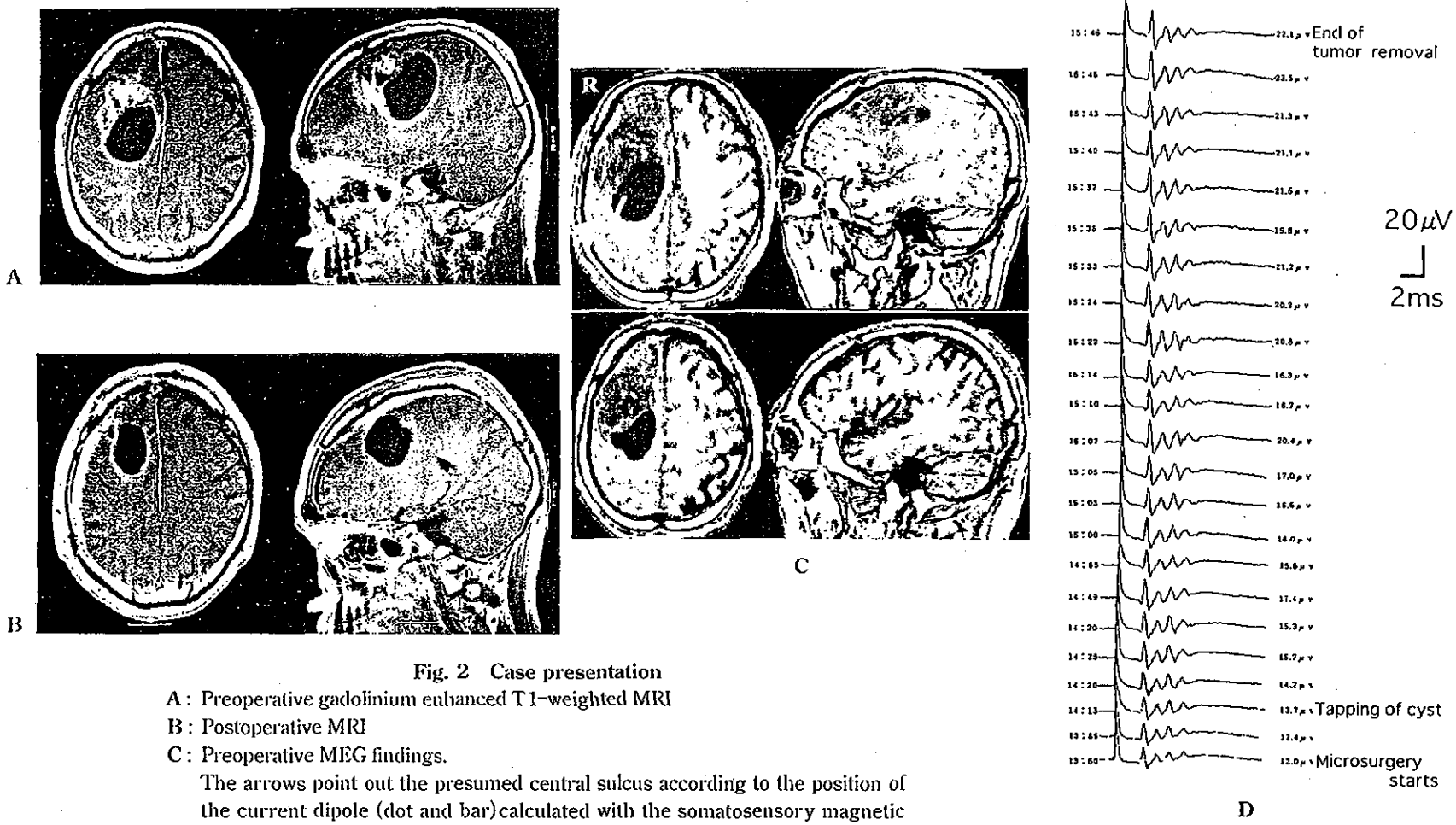

Fig. 2 Case presentation

A : Preoperative gadolinium enhanced T1-weighted MRI

B : Postoperative MRI

C : Preoperative MEG findings.
The arrows point out the presumed central sulcus according to the position of the current dipole (dot and bar) calculated with the somatosensory magnetic evoked fields, which indicates the primary sensory cortex.

D : The arrays of the intraoperative MEPs, showing the increase of the D-response amplitude as the tumor was being resected.

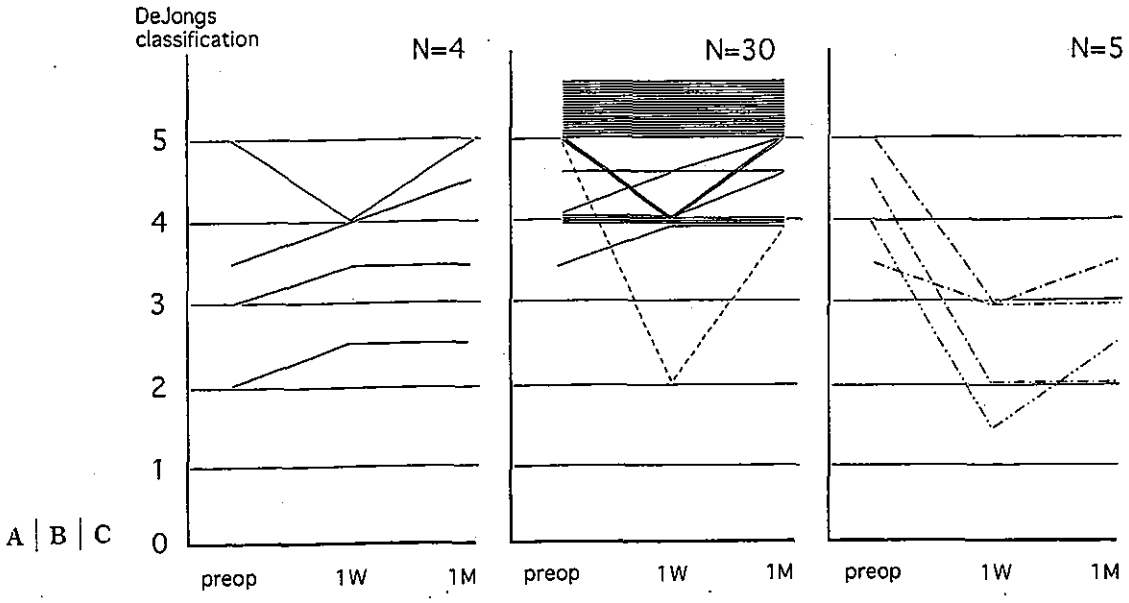

Fig. 3 Pre- and post-operative motor function change
A: "Increase" group, B: "No change" group (Dotted line shows a case with the tumor at supplementary motor area), C: "Diminish, decrease and disappear" cases (diminish group, decrease group, disappear group)
preop: preoperation, 1W: 1 week after operation, 1M: 1 month after operation.

検討した。四肢運動機能はDeJong分類に従い[15]，術直前，術後1週間，術後1カ月に上肢と下肢の平均として評価した。D-responseの振幅の変化との相関は術後1カ月の運動機能との間で評価した。術中MEPのD-responseの振幅変化率を⊿MEP(%)＝(摘出操作終了時D-responseの振幅/摘出操作前D-responseの振幅)×100(%)とし，⊿MEP＞125%を増大群，125%≧⊿MEP＞75%を不変群，75%≧⊿MEP＞50%を減弱群，50%≧⊿MEP＞0%を減少群，⊿MEP＝0%を消失群と定義した。

III. 症例呈示

〈症例〉 43歳男性。左利き，右前頭葉神経膠腫

術前，左片麻痺(DeJong分類：上肢3，下肢4)を認めた。MRIで左前頭葉に最大径4 cmの嚢胞成分を含んだ腫瘍性病変を認め，古典的計測法(Ring法)を用いると一次運動野直下に存在すると考えられたが(Fig. 2A)，MEGによる検討では一次運動野は腫瘍により圧迫され後方へ偏位しており，腫瘍は一次運動野自体へは及んでいないものと推定された(Fig. 2C)。

脳表SEPで中心溝を同定し，右中心前回に刺激電極を置いてMEPを記録した。摘出操作を開始して間もなくD-responseの振幅増大が認められ，⊿MEPは150%であった(Fig. 2D)。術中所見でも，腫瘍は一次運動野には及んでおらず腫瘍を全摘した(Fig. 2B)。術直後より運動麻痺は改善(術後1週：DeJong分類；上肢4，下肢4，術後1カ月：上肢4，下肢5)した。

IV. 結 果

1. MEPの検出率

対象とした45例中，39例(86.7%)で術中MEPの記録が可能であった。30 mA以上の高電位刺激を行っても6例では安定したMEPは得られなかった。これらはいずれも病変が一次運動野や錐体路に及んでおり，術前の運動麻痺はDeJong分類2以下と高度であった。上肢の運動機能がDeJong分類2以下でMEPが記録可能であった症例は7例中1例(14.3%)にすぎなかった。

2. 術中MEPの変化と術前後における運動機能の変化の相関について

39例で運動機能の術前後の変化とMEPとの相関を検討した。

増大群は39例中4例(10.3%)であった。4例のうち，術前運動麻痺を認めた3例では術直後より運動機能の改善が得られた。術前運動麻痺を認めなかった1例は一過性にDeJong分類4の運動麻痺が出現したが，1カ月の時点では運動麻痺は消失していた(Fig. 3A)。

