this report, we assess local tumor control, hearing preservation, neurotoxicity, and associated hydrocephalus in 101 patients with unilateral VS who were consecutively treated with conventional fractionated SRT. The appropriateness of the long-term follow up of patients after tumor irradiation is also investigated, based on the experiences of these patients. Our management policy for VS, which combines neurosurgery and fractionated SRT, is discussed with a special focus on large tumors causing CSF malabsorption.

Clinical Material and Methods

Patient Population

The study population was composed of a consecutive series of 106 patients with VS who were treated by fractionated SRT between 1991 and 2000. Excluding five patients with neurofibromatosis Type 2, a total of 101 patients with unilateral solitary VS were examined. The median age of the patients was 53 years (range 14–82 years) at the time of fractionated SRT and the male/female ratio was 38:63. One patient had a unilateral tumor associated with neurofibromatosis Type 1.

Twelve patients had undergone previous resection of their tumors and, therefore, the histological diagnosis was verified before fractionated SRT commenced by examining the surgical specimens obtained in these patients. The remaining 89 tumors had not been previously treated and were diagnosed by performing neuroimaging studies with the aid of a 1.5-tesla MR imaging system. Seventeen patients had progressive tumors, progressive symptoms, or both after the initial neuroimaging diagnosis. The indications for fractionated SRT in the other patients were as follows: patient preference after receiving full information on possible treatment options; failed previous surgical removal (recurrence of residual tumor); planned adjuvant therapy following bulk-reduction surgery for giant tumors; patient's medical infirmity due to systemic complications or advanced age; or combinations of the aforementioned factors. We often recommended observation only for patients older than 60 years of age who harbored small VSs that did not cause neurological symptoms besides hearing loss.

Seven large tumors that caused a remarkable brainstem deformity and/or obstructive hydrocephalus were initially partially resected, following which the residual mass was managed by fractionated SRT. One patient who had symptomatic communicating hydrocephalus received a VP shunt alone before fractionated SRT. Detailed treatment methods and the preliminary results of this study have been published previously elsewhere.[10,32,35,36]

Measurement of Tumor Size and Radiation Therapy

The sizes of the 101 tumors were measured by reviewing MR images obtained at the initiation of fractionated SRT by one radiologist (H.S.). To assess the rates of tumor control and hearing preservation, tumor size was estimated according to the Committee of Hearing and Equilibrium guidelines for the evaluation of hearing preservation in acoustic neuroma (VS), and the mean diameters of the tumors were defined as (long diameter × short diameter) (1/2).[4] In this series, the median of the calculated mean diameters among the 101 tumors was 15.5 mm (range 3–40 mm). The median of the long diameter was 19 mm (range 3–40 mm). Twenty tumors had a mean diameter equal to or greater than 25 mm and 27 tumors had a long diameter equal to or greater than 25 mm. To avoid confusion in the analyses described in this report, we have not described tumor sizes measured before a resection that was undertaken prior to fractionated SRT. In addition, hereafter the long diameter is described as the maximum diameter so that we may easily compare it with the results of some recent reports.

Small-field irradiation of the tumor was accomplished using a thermoplastic shell for immobilization, with 40 to 50 Gy (median 48 Gy) administered in 20 to 25 fractions (median 23 fractions), as described previously.[36]

Follow-Up Review

Just before fractionated SRT commenced, 82 patients (81%) had measurable (testable) hearing on the affected side. Hearing was classified by Gardner–Robertson score.[8] Hearing preservation (maintenance of useful hearing) after fractionated SRT was defined as a retention of Class I or II hearing at the final audiological examination postfractionated SRT. Class preservation was defined as no decrease in Gardner–Robertson class from the pretreatment class. Hearing and class preservation rates were calculated using both the Kaplan–Meier method and the actuarial method in patients with measurable hearing.

