表2 悪性グリオーマに対するテーラーメイド化学療法

1．耐性のない薬剤の選択 (薬剤耐性遺伝子の検索)

遺伝子名	耐性を示す薬剤
MDR-1	adriamycin, vincristine, cyclophosphamide, methotrexate
MRP-1	adriamycin, etoposide
MRP-2	etoposide, cisplatin
TOPO II α	etoposide, adriamycin
MGMT	nitrosourea
GST-π	cisplatin

2．耐性機構の克服
MGMTに対する O^6-benzylguanine, procarbazine

3．感受性の高い形質を持つ腫瘍の選択
1p, 19q欠失anaplastic oligodendroglioma に対するPCV(PAV)療法

3) 毒素

弱毒化した毒素を直接腫瘍あるいはその周辺に注入して抗腫瘍効果を得ようという治療法である。腫瘍周辺まで十分に毒素が浸透するように，陽圧をかけて持続的に注入する方法 (convection-enhanced delivery system)がとられている。さらに腫瘍との親和性を高めるため，グリオーマの大半に発現しているとされるInterleukin-13 (IL-13)受容体を標的とし，IL-13に緑膿菌毒素PE38を結合させたIL-13-PE38やtransferrinとジフテリア毒素を結合させたtransferrin-CRM107による臨床応用が開始されている[18,32]。

3. テーラーメイド治療

同一疾患に対して，同一のプロトコールによる治療を行い，その効果を判定し，治療の標準化をはかるという臨床研究の方法論に対し，個々の腫瘍の特殊性を見い出し，それに適合した治療法を選択していこうというのが，テーラーメイド治療である。化学療法におけるテーラーメイド治療法としては，主に感受性の高い薬剤の選択という形で研究が進められている(表2)。しかしながら，現在のところ，グリオーマにおいては，胚細胞腫瘍に対するcisplatinやcarboplatinなどのプラチナ系抗癌剤を主体とした治療のような極めて有効な薬剤がなく，テーラーメイド治療が実施できてもその効果はまだまだ不十分である。

1)薬剤耐性遺伝子の検索

脳腫瘍に限らず，多くの悪性腫瘍に薬剤耐性機構の存在が知られている。代表的なものとしては，multidrug resistance (MDR)-1の遺伝子産物であるp-glycoproteinがあり，細胞外に薬剤を排出する働きにより，adriamycin, vincristine, cyclophosphamide, methotrexateなど多くの薬剤に同時に耐性を示す[8]。Multidrug resistance-associated protein (MRP)-1も同様に，etoposideやadriamycinに耐性を示すことが知られている[10]。その他，悪性グリオーマに対する標準治療薬として最も広く使われているnitrosourea系薬剤に対する耐性に関与しているのが，MGMTであると考えられている[21,25]。これらの耐性機構に関係する遺伝子や蛋白の発現を調べ，発現の高い耐性機構と無関係の薬剤を選択して使用するという方法も，消極的な方法ではあるがテーラーメイド治療の1つと言える。

2)薬剤耐性の克服

薬剤耐性を積極的に克服して治療効果を高めようとする試みで，nitrosourea系抗癌剤に対する耐性機構となっているMGMTを低下させた後に，ACNUやBCNUを投与するという治療法である。前述のJCOG臨床試験もこの理論を用いたものであり，摘出した腫瘍細胞でのMGMTをmRNAレベルあるいは蛋白レベルで測定し，その発現が認められれば，それを低下させる作用を持つprocarbazineや O^6-benzylguanineを投与した上で，nitrosourea系抗癌剤を投与するという形をとればテーラーメイド治療の1つとして挙げることができる。

3)染色体1p，19q欠失を示す乏突起膠腫に対するPCV(PAV)療法

分子生物学知見と治療とが明確なつながりをもった数少ない事象の1つである。悪性グリオーマの中でも退形成性乏突起膠腫は，化学療法に反応する疾患とされていたが，その中でも染色体1番の短腕(1p)および19番長腕(19q)の欠失を認める症例においてprocar-

bazine, CCNU, vincristineによる化学療法(PCV療法)が極めて有効であることが示されてきた[3,13]。手術によって採取された腫瘍での1p, 19qの欠失を調べ，それが認められる症例において積極的にPCV療法を行っていくのは，テーラーメイド化学療法といえる。国内においてはCCNUの代わりに同じnitrosourea系抗癌剤のACNUが用いられ，PAV療法として行われている。しかしながら，1p, 19qの欠失が認められなかった場合にそれに代わる治療法がないというのが現状である。