不変群は39例中30例(76.9%)であった。30例中，1例で術後運動機能の悪化を認めたが，その他の29例は術後1カ月の時点で運動機能の悪化を認めなかっ

た(Fig. 3B)。運動機能の悪化を認めた1例は補足運動野の病変を摘出した症例であった。

減弱群は39例中1例(2.6%)であった。術後，運動機能の変化を認めなかった(Fig. 3C)。

減少群は39例中3例(7.6%)であった。3例とも術後に運動機能の悪化を認めた(Fig. 3C)。

消失群は39例中1例(2.6%)であった。術直後に完全麻痺となり，最終的にも強い運動機能障害が残存した(Fig. 3C)。

V. 考 察

1. MEP記録法とその定量性について

開頭術中に一次運動野を直接電気刺激し誘発された錐体細胞の興奮と伝導を記録する方法としては，錐体路脊髄電位記録法，錐体路末梢神経電位記録法，錐体路誘発筋電図記録法の3つがある[6,12,16,18]。錐体路末梢神経電位記録法は，末梢神経の直上の皮膚に記録電極を置くか，あるいは皮下に刺入し，錐体細胞の興奮が引き起こした末梢神経の活動電位を記録する。錐体路誘発筋電図記録法は，刺激に相当する部位の筋肉上または内に記録電極を置き，筋の収縮を筋電図として記録する。いずれも低侵襲で簡便な方法といえるが，これらの方法では安定した電位の記録が難しく，潜時や振幅の個体差が大きい[9]。また，複数のシナプスや神経筋接合部を介するため，麻酔薬や筋弛緩剤といった種々の薬剤の影響を受けやすいことから記録の普遍性に難がある[3,5,13,23]。

われわれは脊髄レベルで活動電位を記録する錐体路脊髄電位記録法を採用した。錐体路脊髄電位の記録には経皮的に硬膜外腔に記録電極を挿入することが必要で，やや侵襲は高いが[11,12]，他の二法では観察不可能な一次運動ニューロンの活動電位であるD-responseが唯一記録可能である。D-responseはシナプスを介さない錐体路第1ニューロンの活動電位であるため，麻酔薬や筋弛緩剤，脳温などの影響を受けにくく安定した記録が可能で，その振幅の変化から錐体路に生じた変化の程度，すなわち運動機能に対する侵襲の程度を評価できる[11,12,15]。

しかし，MEPの変化率と術前後における運動機能の変化を定量的に検討した論文は，われわれが検索し得た限りではわずかに2編のみであった[11,16]。頭髄硬膜外電極を用いたHorikoshiらの報告では，MEPが摘出操作前の50%以上保たれていれば術後運動機能は温存されたとしている[11]。また，筋電図を用いたKombosらの報告では，EMGの振幅が20%以下になると運動機能の悪化が危惧されるとしている[16]。

今回われわれは，摘出操作開始前のD-responseを基準とした術中のD-responseの振幅変化率を5群に分類し，運動機能についてもDeJong分類を用いることで定量性を持たせて評価した。さらに術後患者のQOLの維持，向上を検討する観点から，運動機能評価は術直後ではなく，術後1カ月で行った。その結果，振幅増大群(4例)では，術前に運動麻痺を認めた3例においては術直後より運動機能の改善が得られ，術前の状態よりも改善した。運動麻痺を認めなかった1例は一過性に軽度の運動麻痺が出現したものの，1カ月以内に術前の状態まで回復したことから，運動機能は全例で温存あるいは改善した。

不変群(30例)および減弱群(1例)では，補足運動野に手術侵襲が及んだ1例を除く30例では，一過性の術後運動機能の悪化を認めたものもあったが速やかに改善し，運動麻痺の悪化を認めたものはなかった。減少群(3例)では，全例で術後に運動機能の悪化を認めた。消失群(1例)では，術直後から強い運動麻痺が出現し永続化した。

以上をまとめると，Δ MEP > 125%であれば術前の運動麻痺の改善，125% ≧ Δ MEP > 50%であれば運動機能の温存が期待でき，一方50% ≧ Δ MEPであれば運動機能の術後悪化が予想されることが明らかとなった。

2. MEPの有用性，その応用と限界

術前の運動機能がDeJong分類3以上の症例では39例全例でD-responseの確実な記録が可能であったのに対し，DeJong分類2以下の7例中6例では記録できなかった。MEPは，運動麻痺がDeJong分類2以下と高度な症例においてはその記録が困難で有用性に乏しいといえる。術前の運動麻痺がDeJong分類2以下と高度であった7例中4例は，腫瘍が一次運動野そのものに浸潤していた。一次運動野そのものに腫瘍が浸潤している場合には，運動機能の悪化をきたすことなく腫瘍の全摘出を行うことは不可能であり，このような場合に腫瘍を摘出するか否かの決定にはより高度な判断を要する。

補足運動野に病変が及んでいた1例ではMEPのD-responseの変化からは術後運動麻痺の出現を予測し得なかった。本部位の障害による運動機能障害は，1カ月程度で改善する例が多いことが報告されているが[17,21]，われわれの例においても経過とともに運動機能の改善が認められた。一次運動野や錐体路の障害がなく補足運動野の障害のみ生じた場合，このようにMEPは変化せず術後運動機能障害のモニタリングにはならない。MEPの限界を示すものと考えられる。

結　語

髄内病変45例に対し，開頭術中に露出された大脳一次運動野を直接電気刺激し，頸髄硬膜外腔に挿入した電極からMEPモニタリングを行い，MEPの検出率およびD-responseの振幅変化と術後運動機能との相関につき検討した。

術前運動麻痺がDeJong分類2以下の症例ではD-responseの記録が困難であった。一方，DeJong分類3以上の症例では確実な記録が可能であった。

術中MEPのD-responseの振幅変化をモニタリングすることで術後運動機能を予測することが可能であり，⊿MEP＞50%であれば術後運動機能は温存され，⊿MEP≦50%であれば術後運動機能の術後悪化が予側し得た。

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Abstract

Significance and Usefulness of Corticospinal Motor Evoked Potential Monitoring for Lesions Adjacent to Primary Motor Cortex

by

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This study evaluated the usefulness of intraoperative corticospinal motor evoked potential(MEP) monitoring in preventing postoperative motor deficits, and whether this procedure contributed to surgery on intrinsic brain lesions in the vicinity of the motor area. The subjects were 45 patients with brain tumors located in and around the primary motor area. MEP was recorded through the cervical epidural electrodes in response to stimulation of the motor cortex. The amplitude of D-response of MEP was compared at the beginning and at the end of surgery. Then MEP changes were divided into five groups ; "increase", "no change", "diminish", "decrease" and "disappear". We used the DeJong classification for qualitative analysis of motor function, and reviewed these findings in relation to the change in MEP. It was possible to record MEP when the preoperative motor weakness was DeJong 3 or better. There was no postoperative motor deficit when the MEP amplitude was preserved at better than 50% of a control amplitude. If the amplitude decreased to less than 50%, motor deficits were encoutered. When MEP amplitude increased during the surgery, preoperative motor weakness was improved after the surgery. It is concluded that there is little possibility of causing motor deficits even if tumor removal is aggressively pursued, as long as the amplitude of D-response remains at 50% or more of the baseline. This monitoring procedure is expected to improve the overall surgical results in patients with intrinsic brain tumors around the motor area.

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〈お知らせ〉

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Clinical Article

Routine clinical adoption of magnetic resonance imaging was associated with better outcome after surgery in elderly patients with a malignant astrocytic tumour: a retrospective review

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Summary

Background. There is controversy about extensive surgical treatment for a malignant astrocytic tumour in more elderly patients who may have poorer outcomes and higher complication rates. This retrospective study investigated outcome in elderly patients with malignant astrocytic tumour before and after the adoption of routine clinical use of magnetic resonance (MR) imaging.

Methods. During 1982 through 1999, 88 patients with malignant astrocytic tumour aged 60 years or over were treated in our institute. Thirty-seven patients had an anaplastic astrocytoma and 51 had a glioblastoma. Thirty-seven patients treated from 1982 to 1988 did not have pre-operative evaluation by MR imaging (Group A), 26 patients treated from 1989 to 1995 had preoperative MR imaging evaluation (Group B), and 25 patients treated after 1996 underwent preoperative MR imaging with functional brain mapping and intra-operative navigation system monitoring (Group C).

Findings. The median survival time was 8.8 months in Group A, 12.7 months in Group B, and 17.6 months in Group C. Patients with glioblastoma in Group B (11.7 months, $n = 15$) and Group C (16.0 months, $n = 19$) had significantly longer median survival time than in Group A (6 months, $n = 17$) ($P = 0.0054$ between Groups A and B, $P = 0.0024$ between Groups A and C). Better preoperative performance status, more thorough surgical resection, and better performance status after the initial treatment was obtained after the introduction of MR imaging, and patients with the optimal indicators showed significantly longer survival time compared with the patients without these factors.

Interpretation. Pre-operative MR imaging may contribute to longer survival time by providing an earlier diagnosis in patients with better performance status, by allowing more thorough surgical resection, and resulting in better performance status after the treatment.

Keywords: Malignant astrocytoma; elderly; outcome; surgery.

Introduction

The treatment of patients with a malignant astrocytic tumour is one of the most challenging contemporary neurosurgical problems. Surgical treatment, especially for the elderly, is considered to result in a poor outcome and a high complication rate [3, 7, 8]. The median survival was only 2.2 months in patients older than 60 years with glioblastoma [9]. Craniotomy plus radiotherapy improved the median survival up to 16 weeks in elderly patients (60 years or over) who were treated during 1983 through 1989 [14]. In a series of 146 adults, 27 were older than 65 years and had a median survival of only 4.8 months [6]. These reports illustrate the poor prognosis for elderly patients with malignant astrocytic tumour.