Patients were regularly followed up at the outpatient clinic, every 6 months for 5 years and every 12 months thereafter, in principle, by using interviews, neurological and otological examinations, and MR images. Follow-up MR imaging was performed to include not only the posterior fossa, but also whole ventricles to detect possible hydrocephalus. Tumor enlargement (progression), tumor reduction (regression), and tumor control were defined as described previously.[36]

Any new cranial neuropathy of any severity or any exacerbation of a previously existing neurological deficit, even if either were transient, was considered to be a radiation-induced complication. Newly observed neurological signs or symptoms obviously attributable to hydrocephalus, on the other hand, were excluded from the radiation-induced complications. These included mild mental deterioration (cognitive dysfunction), gait disturbance without limb ataxia, urinary incontinence, chronic headache, and vomiting associated with neuroimaging evidence of either clearly enlarged lateral ventricles or a progressively enlarging CSF space.

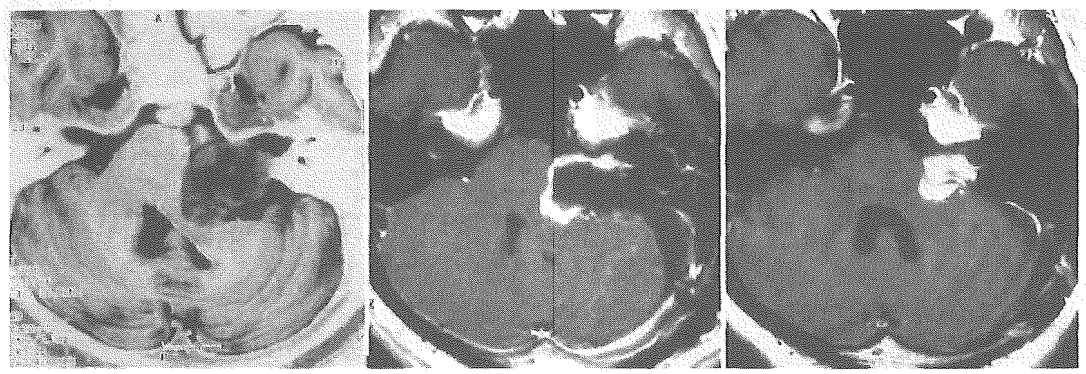


FIG. 1. Magnetic resonance images demonstrating the region in which a VS is located. *Left:* A large tumor causing a marked brainstem deformity. *Center:* An intended partial resection was performed via a translabyrinthine approach, leaving a tumor boundary attached to the facial nerve. *Right:* Three months postoperatively, the residual tumor has shrunk spontaneously, remarkably reducing the brainstem deformity. The tumor is now treated with fractionated SRT (50 Gy in 25 fractions).

Irrespective of the patient's age before fractionated SRT, 14 (14%) of 101 patients had obvious neuroimaging evidence of enlarged lateral ventricles. An additional eight patients had equivocal enlargement of the CSF space, such as an expanding sylvian fissure with a slight enlargement of the lateral ventricles. Therefore, 22 patients may have had asymptomatic CSF malabsorption before fractionated SRT. In this report, however, we required an objective definition of any progression in either clinical or imaging findings related to hydrocephalus during the follow-up period to substantiate a diagnosis of hydrocephalus associated with VS. The requirement was made because of the difficulty in evaluating age-related changes in neuroimaging findings and neurocognitive symptoms in some elderly patients.

Results

Tumor Control

In all 101 patients who received fractionated SRT, the median follow-up period was 45 months (range 6–128 months). The 5-year actuarial rate of tumor control was 91.4% (95% CI 85.2–97.6%). Three patients (3%) underwent salvage tumor resection surgery to counter continuous tumor growth or cystic expansion after fractionated SRT. Those microsurgical excisions were performed 14, 34, and 44 months after fractionated SRT. The maximum diameters of the tumors at the initiation of fractionated SRT were 30, 20, and 27 mm, respectively, and the tumors were cystic, cystic, and solid, respectively. These three cases are considered to be failures of fractionated SRT. From another point of view, 25 (92.6%) of 27 large tumors (maximum diameter $\geq$ 25 mm) were controlled by fractionated SRT and only one (1.4%) of 74 small tumors (maximum diameter $<$ 25 mm) required salvage excision.