おわりに

膠芽腫をはじめとする悪性グリオーマの治療成績は，残念ながら30年前と比べほとんど改善していないといえる。手術方法がいかに進歩しても手術侵襲を加えることのできない領域があり，将来的にも手術のみによって予後を改善させることは期待できない。BCNUやACNUが主な治療薬として用いられていた時代から考えると，近年その有効性が統計的に証明されている薬剤が出現してきたが，その効果も数カ月の生存期間延長を示すのみである。個々の腫瘍の性質に合わせたテーラーメイド治療も工夫されているが，現在までのところ画期的な効果を示す方法は出現していない。このような状況下で今しなければならないことは，将来に向けて，より良い治療法を求めてのエビデンスの蓄積であり，しっかりとしたデータ管理システムのもとに臨床研究を進め，わずかでも治療成績の優れた治療法を1つひとつ積み重ねていくことであるといえる。

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星細胞腫grade3/4に対するACNU vs ACNU+PCZによる第II/III相試験(JCOG 0305臨床試験)

A phase II/III study for astrocytoma grade 3 and 4 using ACNU versus procarbazine and ACNU : Japan Clinical Oncology Group Study (JCOG 0305)

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【はじめに】

1970年代より欧米では、悪性グリオーマに対する多施設共同試験が行われ、この疾患に対するエビデンスの蓄積がなされてきたのに対し、国内ではそのような基盤が構築されておらず、世界に発信できるエビデンスが存在しないと言っても過言ではない[1-4]。悪性グリオーマに対する化学療法剤として、国内でひろく用いられているnimustine hydrochloride(ACNU)さえもTakakuraら[5]の第III相試験の結果があるのみで、その結果としては術後の放射線単独治療群に比べ、ACNU併用の放射線治療が生存率において有意な差をもって優っているというものではなかった。すなわち、国内においては、悪性グリオーマに対する標準治療が存在しているとは言えず、community standardとしてACNUが用いられているに過ぎない。このような状況下で、平成14年、厚生労働科学研究費の補助により、国内における標準的治療を確立する目的でJCOG脳腫瘍グループが結成され、星細胞腫grade 3および4に対する多施設共同試験が開始された。

【日本臨床腫瘍研究グループ(Japan Clinical Oncology Group ; JCOG)とは】

JCOGは1978年厚生省がん研究助成金指定研究「がんの集学的治療の研究」班(主任研究者 末舛恵一)を前身とし、1987年「固形がんの集学的治療の研究」班(主任研究者 下山正徳)を経て1990年設立された。その目的は、当時、国内の各施設、各グループで個別に実施され、その解析方法も曖昧であった臨床研究をエビデンスとなり得る科学的研究にするための支援であり、国立がんセンターに置かれた統計センターがその基礎となった。現在、約190の医療機関、400の診療科が参画し、主に第II相・第III相臨床試験を行って新治療の効果の評価や標準治療の確立に努めている(Fig.1)。