Total surgical resection with adjuvant radiochemotherapy is considered to be optimal leading to prolonged survival time and improved neurological status in patients with a malignant astrocytic tumour [12]. However, the merits of extensive surgical resection in elderly patients with a malignant astrocytic tumour, remain controversial [8]. Extensive or repeated surgery in an elderly patient may have greater risks of surgical morbidity and death and there are several reports that radical surgery provides little benefit for elderly patients with a malignant astrocytic tumour [5, 7]. Nevertheless, in another report the optimal results in elderly patients were achieved in those in better performance status by thorough surgical resection and definitive radiation therapy [10].

The present study is based on a comprehensive analysis of the medical records in our department during 1982 through 1999 in order to assess the outcome in elderly patients with a malignant astrocytic tumour

before and after the introduction of magnetic resonance (MR) imaging. We analyzed the prognostic importance of pre- and postoperative performance status, extent of surgical resection at operation, and postoperative complications.

Methods and material

Case material

During 1982 through 1999, 281 patients with malignant astrocytic tumour were treated by surgical procedures and/or radio-chemotherapy in our department. One hundred and seven patients treated from 1982 to 1988 had no pre-operative evaluation by MR imaging (Group A), 84 patients from 1989 to 1995 underwent pre-operative MR imaging evaluation (Group B), and 90 patients after 1996 underwent preoperative MR imaging including functional brain mapping and surgery under guidance from an intra-operative navigation system (Group C). Intra-operative functional mapping was also used for patients with malignant astrocytic tumour in eloquent areas in Group C.

The present study included 88 patients who were aged 60 years or over. The 51 male and 37 female patients were aged from 60 to 78 years (mean age 66.8 ± 4.7 years). Twenty-seven patients were older than 70 years. There were 37 patients in Group A, 26 patients in Group B, and 25 patients in Group C.

Histological confirmation was required for inclusion in this study. The histological diagnosis was established using the new World Health Organization classification. The 281 patients with malignant astrocytic tumour included 154 cases of anaplastic astrocytoma and 127 cases of glioblastoma. Thirty-seven (24.0%) of the cases of anaplastic astrocytoma, and 51 (40.2%) of the cases of glioblastoma occurred in elderly patients.

Treatment

The treatment protocol was relatively uniform but not identical for all patients. Thirty patients (34.1%) underwent gross total resection, and 58 patients (65.9%) underwent partial resection or stereotactic biopsy. Nineteen patients were treated by radiation therapy. The standard radiation therapy consisted of 30 Gy in 15 fractions to the tumour and peritumoral brain and 30 Gy in 15 fractions to the whole brain before 1987, and 60 Gy in 30 fractions to the local brain thereafter. The standard radiotherapy protocol was a total dose of 60 Gy in 30 fractions of 2 Gy, 5 days per week over 6 weeks, delivered to the local brain by parallel opposed ports with megavoltage equipment. 1-(4-Amino-2-methyl-5-pyrimidinyl) methyl-3-(2-chloroethyl)-3-nitrosourea (ACNU) was administered intravenously or intra-arterially for 58 patients.

Clinical investigation

The pre- and postoperative performance status was classified using the Eastern Co-operative Oncology Group (ECOG) scale ranging from 0 to 4. The postoperative performance status was determined between 1 and 3 months after surgery. Surgical morbidity was defined as postoperative intracranial haematoma, iatrogenic neurological deficit, and sepsis at the surgical site. Follow-up analysis was obtained by review of the patient's records or by contact with the family. Eighty-three of the 88 patients (94.3%) had died by the cut-off date for data analysis, June 30, 2001. For survival analysis, day 0 was defined as the first day of admission.

Statistical analysis

Survival rates were determined using the Kaplan-Meier method. The statistical significance between life table curves was determined using the logrank test.

Results

The median survival time of the 88 elderly patients was 11.7 months, which was significantly shorter than that of patients under the age of 60 years. Median survival times of the elderly patients with anaplastic astrocytoma and glioblastoma were significantly shorter than those of the younger patients with these tumours. The median survival time of elderly patients with anaplastic astrocytoma was significantly longer than that of elderly patients with glioblastoma (Table 1).

As shown in Table 2, median survival times of elderly patients with glioblastoma in Groups B (11.7 months, $n = 15$) and C (16.0 months, $n = 19$) were significantly longer than those in Group A (6 months, $n = 17$), respectively ($p = 0.0054$ between A and B, $p = 0.0024$ between A and C). Median survival time was somewhat longer after the introduction of functional brain mapping and

Table 1. *Survival in patients undergoing surgery for malignant astrocytic tumour*

Histology	No. of patients	Median survival time (months)	Probability
Total	281		
–under 60 year	193	22.6	P < 0.0001
–60 year or over	88	11.7	
Anaplastic astrocytoma	154		
–under 60 years	117	29.3	P = 0.0006
–60 years or over	37	14.7*	
Glioblastoma	127		
–under 60 years	76	16.3	P = 0.0021
–60 years or over	51	10.8*	

* P = 0.0105.

Table 2. *Survival in elderly patients undergoing surgery for malignant astrocytic tumour*

Histology	No. of patients	Median survival time (months)	Probability	
Total	88			
Group A	37	8.8		
Group B	26	12.7	NS	
Group C	25	17.6		
Anaplastic astrocytoma	37			
Group A	20	10.3		
Group B	11	13.8	NS	
Group C	6	34.9		
Giloblastoma	51			
Group A	17	6.0	P = 0.0054*	
Group B	15	11.7		P = 0.0024**
Group C	19	16.0		

* Between Group A and B, ** between Groups A and C.

intra-operative navigation system monitoring in Group C (16.0 months, n = 19) compared to B (11.7 months, n = 15), but there was not a statistical significance between the groups (p = 0.5729).

The number of patients with better pre-operative performance status of ECOG 0-2 increased after the introduction of MR imaging. The median survival time of the patients with better pre-operative performance status was significantly longer than that of the patients with lower performance status of ECOG 3-4 (Table 3).

Gross total resection was achieved in more patients after the introduction of MR imaging. The median survival time of patients with gross total resection was significantly longer than that of patients with partial resection or biopsy (Table 3).

More patients had better postoperative performance status after the introduction of MR imaging. The median survival time of patients with better postoperative performance status was significantly longer than that of patients with lower performance status (Table 3).

The overall morbidity was 30.7%. The surgical morbidity was 17.1% and the medical complication rate was 13.6%. The operative mortality was 0%. Functionally significant neurological worsening occurred in eleven patients, which was caused by cerebral vascular damage during the operation in four patients, surgical intervention extending to eloquent areas in four patients, postoperative intraparenchymal haematoma in one patient, status epilepticus following surgery in one patient, and encephalitis following cerebrospinal fluid leakage in one patient. The median survival time of the patients with or without complications was 8.5 months (n = 27) and 13.8 months (n = 61), respectively, with no statistically significant difference.

Table 3. *Effect of neuroimaging methods on outcome in elderly patients*

	No. of patients				Median survival time (months)	Probability
	Group A	Group B	Group C	Total		
Preoperative ECOG						
0–2	14	14	20	48	17.9	P = 0.0013
3–4	23	12	5	40	7.5	
Postoperative ECOG						
0–2	12	17	19	48	17.6	P = 0.0004
3–4	25	9	6	40	5.7	
Extent of removal						
Gross total	8	6	16	30	19.3	P < 0.0001
Partial or biopsy	29	20	9	58	8.5	

Discussion

The present study indicates that the adoption of pre-operative MR imaging and additional imaging modalities was accompanied by a lengthening in survival time after surgery in elderly patients with a malignant astrocytic tumour. Among the factors in this may have been an earlier diagnosis and thus better performance status at surgery, allowing more thorough surgical resection, and better performance status after the initial treatment. Our analysis found that patients with malignant astrocytic tumour aged 60 years or over could survive as long as 17.6 months using current treatment modalities such as MR imaging with functional mapping, intra-operative navigation system, and intra-operative functional mapping under "awake" craniotomy or under generalized anesthesia. Median survival times extend further after the introduction of functional brain mapping and intra-operative navigation system monitoring in patients with glioblastoma, although there was no statistical significance between Group B and C. The lack of the statistical significance may be due to the small patient population (in which patients with tumour in eloquent area are further less). Future evaluation with a larger number of patients would address this important issue. Alternatively, we do not rule out the possibility that multiple factors including the surgeon's experience, awareness of the referring physician, and development of the operative microscope also contributed, at least in part, to the better outcome.

Most previous studies have found that surgical treatment for elderly patients with malignant astrocytic tumour resulted in high mortality and morbidity as well as a high complication rate [2, 4, 13]. In a series of 207 consecutive patients (mean age 53 years), 53 patients over 65 years old had a complication rate of 30.2%, and 20 patients over 70 years old had a complication rate of 50% [4]. Both rates were much higher than the overall complication rate of 25.1%. In a series of 80 patients aged over 65 years who underwent craniotomy for intra-axial tumour, the death rate was 3.8%, and worsening of the neurological state occurred in 16.3% and medical complications in 28.8% [13]. Surgical treatment for elderly patients clearly carries the risk of a worse outcome and a high complication rate. No significant improvement of survival time was found in 40 patients aged over 65 years treated by aggressive surgery plus radiotherapy compared with 88 patients treated by stereotactic biopsy plus radiotherapy [7]. In their series, the optimal treatment with resection plus radiation for elderly patients with glioblastoma resulted in an average survival of 30 weeks. In contrast, our results demonstrate that patients treated by gross total resection had a significantly longer median survival time (19.3 months) than patients with partial resection or biopsy (8.5 months) ($P < 0.0001$). Gross total resection was obtained in more patients after the introduction of MR imaging, suggesting that pre-operative MR imaging with or without functional mapping provides more precise anatomical and/or functional information, and contributes to more thorough surgical resection.