Twelve patients with either postoperative residual (seven patients) or recurrent (five patients) tumors received fractionated SRT as an adjuvant therapy or a salvage therapy, respectively. In the former seven cases, the interval between resection and fractionated SRT varied from 1 to 14 months. The variations in interval were mainly due to varying degrees of spontaneous postsurgical shrinkage of the residual tumor (Fig. 1). The maximum diameters of the tumors at the time of radiotherapy ranged from 15 to 40 mm (median 26 mm) and the median follow-up period was 45 months (range 20–113 months). None of the 12 patients suffered from tumor regrowth during the follow-up period.

It is noteworthy that the volume of the posterior fossa in the Japanese population is smaller than that in Western populations. We frequently encountered a tight posterior fossa and a narrow cerebellopontine angle cistern, as shown in Fig. 1, and therefore it was difficult to apply grading systems such as the Koos grading system[12] or the Hannover tumor-extension grading system.[34] In the present series, a medium-sized VS in a tight posterior fossa often caused a slight brainstem deformity.

Hearing Preservation

In this series, 748 audiological examinations were performed by otologists during the postfractionated SRT follow-up period in 82 patients in whom the PTA was assessable (Fig. 2). The median follow-up period in this population was 43 months (range 6–128 months), and the

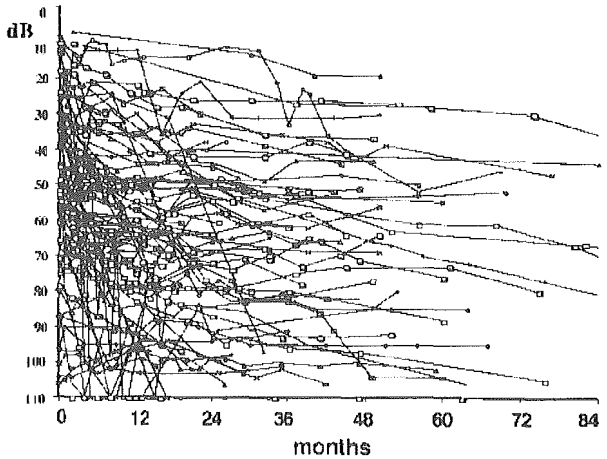


FIG. 2. Graph showing individual chronological changes in PTA after fractionated SRT. In this series 748 audiometrical examinations were performed in 82 patients who had testable hearing before radiotherapy.

TABLE 1

*Correlation between symptomatic communicating hydrocephalus requiring a shunt placement operation and both follow-up period and size of tumor**

Follow-Up Period	Tumor Size (max diameter)	VP Shunt (no. of patients)	
		No	Yes
<5 yrs	<25 mm	45	4
	≥25 mm	13	6
≥5 yrs	<25 mm	23	0
	≥25 mm	5	1

* Includes 97 patients who underwent MR imaging and neurological examinations, but did not undergo tumor resection.

mean number of examinations per patient was 7.6 (range 2–24). In five of the 43 patients who exhibited decreased hearing (Gardner–Robertson Classes II–V) before undergoing fractionated SRT the PTA improved. In four of the 82 patients in whom the PTA was assessable deafness occurred. Twenty-eight of 36 patients with Gardner–Robertson Class I or II hearing just before fractionated SRT retained Class I or II hearing at their last otological examination. Five years postfractionated SRT, the actuarial rate of hearing preservation (Gardner–Robertson Classes I–II) was 71.7% (95% CI 54.5–88.9%) in patients with useful hearing before fractionated SRT. The actuarial 5-year rate of class preservation, including Classes I to V, was 64.6% (95% CI 53.3–75.9%). None of the 20 patients who were audiologically monitored for longer than 5 years experienced any remarkable hearing deterioration after 5 years.