Our study indicates that pre-operative as well as post-operative performance status is also a significant contributing factor for better prognosis. Elderly patients with better performance status (≥70 Karnofsky performance status score) treated by maximal resection and definitive radiotherapy had a longer survival time than those treated by palliative radiation and biopsy [10]. Median survival was found to be longer in elderly patients who were more functional [1]. Patients older than 70 years with Karnofsky performance status score of more than 70 may benefit from surgical treatment for malignant astrocytic tumour followed by reduced doses of limited field radiotherapy [11].

We propose, based on the findings of this retrospective study that thorough surgical resection should be considered even in elderly patients with malignant astrocytic tumour if their performance status is good and preoperative evaluation by MR imaging is available.

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Technical note

Intraoperative localisation of the lip sensory area by somatosensory evoked potentials

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Summary Accurate localisation of the central sulcus enables maximum tumour resection with minimum morbidity in peri-Rolandic surgery. We investigated intraoperative somatosensory evoked potentials (SSEPs) with combined recording of lower lip and median nerve stimuli during craniotomy in nine patients with peri-Rolandic glioma. Using a custom clip electrode, the lip mucous membrane was stimulated with biphasic pulses with 0.2 ms duration, 10–14 mA intensity and a frequency of 0.7 Hz. Polarity inversion of the SSEP was detected across the central sulcus using median nerve and/or lower lip stimulation in eight of the nine patients in whom the tumour did not infiltrate the lip or hand sensory area. Recording of SSEPs with lower lip stimulation is useful if the resection margin is planned lateral to the hand representation area, if the hand representation area is not exposed by the craniotomy, or if the SSEPs for median nerve stimulation are not clear due to tumour infiltration.

Keywords: central sulcus; glioma; lower lip; somatosensory evoked potential; trigeminal nerve

INTRODUCTION

Recording of median nerve somatosensory evoked potentials (SSEPs) on the cortex is a simple way to identify the central sulcus[1–5] using the hand representation areas of the somatosensory and motor cortex. The electrode strip is placed perpendicular to and across the proposed location of the central sulcus at the hand representation area, angling it more medially at the frontal end.[4,5] Inexact alignment of the electrode over the sensory and motor hand areas will result in the absence of phase reversal. Additionally, recording success rate is much lower when a large peri-Rolandic mass lesion is present.[3] Localisation of the central sulcus at only the hand area may not provide adequate information for more lateral resection in or near the face representation and in these cases, the hand representation area may not be exposed by the craniotomy.

Techniques for monitoring intraoperative SSEPs for the orofacial area have been described but there was both intra- and inter-patient variation in the waveforms and latency.[2] Consequently, orofacial SSEPs have not been used routinely at most centres. We have previously developed optimal parameters for lip stimulus and reported that electrical stimulation of the lower lip evoked the initial cortical response of the trigeminal somatosensory evoked magnetic fields.[6] The initial contralateral response was detected at a latency of 14.6 ± 1.3 ms and was named N15m. The equivalent current dipole of N15m was localised at the posterior bank of the central sulcus with anterior and superior orientation, and inferior to the dipole of N20m for median nerve stimulation.

The present study applies these previously developed clip electrodes and parameters for stimulation of the lower lip and biphasic pulses with a larger stimulation intensity and longer inter-stimulus intervals to record reproducible SSEPs intraoperatively. Lip SSEPs could be utilised for identification of the central sulcus during surgery in and around the orofacial region of the central sulcus.

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MATERIALS AND METHODS

Patients

This study included nine patients, aged 21–69 years (mean 48 years), with gliomas located around the motor-somatosensory cortex manifesting as seizures, sensory disturbance, paresis, speech disturbance, Gerstmann syndrome or headache (Table 1). Informed consent was obtained from all patients.

Somatosensory evoked potentials

All patients, except case 4, underwent surgery under general anaesthesia using propofol, fentanyl, and a short-acting muscle relaxant. Muscle relaxants were suspended during the SSEP recording. Case 4 had an awake craniotomy for language mapping. Techniques for awake craniotomy have been described previously.[7] A frameless stereotactic navigation device (ViewScope; Elekta IGS, Grenoble, France) was used in cases.

Lower lip SSEPs were measured by stimuli of the contralateral lower lip during craniotomy. A clip electrode, developed and produced at our hospital, was attached to the surface of the mucous membrane of the lip (Fig. 1). The electrical stimuli were constant current biphasic pulses of 0.2 ms duration, an intensity of 10–14 mA and a frequency of 0.7 Hz.

Median nerve SSEPs were also measured for comparison. An electrical square wave of 0.2 ms duration was delivered transcutaneously at 3 Hz to the unilateral median nerve. The current intensity was increased between 5 and 10 mA until slight twitches of the thumb were obtained.

A silicone sheet containing eight electrodes (4 × 2 contact grid or 8 contact strip electrode) with 10 mm inter-electrode spacing was placed on the cortical surface, perpendicular to the central sulcus. The resulting data were averaged based on 50 stimulus presentations for both lower lip and median nerve SSEP recordings.

Table 1 Patient characteristics

Case no.	Age	Sex	Diagnosis	Tumour location	Presenting symptoms	Lower lip SSEPs	Median nerve SSEPs	Direct cortical stimulation	Neuronavigation system	Anaesthesia
1	38	M	Anaplastic astrocytoma	R precentral gyrus (face motor area)	L facial seizure	Phase reversal	Phase reversal	Yes	Yes	General
2	54	F	Glioblastoma	L angular-supramarginal gyrus	Speech disturbance and Gerstmann syndrome	Phase reversal	Phase reversal	No	Yes	General
3	66	M	Anaplastic oligodendroglioma	L angular-supramarginal *gyrus*	Speech disturbance and Gerstmann syndrome	Phase reversal	Phase reversal	No	Yes	General
4	45	F	Astrocytoma	L insulo-operculum	Headache	Phase reversal	Not examined (outside craniotomy)	Yes	Yes	Awake
5	51	M	Glioblastoma	R precentral gyrus (hand-digit motor area)	L hand-digit seizure followed by L hemiconvulsion and L upper arm-hand-digit paresis	Phase reversal	No clear response	Yes	Yes	General
6	69	F	Glioblastoma	R precentral gyrus–postcentral gyrus (hand-digit-face sensorimotor area)	L facial seizure followed by L hemiconvulsion	Phase reversal	No clear response	Yes	Yes	General
7	32	M	Anaplastic ependymoma	R postcentral gyrus (hand-digit-face sensory area)	L hand-digit seizure followed by generalised convulsion and L hand-digit sensory disturbance	Phase reversal	No clear response	No	Yes	General
8	21	F	Astrocytoma	L postcentral gyrus (face *sensory area*)	R facial seizure followed by generalised convulsion	No clear response	Phase reversal	No	Yes	General
9	59	F	Glioblastoma	R postcentral gyrus (hand-digit-face sensory area)	L face-upper arm seizure followed by L hemiparesis and L hemisensory disturbance	No clear response	No clear response	Yes	Yes	General

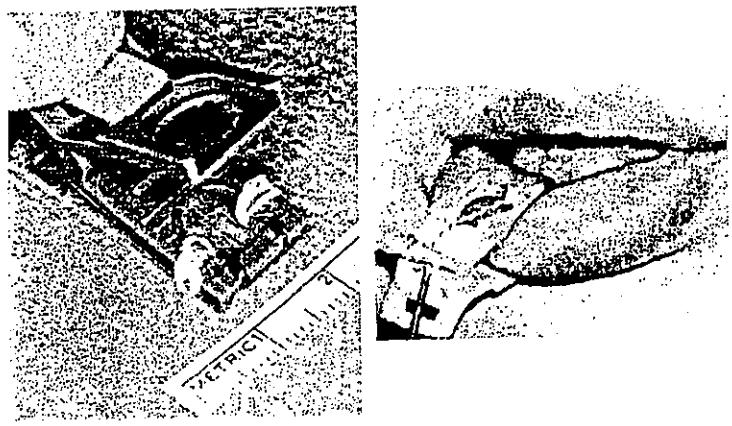

Fig. 1 Stimulation electrode for the lower lip.

The SSEPs were recorded at least twice to assess reproducibility. Recordings from bipolar chains of electrodes were used for the lower lip SSEPs. The reference electrode was placed at the nasion for the median nerve SSEPs.

RESULTS

The first cortical component for contralateral lower lip stimulus (N15), with a peak latency around 15 ms,[6] was obtained in seven of the nine patients. A mass lesion involving the hand and/or face area of the somatosensory cortex was found to abolish the median nerve and/or lower lip SSEPs. Neither lower lip nor median nerve SSEPs could identify the central sulcus in case 9, where identification of the motor cortex by direct stimulation was used with the aid of the neuronavigation system. The lesion in case 7 was also located in the hand-digit-face sensory area, but polarity inversion of the lower lip SSEPs was obtained because the inferior extension of the tumour was more limited than in case 9, preserving the lower lip somatosensory area. The area of the hand representation was not exposed by the craniotomy in case 4.