Patients With Hydrocephalus

After fractionated SRT hydrocephalus became symptomatic in 12 (12%) of 101 patients, who therefore required placement of a VP shunt performed using a programmable shunt system. The shunt placement operation resolved all symptoms related to hydrocephalus in all patients. In one patient, communicating hydrocephalus developed with simultaneous enlargement of the VS; the tumor was neurosurgically removed as described earlier, after which the patient's persistent symptomatic communicating hydrocephalus was treated by placement of a shunt.

In the remaining 11 patients (11%), communicating hydrocephalus became clearly symptomatic without any evidence of tumor enlargement after fractionated SRT. These cases were considered to be instances of communicating hydrocephalus probably due to CSF malabsorption associated with VS, although it was possible that the effect of radiotherapy aggravated the CSF malabsorption by causing tumor tissue necrosis. The 11 patients received a shunt without tumor resection 4, 7, 7, 8, 10, 12, 13, 13, 16, 18, or 20 months (median 12 months) after fractionated SRT, respectively; all 11 cases of communicating hydrocephalus that required a shunt operation became symptomatic within 2 years after fractionated SRT. In the 29 patients who were followed up for 5 years or longer with MR imaging and accurate neurological examinations to evaluate hydrocephalus, the incidence of symptomatic hydrocephalus did not increase along with the longer observation period (Table 1).

It should be noted that one patient underwent fractionated SRT for tumor recurrence 2 years after a subtotal resection. This patient experienced symptomatic hydrocephalus 10 months postfractionated SRT without causing tumor regrowth. Among the 12 patients who underwent resection before fractionated SRT, one (8%) experienced hydrocephalus.

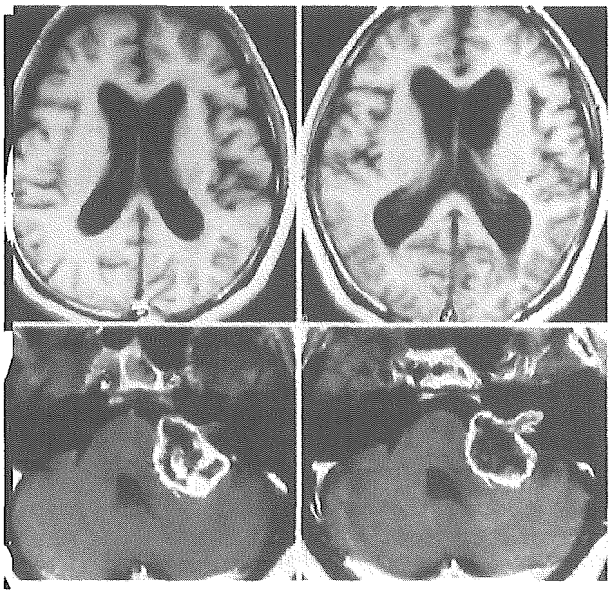


FIG. 3. Magnetic resonance images. *Upper* and *Lower Left:* At the time of the radiotherapy, this 54-year-old man has a large VS and asymptomatic enlarged ventricles. *Upper* and *Lower Right:* Symptoms such as mental deterioration and gait disturbance have become apparent 6 months after radiotherapy, but the VS is stable in size and its central necrosis is evident.

Among the 11 patients, one experienced subacute hydrocephalus 4 months postfractionated SRT with evidence of a mildly increased level of lumbar CSF pressure (250 mm H_2O), although ventricular dilation had been remarkable even before the fractionated SRT and the fourth ventricle was found to be open. In this patient, the possibility of a CSF flow obstruction at the exit of the fourth ventricle could not be completely discounted, and thus it was not clear whether the hydrocephalus was obstructive or communicating. Symptoms in the remaining 10 patients appeared and developed slowly over a couple of months with clear evidence on MR images of an open fourth ventricle. The CSF pressure measured in six patients by lumbar puncture remained within the normal range or was slightly elevated (range 105–220 mm H_2O). The patients' neurological symptoms included chronic headache with or without occasional vomiting, gait disturbance or unsteadiness, occasional urinary incontinence, and/or mild cognitive deterioration such as memory disturbance, decreased daily activity, and loss of attention.