Representative case report

Case 1: A 38-year old male presented with a protoplasmic astrocytoma manifesting as left facial seizures in August 2000. He underwent partial tumour resection and five courses of three-drug

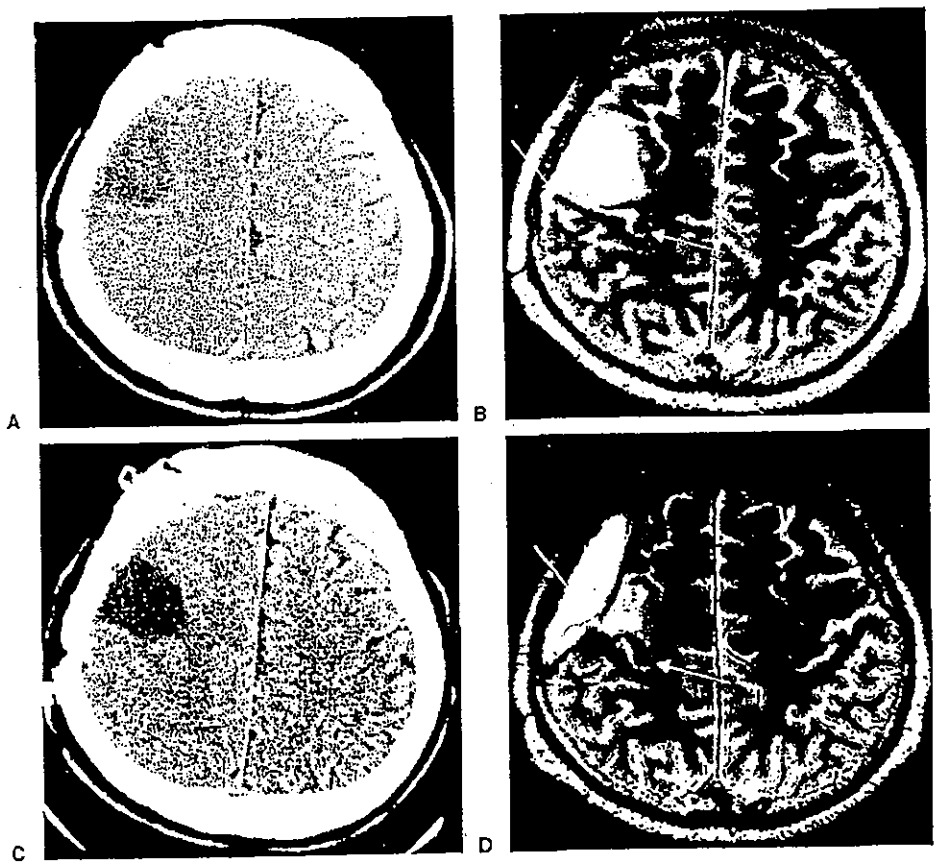

Fig. 2 *Case 1*. Arrows indicate the central sulcus: (A) Preoperative unenhanced computed tomography (CT) scan showing a hypodense glioma close to the central sulcus; (B) Preoperative axial T2-weighted magnetic resonance (MR) image showing the hyperintense glioma; (C) Postoperative CT scan; (D) Follow-up axial T2-weighted MR image.

chemotherapy. However, seizure activity increased in May 2002 and he was admitted to our hospital in July 2002. Left facial seizures occurred approximately 10 times per day. T2-weighted magnetic resonance (MR) imaging demonstrated a hyperintense lesion in the right precentral gyrus. The lesion was hypodense on CT and did not enhance with contrast (Fig. 2(A) and (B)). The tumour was located in the face motor area based on anatomical landmarks, including the inverted omega-shaped central sulcus on axial and functional MR imaging. Neurological and neuropsychological examinations were normal.

A frontoparietal craniotomy was performed under general anaesthesia. After incision of the dura, a silicone sheet containing eight electrodes was placed on the brain perpendicular to the central sulcus to record cortical SSEPs (Fig. 3(A) and (B)). Phase reversal of the lower lip SSEPs at about 15 ms was observed between electrodes 1–2 and 2–3 (Fig. 3(D)). Thus, the central sulcus was identified to be under electrode 2. Polarity inversions of the median nerve SSEPs across the central sulcus at about 20 ms were observed between electrodes 2 and 3 (Fig. 3(E)). The distance between these two points along the central sulcus was 35 mm. The tumour was totally removed up to the hand-digit motor area, using direct cortical and subcortical stimulation techniques and a neuronavigation system (Fig. 2(C), (D), and 3(D)).

Postoperatively, no neurological or neuropsychological deficits were observed. Left facial seizure activity disappeared. Histopathological examination revealed that the tumour had transformed to an anaplastic astrocytoma. As adjuvant therapy, the patient received 72 Gy of hyperfractionated radiation to an extended local field and chemotherapy using nimustine hydrochloride (ACNU). Careful, repeated observation for 46 months has not indicated any recurrence. Karnofsky score was 100% at last follow up.

DISCUSSION

The method presented for recording SSEPs using lower lip stimulation is straightforward with low risk. Seizures do not occur during evoked potential recording and anaesthetic variability is less prominent than during cortical stimulation. Evoked potential localisation can also be used in young children, in whom the exposed cortex is typically electrically poorly excitable.[4]

Recording of SSEPs has several limitations. Loss of N20 or P20 occurs in 9% of patients, thus phase reversal is not identified, presumably because electrodes are not exactly aligned over the sensory and motor hand areas.[1] Such "off axis" alignment of electrodes may also provide misleading results during localisation of the central sulcus.[5] SSEP phase reversal of N20–P20 was successful in 92% of 230 patients with tumours of the sensorimotor region, but recording of a typical N20–P20 phase reversal may be difficult in cases of large central and postcentral lesions.[3] In these situations, combined cortical SSEP recording for median nerve and trigeminal nerve lower lip stimulation can localise the central sulcus, and also trace its course between two points.

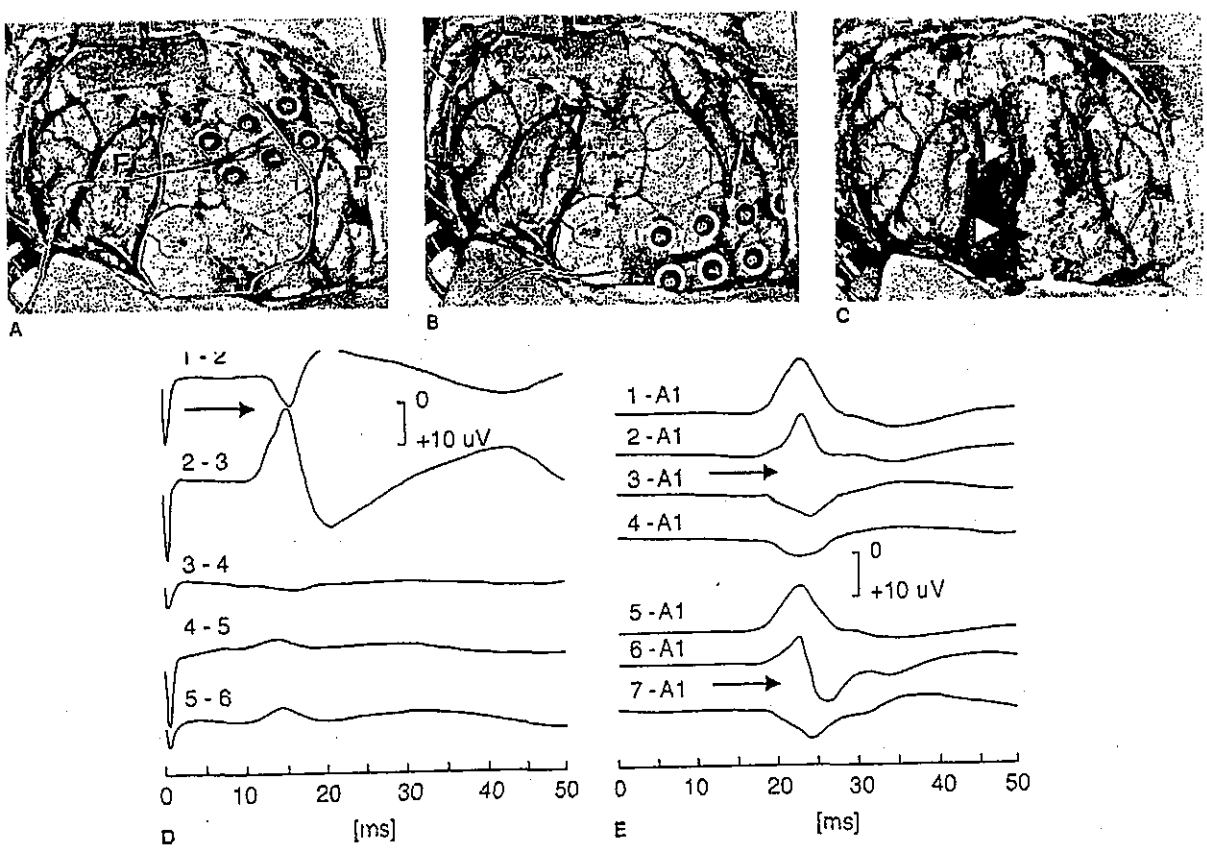

Fig. 3 *Case 1.* (A) and (D) Direct cortical somatosensory evoked potential recordings from stimulation of the lower lip. Electrodes 1, 2, 5, and 6 are posterior (parietal) and electrodes 3, 4, 7, and 8 are anterior (frontal). Recordings from bipolar chains of electrodes were used. Phase reversal is seen between electrodes 1–2 and 2–3, marking the position of the central sulcus (black arrow, D). The continuous white line (A) indicates the location of the tumour. The white arrow indicates the central sulcus. F = frontal lobe; P = parietal lobe. (B) and (E) Direct cortical somatosensory evoked potential recordings from stimulation of the median nerve. Electrodes 1, 2, 5, and 6 are posterior (parietal) and electrodes 3, 4, 7, and 8 are anterior (frontal). Phase reversal is seen between electrodes 2–3 and 6–7, marking the position of the central sulcus (black arrows, E). The white arrow indicates the central sulcus. (C) Intraoperative photograph after gross total resection of the tumour. Arrowheads indicate the resection cavity.

Previously reported methods of SSEP recording[2] using stimulation of the chin, lips, tongue and palate have localised the face area of the human sensorimotor cortex. The upper and lower lip representations overlap adjacent to the hand area, and have been reported to provide little additional localising information if the hand area has been identified. The representation of the lower lip is slightly more lateral than the upper lip, but separate stimulation of the upper and lower lip provides no practical advantage. Polarity inversion of potentials across the sulcus has been reported to be a less reliable criterion for trigeminal SSEPs, partly because most recordings are made with 10 mm inter-electrode spacing, and inconsistent recording of polarity inversions may simply be due to lack of optimal recording sites, or because the dipole generators may have a more radial orientation, with little or no polarity inversion across the cortical surface.[2]

In contrast, our study indicates that lower lip SSEPs can localise the face representation areas of the somatosensory and motor cortex under general anaesthesia using polarity inversion. Our stimulating apparatus was tightly attached to the lower lip, resulting in constant stimulation and we used higher intensity and lower frequency stimuli than the 0.4 and 4 Hz frequency, and intensities of two or three times the sensory threshold used in previous studies of trigeminal SSEPs.[8–12] The most suitable intensity of nine times the sensory threshold was indicated by a previous magnetoencephalography (MEG) study and was well tolerated, even when the patient was awake. Our experience is that the stable pressure of the clip electrode is particularly useful to maintain constant resistance and electrode contact and to achieve a constant stimulus intensity, which helps to minimise subject apprehension. Longer inter-stimulus intervals evoked a larger amplitude of N15m. The present study used biphasic waveforms for electrical stimulus and recordings from bipolar chains of electrodes, which reduces artefacts.

We could not establish the normal distance between the phase reversal points of median nerve and lower lip SSEPs, because pin-point definition of the phase reversal was difficult in cortical SSEPs using strip electrodes, and because some patients had no clear-cut phase reversal of median nerve SSEPs. Our MEG study of normal subjects found that the distance between the N15m source of the lower lip somatosensory evoked fields (SEFs) and the N20m source of the median nerve SEFs is 23.0 ± 7.2 mm (mean ± sd) in the left hemisphere and 18.6 ± 2.1 mm in the right hemisphere.[1] This distance may increase and/or the SSEP sources may shift upward in patients with gliomas in and around the orofacial central region. Combination stimulus of the median nerve and the lip would be particularly useful in such cases.

CONCLUSION

Recording of SSEPs using median nerve and lower lip stimulation as described above can be used to localise the central sulcus and the hand and orofacial area laterally and adjacent to the Sylvian fissure.

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The influence of sex and the presence of giant cells on postoperative long-term survival in adult patients with supratentorial glioblastoma multiforme

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Object. Glioblastoma multiforme (GBM) remains incurable by conventional treatments, although some patients experience long-term survival. A younger age, a higher Karnofsky Performance Scale (KPS) score, more aggressive treatment, and long progression-free intervals have been reported to be positively associated with long-term postoperative patient survival. The aim of this retrospective study was the identification of additional favorable prognostic factors affecting long-term survival in surgically treated adult patients with supratentorial GBM.

Methods. Of 113 adult patients newly diagnosed with histologically verified supratentorial GBM who were enrolled in Phase III trials during the period between 1987 and 1998, six (5.3%) who survived for longer than 5 years were defined as long-term survivors, whereas the remaining 107 patients served as controls. All six were women and were compared with the controls; they were younger (mean age 44.2 years, range 31–60 years), and their preoperative KPS scores were higher (mean 85, range 60–100). Four of the six patients underwent gross-total resection. In five patients (83.3%) the progression-free interval was longer than 5 years and in three a histopathological diagnosis of giant cell GBM was made. This diagnosis was not made in the other 107 patients.

Conclusions. Among adult patients with supratentorial GBM, female sex and histopathological characteristics consistent with giant cell GBM may be predictive of a better survival rate, as may traditional factors (that is, younger age, good KPS score, more aggressive resection, and a long progression-free interval).

KEY WORDS • **supratentorial glioblastoma multiforme** • **long-term survival** • **giant cell glioblastoma multiforme**

DURING the past two decades, treatment outcomes in patients with GBM have remained unsatisfactory; the median survival time has been approximately 1 year.[12,18,24,36,53,60] Among the few long-term survivors,[10,11,42,46,47,50,54,58] a younger age, higher preoperative KPS score, more extensive tumor resection, long PFS period, radiotherapy, and adjuvant chemotherapies have been considered positively associated factors.[10,11,33,42,45–47,50,55,57,58]

To identify additional factors that may be associated with prolonged survival in adult patients with supratentorial GBM, we selected long-term survivors enrolled in clinical trials from a uniform Japanese population. We compared data obtained in these patients with those obtained in patients with GBM who underwent surgery and died despite receiving the same postoperative adjuvant therapies. This approach enabled us to identify female sex and histopathological characteristics consistent with giant cell GBM as factors positively associated with long-term survival. We also analyzed and compared available clinical details in 150 long-term survivors harboring GBM treated by us and by others to test our current findings.

Abbreviations used in this paper: ACNU = 3-{(4-amino-2-methyl-5-pyrimidinyl)methyl}-1-(2-chloroethyl)-1-nitrosourea hydrochloride; CT = computerized tomography; GBM = glioblastoma multiforme; IA-ACNU = intraarterial ACNU administration; IV-ACNU = intravenous ACNU administration; KPS = Karnofsky Performance Scale; MR = magnetic resonance; PAV = procarbazine, ACNU, and vincristine; PAV-I = PAV plus interferon-β; PFS = progression-free survival.

Clinical Material and Methods

Patient Characteristics

We defined long-term survivors as patients who survived more than 5 years after the initial diagnosis. The study population consisted of 113 adult patients with a new and histologically verified diagnosis of supratentorial GBM who participated in two randomized prospective Phase III trials that ended on August 31, 1998 (that is, > 5 years ago) and received postoperative ACNU-based chemotherapy in conjunction with radiation therapy. The first protocol (No. 8701, active from December 1987 until June 1995) was de-

TABLE 1

*Characteristics of six long-term survivors with GBM**

Case No.	Age (yrs), Sex	Symptom (wks†)	Disease Site	Preop KPS Score	Type of Surgery	Treatment Arm	Prog Dis	PFS (yrs)	OS (yrs)	Outcome	Final Diagnosis
1	41, F	IH (6.1)	RF	90	PR	IA-ACNU	yes	6.229	6.732	dead	GBM
2	39, F	IH (6.0)	LT	60	GTR	IA-ACNU	yes	7.094	7.368	dead	GBM
3	42, F	IH (4.3)	RF	100	GTR	IV-ACNU	no	6.204‡	6.538	dead	GCGBM
4	31, F	IH (4.7)	LF	100	GTR	IV-ACNU	yes	7.578	8.282‡	alive	GCGBM
5	52, F	IH (4.3)	BF	60	PR	IV-ACNU	yes	0.433	7.422	dead	GBM
6	60, F	ES (3.4)	LF	100	GTR	PAV-I	no	5.210‡	5.210‡	alive	GCGBM

* BF = bifrontal; ES = epileptic seizure; GCGBM = giant cell GBM; GTR = gross-total resection; IH = intracranial hypertension; LF = left frontal; LT = left temporal; OS = overall survival; Prog Dis = progressive disease; PR = partial resection; RF = right frontal.

† Duration from onset to diagnosis.

‡ Time at which future data were censored.

signed to compare the effectiveness of IA-ACNU with IV-ACNU in patients also receiving radiotherapy (extended local treatment with 40 Gy, local treatment with 20 Gy, total treatment with 60 Gy, 2 Gy five times per week for 6 weeks).[28] The second protocol (No. 9501, active from July 1995 until April 2003) was designed to compare the effectiveness of PAV with that of PAV-I in patients receiving the same radiation treatments administered under Protocol No. 8701. Of the 113 patients, six (5.3%) were identified as long-term survivors, whereas the remaining 107 patients served as controls.

Histopathological Criteria

Two neuropathologists (J.I.K. and Y.I.) independently reviewed histopathological findings according to the criteria published by the World Health Organization.[25,26] Tumors exhibiting prominent microvascular proliferation and/or necrosis in addition to high cellularity, marked nuclear atypia, and remarkable level of mitotic activity were diagnosed as GBM. The presence of necrosis was required for a diagnosis of GBM; cases without necrosis were excluded. Tumors with significant oligodendroglial components were classified as anaplastic oligodendrogliomas or anaplastic oligoastrocytomas and excluded from this study.[4,9,28,29]

Criteria for Determining the Extent of Resection

The extent of resection was determined by inspecting contrast-enhanced CT scans and MR images obtained within 1 or 2 weeks postoperatively and, since 1994, within 72 hours following surgery to exclude the effect of time-lapse changes attributable to the surgical procedure.[2] Gross-total resection was recorded when there was no contrast-enhanced lesion; subtotal resection and partial resection were recorded when less or more than 10%, respectively, of the preoperatively contrast-enhanced lesion remained. Subtotal resection and partial resection were subsumed into the partial resection classification.