The mean size (25.5 ± 7.8 mm) of the 11 tumors that caused symptomatic communicating hydrocephalus was significantly larger than that (18.2 ± 8.7 mm) of the 86 tumors unrelated to hydrocephalus ($p = 0.011$, Mann–Whitney U-test). The maximum diameters of the 11 tumors that caused hydrocephalus ranged from 15 to 40 mm, and seven of these tumors had diameters larger than 25 mm. Only four (5.6%) of 72 patients harboring a tumor with a maximum diameter smaller than 25 mm received a shunt (Table 1).

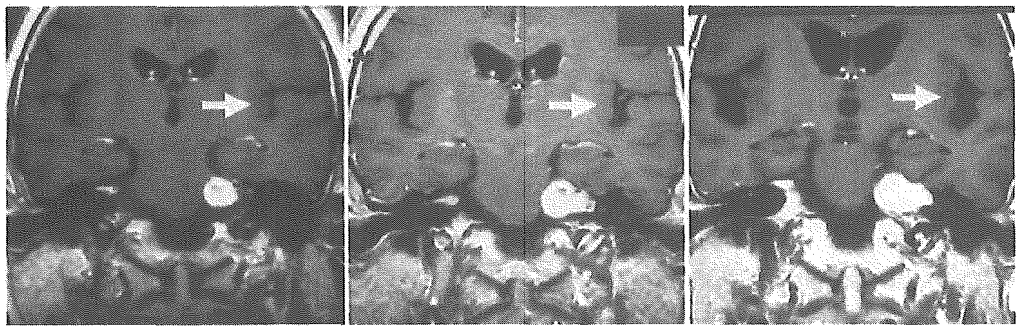


FIG. 4. Magnetic resonance images. *Left:* At the initial diagnosis of VS and 41 months before radiotherapy was initiated in a 71-year-old woman, the CSF space appears normal in size and shape. *Center:* At the time of radiotherapy, the CSF space is enlarged. *Right:* Thirteen months later, the patient's communicating hydrocephalus has become symptomatic. Note the gradual dilation of the cisterns and fissures *(arrows)*.

Figure 3 demonstrates a representative case. This 54-year-old man had a large VS and asymptomatic enlarged ventricles at the initiation of fractionated SRT. His family noted changes in his behavior, with low activity in daily life, memory disturbance, and unsteady gait 6 months after radiotherapy. Although the VS was almost stable, the lateral ventricles had slightly increased in size. The patient received a VP shunt and his symptoms disappeared completely.

One characteristic feature of progressive communicating hydrocephalus observed by serial MR imaging was the gradual dilation of the sulci and fissures, as well as the ventricles, as shown in Fig. 4. Such abnormal widening of the CSF space due to CSF malabsorption was indistinguishable from age-related dilation, particularly among elderly patients. If such patients complained of mild headache, unsteadiness of gait, balance disturbance without cerebellar signs, or slight memory disturbance, it was often extremely difficult to identify an indication for shunt placement surgery. In some patients, ventricular dilation occurred after fractionated SRT without causing any symptoms, as shown in Fig. 5. Remarkable dilation of the CSF space mostly occurred and progressed between approximately 6 and 24 months after fractionated SRT, in both symptomatic and asymptomatic cases.

Neurological Complications and Outcome

Apart from symptoms caused by hydrocephalus, the complications of fractionated SRT were transient facial nerve palsy (weakness), trigeminal neuropathy (facial numbness), or dysequilibrium (balance disturbance), which were observed in 4% (four patients), 13.9% (14 patients), and 16.8% (17 patients) of the 101 patients, respectively. It is noteworthy that gait unsteadiness, which had been attributed to VS or considered an adverse effect of fractionated SRT, often improved after treatment with a VP shunt for communicating hydrocephalus.