Clinical Characteristics of Patients

Clinical details, including the patient's age at the time of diagnosis, sex, preoperative KPS score, tumor location, symptoms, symptom duration from onset to diagnosis, extent of resection, chemotherapy treatment arm (IA-ACNU compared with IV-ACNU or PAV compared with PAV-I), and the recorded date of disease progression or death were noted.

Disease progression was evaluated by reviewing contrast-enhanced CT scans or MR images, which were obtained at the onset of clinical deterioration and immediately before the inception of every 6-week course of adjuvant therapy. In all cases in which it was difficult to discriminate on neuroimages between tumor recurrence and radiation injury, biopsy specimens were examined histopathologically. Overall survival was calculated as the interval between the day of diagnosis and the day of death, and PFS as the time between the day of diagnosis and the day of neuroimaging-confirmed progressive disease. Data on patients in whom the day of death or disease progression was uncertain were censored as of the last known day of life or disease-free life; data on patients alive on the day of analysis were censored as of August 31, 2003.

Results

The study population consisted of 113 adult patients with supratentorial GBM. Of these, Cases 1 to 6 were classified as long-term survivors and their characteristics are summarized in Table 1. The other 107 patients represented the control group; their characteristics are shown in Table 2. The mean age of the long-term survivors was younger than that of the controls (44.2 years, range 31–60 years compared with mean 56.4 years, range 16–78 years). The male/female ratio in the control group was 1.5:1; all six long-term survivors were women. In five of the long-term survivors the symptom at onset was intracranial hypertension; in the sixth (Case 6) the patient suffered an epileptic seizure. The mean interval between symptom onset and diagnosis was 4.8 weeks (range 3.4–6.1 weeks) in the long-term survivors and 19.1 weeks (range 1.3–309.4 weeks) in the controls. At 85 (range 60–100), the mean KPS score was higher in long-term survivors than in controls (mean 69.4, range 40–100).

The frontal or temporal lobe was the site of the tumor in approximately half of the control patients; five long-term survivors had frontal lobe tumors and the other had a tumor located in the temporal lobe. With the exception of the patient in Case 5, none of the tumors in the long-term survivors was located in a bilateral or midline structure and there was no difference between the survivors and controls with respect to tumor laterality. Gross-total resection, partial resection, and biopsy were performed in 29, 54.2, and 16.8% of the controls, respectively. The six long-term survivors exhibited a bias for having undergone extensive resection: four underwent gross-total resection and two underwent

partial resection. Of the two long-term survivors alive on the day of analysis, one manifested disease progression and the other was able to pursue a normal life without tumor recurrence. The patient in Case 3 died of an unrelated disease without tumor recurrence. In three of four patients with tumor progression, death was directly attributable to progressive disease (Cases 1, 2, and 5). Two of these four patients had undergone partial resection and suffered local disease progression at the site of the primary residual lesion; the other two patients had undergone gross-total resection and manifested new regional disease in a previously uninvolved site. The patient in Case 2, whose primary tumor was in the temporal lobe, suffered an isolated recurrence in the brainstem and the patient in Case 4 had a tumor in the frontal lobe contralateral to the site of the original lesion.

The overall survival and PFS among the six long-term survivors ranged from 5.21 to 8.282 years and 0.433 to 7.578 years, respectively. All but the patient in Case 5 survived without disease progression for longer than 5 years. In the patient in Case 5 there was evidence of residual tumor progression approximately 5 months postdiagnosis. Although this patient was bedridden, her disease remained stable for approximately 6.5 years after additional treatment for the tumor recurrence.

Macroscopically the demarcations of the four tumors that were aggressively removed (Cases 2–4 and 6) were better than that typical for GBM. All tumors in the long-term survivors manifested the typical histopathological features of GBM. In Cases 3, 4, and 6 the presence of large areas composed of extremely unusual multinucleated giant cells resulted in a diagnosis of giant cell GBM. Interestingly, none of the 107 controls had giant cell GBM.

In Table 3 we present available clinical details on 150 patients with GBM who survived for longer than 5 years; patients in this study as well as patients described by other clinicians are included.[1,3,5,6,10–12,14–17,20–23,27,30–32,34,35,38,40–44,46,47,50,52,54,56,58,59,61] The mean age, available in 114 patients, was 38.6 years; the mean KPS score, available in 65 patients, was 84. Of the 122 patients whose sex was identified, 61 (50%) were female, resulting in a male/female ratio of 1:1. Gross-total or radical resection was performed in 65 (58%) of 112 patients; 128 (94.1%) of 136 patients received postoperative radiotherapy and 71 (55.5%) of those 128 patients also underwent chemotherapy. Interestingly, in 18 (69.2%) of 26 patients in whom histopathological details were available, a diagnosis of giant cell GBM was made or the predominance of giant cells was reported, although in two[6,23] of these patients the lesions may have been other types of tumors, for example, anaplastic oligoastrocytoma or pleomorphic xanthoastrocytoma. Fourteen (82.4%) of 17 patients with giant cell GBM in whom details regarding the extent of resection were available underwent gross-total or radical resection.

TABLE 2

*Characteristics of 107 patients with GBM without long-term survival**

Variable	Value (%)
age in yrs	
mean ± SD	56.4 ± 11.9
median	58
range	16–78
sex	
male	64
female	43
M/F ratio	1.5:1
duration of symptoms in wks†	
mean ± SD	19.1 ± 48.1
median	7
range	1.3–309.4
location of GBM—no. of patients	
frontal	31 (29.0)
central	11 (10.3)
parietal	12 (11.2)
temporal	24 (22.4)
occipital	8 (7.5)
BG/thalamus	8 (7.5)
diffuse	8 (7.5)
unknown	5 (4.7)
side of lesion—no. of patients	
rt	45 (42.1)
lt	49 (45.8)
bilat	6 (5.6)
midline	1 (0.9)
unknown	6 (5.6)
preop KPS score	
mean ± SD	69.4 ± 17.3
median	70
range	40–100
type of surgery—no. of patients	
GTR	31 (29.0)
PR	58 (54.2)
biopsy	18 (16.8)
treatment arm—no. of patients	
Protocol No. 8701: 70 patients	
IA-ACNU	34 (31.8)
IV-ACNU	36 (33.6)
Protocol No. 9501: 37 patients	
PAV	17 (15.9)
PAV-I	20 (18.7)
PFS	
no. of patients in whom data were censored	10 (9.3)
median no. of yrs	0.416
range	0.115–4.635
OS in yrs	
no. of patients in whom data were censored	1 (0.9)
median no. of yrs	1.117
range	0.200–4.997
GCGBM—no. of patients	0 (0.0)

* BG = basal ganglia; SD = standard deviation.

† Duration of symptoms from onset to diagnosis; data were available for 93 patients.

Illustrative Cases

Case 3

This 42-year-old woman experienced severe headache and nausea for approximately 1 month. Magnetic resonance imaging demonstrated a ringlike enhanced mass lesion in her right frontal lobe (Fig. 1A). Intraoperatively, the tumor appeared to be better demarcated macroscopically than is typical of GBM. The patient underwent gross-total resection in November 1992 (Fig. 1B) and a histopathological diagnosis of giant cell GBM was made (Fig. 2A and B). She received radiation therapy in conjunction with seven courses of IV-ACNU therapy (total 840 mg) over a period of 16 months. Nevertheless, 2 years after the diagnosis was made, contrast-enhanced MR imaging detected spots in the bifrontal lobes. A biopsy was performed and the lesions were identified as areas of radiation injury rather than tumor

TABLE 3

*Review of the literature in patients with GBM who survived longer than 5 years**