Normal facial nerve function (House–Brackmann[9] Grade I) was preserved in all 92 patients who had normal facial function at fractionated SRT. Facial weakness transiently worsened in four patients who had facial palsy before fractionated SRT. These patients were treated with steroid medications and experienced successful improvement thereafter, and the palsy in one patient improved on that observed before fractionated SRT. Only in one patient (0.9%) with mild facial palsy (House–Brackmann Grade III) due to previous resection did facial weakness progress slightly after fractionated SRT and remain persistent (House–Brackmann Grade III). Apart from weakness, several patients complained of loss of taste or an excess or loss of tearing, but most of these symptoms were ameliorated spontaneously.

Normal trigeminal nerve function was preserved in 94 (96%) of 98 patients who had intact trigeminal function before fractionated SRT. The dysequilibrium described by patients as minimal dizziness, temporary vertigo, imbalance, or unsteadiness, occurred de novo or was exacerbated in 17 patients, but did not hamper their daily lives, whereas tinnitus improved in 11 of 37 patients and dizziness or vertigo improved in 11 of 20 patients. One patient experienced vagal palsy, which presented as a cough, hiccups, and hoarseness, but recovered completely. Apart from three patients who underwent salvage neurosurgery, some other neurological symptoms occurred in seven patients harboring large tumors during the period of transient enlargement of the tumor, which compressed the cerebellum and the pons. In five of the seven patients, perifocal pontine edema adjacent to the tumor was evident on MR images. The symptoms were cerebellar ataxia in four patients, hemifacial spasm in four patients, and very slight hemiparesis in three patients. These complications were well controlled, however, with oral administration of steroid medications. Two patients who underwent salvage surgery after fractionated SRT were doing well, with no additional neurological deficit. The neurological status of one patient with a large cystic VS worsened after salvage tumor removal, but gradually improved to the level observed just before the operation. This was a complication of the microsurgery itself and the surgery was not hampered by the patients'history of fractionated SRT.

Discussion

Because there have been numerous publications on the effects of stereotactic delivery of radiation for both fractionated SRT and SRS,[2,5–7,10,11,13,14,16–19,21,22,27–31,34–36,38,39,43] we will focus on the management of associated communicating hydrocephalus (CSF malabsorption).

Overall Results

The overall results of using fractionated SRT in this se-

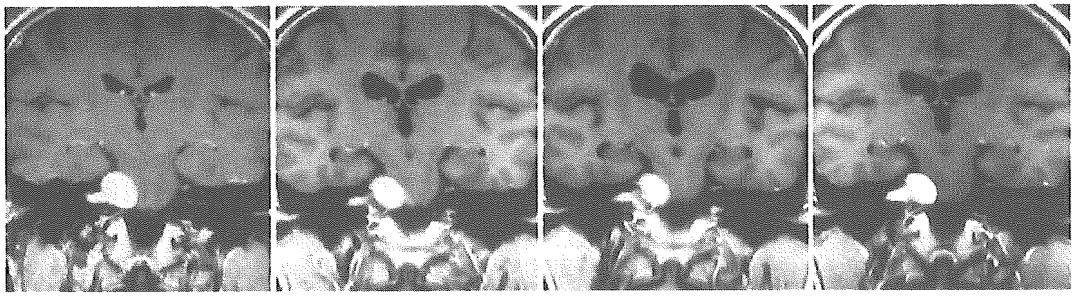


FIG. 5. Magnetic resonance images obtained in a 50-year-old woman with a right-sided VS. At the time of SRT, the size of the woman's ventricles was normal *(left)*, but began to increase 15 months after therapy *(center left)*. Twenty-seven months posttherapy the ventricles have enlarged to their greatest size and the patient's total intelligence quotient is 108 without any symptoms related to the ventricular dilation *(center right)*. Forty-three months posttherapy the ventricles have decreased in size *(right)*.

ries, including the tumor control rate and the incidence of diverse complications, are comparable to the best result of single-fraction radiosurgery published in recent reports.[5,6,27,30,31,38]

In 1998, in a preliminary report we noted a hearing preservation rate of 69% in 24 patients at 2 years postfractionated SRT (median follow-up period 22 months).[32] Despite the increased number of patients, longer observation periods, and larger tumors treated in the present study, the actuarial 5-year rate of useful hearing preservation (Gardner–Robertson Class I or II) was 72%, which is equivalent to or better than our previous results. In 2002, Regis and colleagues[31] reported that 24 (50%) of 48 patients whose preoperative hearing was useful (Gardner–Robertson Class I or II) retained useful hearing after SRS. The median tumor size in our study was larger than that in their study. In 2001, Spiegelmann, et al.,[38] described a hearing preservation rate (speech-discrimination score > 70%) of 77% (10 of 13 patients) after a mean follow-up period of 32 months. In that study the maximum mediolateral diameter of the tumors ranged from 10 to 30 mm (mean 20 mm). In 2001, Flickinger, et al.,[5] reported that serviceable hearing (Gardner–Robertson Class I or II) was preserved in 61 of 75 patients who previously had a hearing level of Class I or II, giving a 5-year actuarial preservation rate of 73.5%. The median transverse tumor diameter in their study was 19 mm (range 4–52 mm). In 2000, Prasad[29] observed that 58% of patients who had useful hearing (analyzed by Gardner–Robertson classification) before SRS had preservation of hearing at a mean follow-up review of 4.3 years. Although a simple comparison with other reports seems difficult, the preservation rate in the present series is one of the best results reported for large series in which the authors have described various radiation therapies for VS and precise audiological outcomes.

Cerebrospinal Fluid Malabsorption

Obstruction of the CSF pathway and compression symptoms are often compelling indications for larger tumors to be resected or at least decompressed.[29] Currently, the obstructive hydrocephalus caused by such large VSs is seen infrequently because these tumors are detected much earlier than was previously the case. Nevertheless, enlargement of the CSF space or hydrocephalus resulting from the CSF malabsorption associated with VS is still common. This has been tentatively explained by the high content of protein in the CSF, which impedes reabsorption through pacchionian granulations when hydrocephalus associated with VS is observed in the absence of obvious obstructions.[42] Although it was difficult to find a report in which the outcomes of patients with hydrocephalus after radiotherapy for VS was precisely described, to our knowledge communicating hydrocephalus requiring treatment with a shunt may not be an infrequent phenomenon in patients with VS.

Although little information has been published regarding the association of hydrocephalus and VS,[25] it has been reported that 3.7 to 15% of patients with VS experience hydrocephalus, and the most frequent clinical manifestations are usually similar to those of NPH.[1,3,24] Atlas, et al.,[1] observed 14 patients with hydrocephalus, including obstructive hydrocephalus, in a series of 104 consecutive cases of VS, and detected a significant correlation between the hydrocephalus and increasing tumor size.

Pirouzmand, et al.,[25] reported that 39 (13.7%) of 284 patients with cerebellopontine angle tumors, mostly VSs, had hydrocephalus. According to their report, only five patients had obvious obstructions at the level of the fourth ventricle and the symptoms of the remaining 34 patients were consistent with those of NPH. Fifteen patients underwent shunt placement procedures, as the only treatment (three patients), after microsurgical tumor excision (five patients), after radiosurgery (three patients), or as expectant management (four patients).[25] In their series, three (6.5%) of 46 patients received a shunt after SRS. In our series, 14 (14%) of 101 patients were suspected of having an enlarged CSF space before fractionated SRT, although this was not definitive, and as a result, 11 patients (11%) underwent VP shunt placement procedures for communicating hydrocephalus.

The CSF pressure at the lumbar level was high in some patients who complained of headaches. Many patients with NPH are known to have episodes of increased intracranial pressure that are not discovered because only a few lumbar punctures are performed.[37] The lack of a cohesive theory to explain communicating hydrocephalus means it is difficult to predict which patients with enlarged CSF spaces will respond to shunts. In fact, the diagnosis of NPH is still best made on the basis of clinical symptoms including gait disturbance, general psychomotor retardation, memory loss, and urinary incontinence.[37]

Gait disturbance may appear first as the sole symptom or