Authors & Year	No. of Cases	Mean Age (yrs)	M/F Ratio	Mean KPS Score	No. of Patients w/ (%)				OS (no. of patients)	
					GTR	RT	Chemo	GCGBMs	<10 Yrs	>10 Yrs
Netsky, et al., 1950	5	24–42†	1:1‡	NA	NA	2‡	NA	NA	4	1
Bouchard & Peirce, 1960	9	NA	NA	NA	NA	9	0	NA	4	5
Roth & Elvidge, 1960	12	NA	4:8	NA	7	8	0	NA	9	3
Ley, et al., 1962	3	NA	NA	NA	NA	3	0	NA	3	0
Taveras, et al., 1962	7	NA	NA	NA	0	7	0	NA	7	0
Elvidge & Barone, 1965	2§	24.5‖	1:1	NA	2	1	0	1	0	2
Gullotta & Bettag, 1967	1	45	1:0	NA	1	1	0	NA	0	1
Jelsma & Bucy, 1967	4	39‖	3:0‡	NA	4	3‡	0	NA	4	0
Takeuchi, 1975	2	38.5‖	2:0	NA	NA	2	2	NA	2	0
Dara, et al., 1980	1	32	NA	NA	NA	1	1	NA	1	0
Johnson, 1981	1	32	0:1	NA	1	0	0	1: PXA?	0	1
Hatanaka, et al., 1984	1	50	1:0	100	0	1	0	NA	0	1
Bucy, et al., 1985	1	30	1:0	NA	1	1	0	1: AOA?	0	1
Salford, et al., 1988	2	14.5‖	1:1	NA	1	2	0	1**	0	2
Akslen, et al., 1989	2	41.5‖	1:1	NA	2	2	1	2	2	0
Ishikura, et al., 1989	1	8	0:1	NA	1	0	0	1	1	0
Margetts & Kalyan-Raman, 1989	1	41	1:0	NA	1	1	1	1	1	0
Imperato, et al., 1990	5	42.6‖	3:2	NA	5	5	4	NA	3	2
Shibamoto, et al., 1990	1	51	1:0	NA	1	1	0	NA	1	0
Rutz, et al., 1991	1	21	1:0	NA	1	1	0	NA	0	1
Vertosick & Selker, 1992	10	39.9‖	6:4	86‖	NA	10	10	NA	6	4
Chandler, et al., 1993	22	39.2	10:12	80	2	22	18	NA	17	5
Hiesiger, et al., 1993	4	41.5‖	NA	92.5‖††	0	4	4	NA	4	0
Phuphanich, et al., 1993	1	33	1:0	90	NA	1	1	1	1	0
Archibald, et al., 1994	7	37.7‖	2:5	NA	2	7	7	NA	7	0
Wester, et al., 1994	1	45	0:1	NA	1	1	0	0	1	0
Morita, et al., 1996	10	39.2‖	7:3	NA	10	NA	NA	NA	8	2
New, et al., 1997	1	34	0:1	100	1	1	1	NA	1	0
Pollak, et al., 1997	2	20‖	1:1	NA	2	2	0	0	0	2
Cervoni, et al., 1998	1	13	0:1	80	1	1	1	1	0	1
Klein, et al., 1998	1	11	0:1	NA††	1	1	1	1	0	1
Puzzilli, et al., 1998	1	50	1:0	90	0	1	0	1	0	1
Salvati, et al., 1998	11	39	5:6	80	11	11	11	NA	10	1
Scott, et al., 1999	7	46.9‖	4:3	88.6‖	NA	7	NA	NA	4	3
Yoshida, et al., 2000	2	40‖	1:1	NA	1	2	2	2	0	2
Sabel, et al., 2001	1	69	1:0	NA	1	0	0	1	0	1
present study	6	44.2	0:6	85	4	6	6	3	6	0

* AOA = anaplastic oligoastrocytoma; chemo = chemotherapy; NA = not available due to insufficient data; PXA = pleomorphic xanthoastrocytoma; RT = radiation therapy; ? = possibly.

† Only the age range was available.

‡ Data were only available for some patients.

§ Data on these patients were included in the report by Roth and Elvidge.

‖ Specific data not given in original publication, but were calculated on the basis of data that were provided.

** Patient underwent PR.

†† Postoperative KPS score.

recurrence. The patient suffered a gradual disturbance in consciousness that was attributable to radiation-induced, progressive diffuse brain atrophy (Fig. 1C) and died of respiratory complications approximately 6.5 years after establishment of the diagnosis.

Case 4

This 31-year-old woman experienced a progressively worsening headache for approximately 1 month. Magnetic resonance images demonstrated a ringlike enhanced mass lesion in the left frontal lobe (Fig. 1D). Macroscopically, the tumor appeared to be better demarcated than is typical of GBM, and the patient underwent gross-total resection in May 1995 (Fig. 1E). A histopathological evaluation returned a diagnosis of giant cell GBM (Fig. 2C and D). During a 1-year period, the woman received radiation therapy in conjunction with five courses of IV-ACNU (total 540 mg). She was able to resume her normal life and had a KPS score of 100. Seven and one-half years after the initial diagnosis, an irregular contrast-enhanced lesion was demonstrated by MR imaging in the contralateral frontal lobe (Fig. 1F). Although biopsy confirmed tumor recurrence, at the time of this writing the patient remains alive but bedridden.

Case 6

This 60-year-old woman was involved in a traffic accident caused by an epileptic seizure she experienced in May 1998. Computerized tomography scans demonstrated a ringlike enhanced mass lesion in her left frontal lobe (Fig. 1G). Intraoperatively the tumor appeared well demarcated

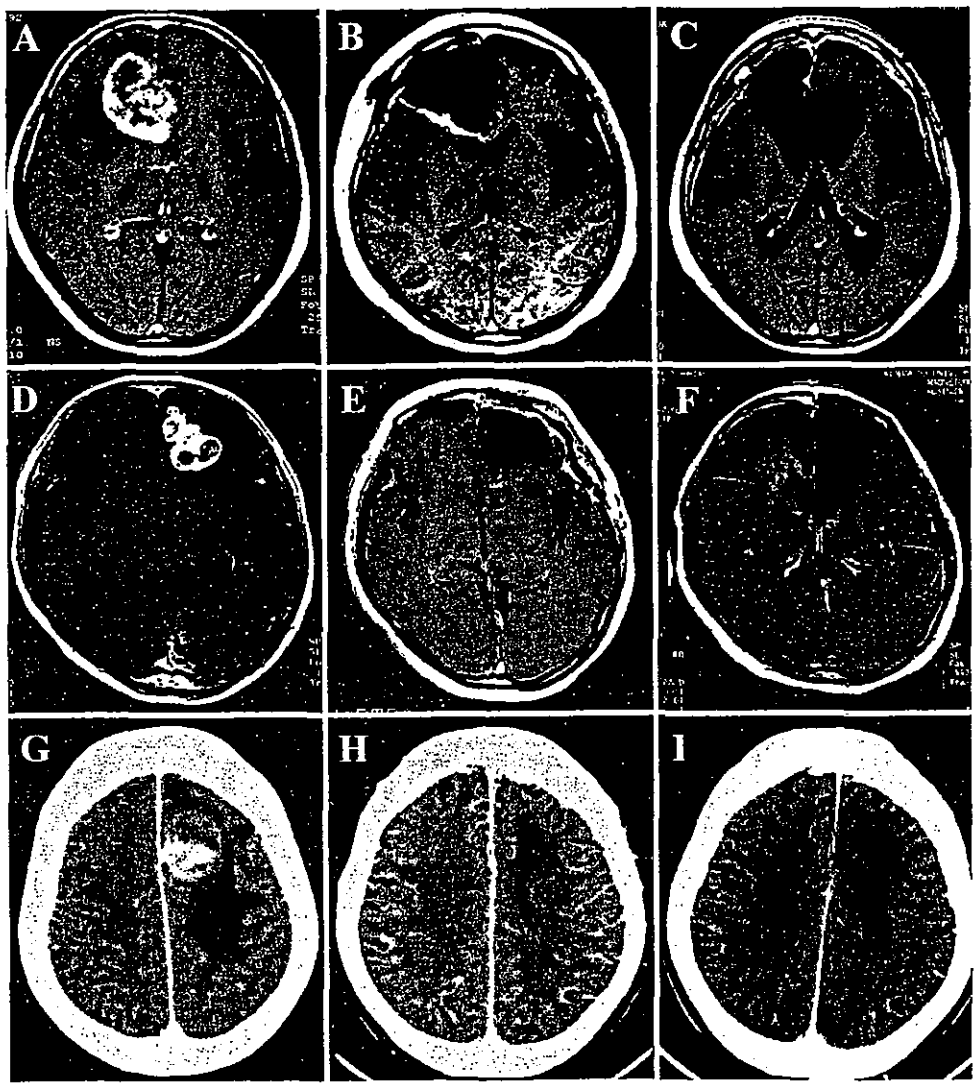

FIG. 1. Contrast-enhanced CT and MR images. A–C: Case 3. Note the irregularly shaped ringlike enhanced mass lesion with peritumoral edema on this preoperative image (A). Following gross-total resection an area of hyperintensity at the bottom of the resection cavity is a local postoperative change (B). Six years after gross-total resection there is a marked brain cortical atrophy (C). D–F: Case 4. The left frontal tumor (D) was totally resected (E). Enhanced lesions in the right frontal lobe were visualized 7.5 years later (F) and tumor recurrence was confirmed by biopsy. G–I: Case 6. The left frontal tumor (G) was totally removed (H), and there was no sign of tumor recurrence 5 years later (I).

and a gross-total resection was performed (Fig. 1H). A histopathological diagnosis of giant cell GBM was returned (Fig. 2E and F). The patient received radiation therapy in conjunction with PAV-I; procarbazine (total 90 mg), ACNU (total 105 mg), vincristine (total 4 mg), and interferon-β (3×10^6 U three times per week) were administered in a one 6-week course. At the time of this writing she is able to pursue her normal life, her KPS score is 100, and there has been no tumor recurrence (Fig. 1I).

Discussion

Glioblastoma multiforme has remained incurable despite the use of multimodal aggressive treatments; the median duration of survival among patients with GBM is approximately 1 year[13,18,24,36,53,60] and only 1 to 5% of patients with this disease survive for more than 3 to 5 years.[11,42,46,47,49,50,55,58] The long-term survival rate in patients treated at our institution and assessed in this study was 5.3%, similar to the reported rate.

Reported positive prognostic factors associated with long-term survival are a relatively young age, a higher preoperative KPS score, aggressive resection, radiotherapy, adjuvant chemotherapies, and a prolonged PFS period.[10,11,33,42,45–47,49,50,55,57,58] To identify other potentially favorable prognostic factors in adult patients with supratentorial GBM, we analyzed the clinical data in six long-term survivors selected from a uniform population of Japanese patients enrolled in clinical trials. All had undergone a variety of surgical interventions and subsequent combined radiotherapy and ACNU-based chemotherapy (Table 1). The control