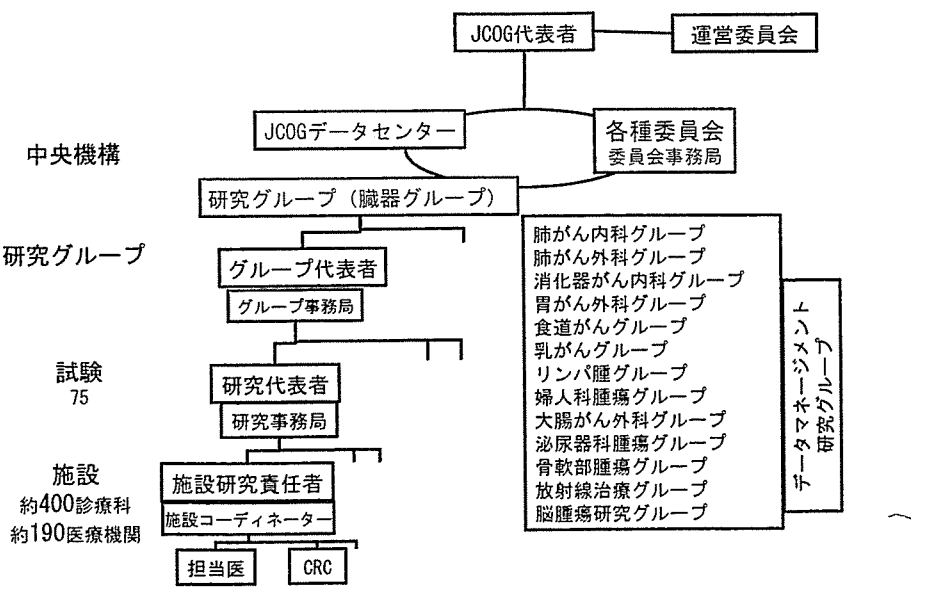

Fig.1
JCOGの機構

JCOG脳腫瘍グループについては、2002年度に厚生労働科学研究費「効果的医療技術の確立推進臨床事業(現がん臨床研究事業)」の「悪性脳腫瘍の標準的治療法の確立に関する研究(主任研究者 渋井壮一郎)」班が母体となり、JCOG内13番目の臓器グループとして組織された。2003年には同研究事業「転移性脳腫瘍の標準的治療法の確立に関する研究(主任研究者 嘉山孝正)」班も加わり、国立がんセンター中央病院に事務局を置き、悪性グリオーマおよび転移性脳腫瘍に関するJCOG臨床研究を実施している。今回は、現在登録進行中である星細胞腫grade 3/4に対する臨床研究について紹介する。

【JCOG脳腫瘍グループによる臨床試験】

JCOG 0305臨床試験は「星細胞腫grade3・4に対する化学放射線治療としてのACNU単独療法とProcarbazine+ACNU併用療法とのランダム化比較試験(Phase II/III試験)」というタイトルで、国内における悪性神経膠腫の標準治療を確立することを目的としている[6]。国内においては悪性神経膠腫に対し、術後にACNUを併用した化学放射線治療が広く用いられているが、脳腫瘍全国統計による5年生存は、星細胞腫grade 3(退形成性星細胞腫)で23%、grade 4(膠芽腫)では7%に過ぎない[7]。その原因のひとつが、nitrosourea系抗癌剤に対する耐性機構O^6-methylguanine-DNA methyltranferase(MGMT)であるとされている。MGMTはnitrosourea系薬剤によってmethyl化されたguanineからそのmethyl基を奪い、DNA二重らせん間架橋形成を防ぐことにより耐性を発揮する。ProcarbazineもO^6-alkylguanineを形成することから、procarbazineで前処置をすることにより、それによって形成されたO^6-methylguanineのmethyl基に作用することでMGMTが消費され、その結果nitorosourea系抗癌剤の効果を上げることが期待できる。Valavanisら[8]の行ったラットでの実験でもprocarbazineを投与することで、肝臓、骨髄、リンパ節、白血球中のO^6-methylguanineの上昇がみられ、同時にMGMTの低下を確認している。これを受けてBrandesら[9]は再発glioblastoma 58例に対し、day 1-5にprocarbazine 100mg/m^2 5日間経口投与、day 3および5にBCNU 80mg/m^2 静脈内投与、day 3にvincristine 1.4mg/m^2 静脈内投与という治療法を8週ごとに繰り返し、complete response 6例(10.3%)、partial response 11例(19.0%)という治療効果を得ている。これらの事実をもとにprocarbazineをACNUに先立って投与する方法を新治療とし、従来のACNU単独療法との効果を比較し、国内での標準的治療法を確立する臨床試験を開始するに至った。

【JCOG 0305プロトコール】

JCOG 0305臨床試験の概要は下記のとおりである。

1. 適格基準

1) 手術または生検により、組織診断が星細胞腫grade 3または4と証明されている。
2) 術前の画像診断により、腫瘍体積の50%以上がテント上に存在すると考えられる。
3) 術前MRIにて、視神経・嗅神経・下垂体に腫瘍を認めない。
4) 術前MRIにて、多発病変・播種のいずれも認めない。
5) 60Gyまで照射される計画照射体積が大脳の1/3未満と考えられる。
6) 星細胞腫手術(摘出またはもしくは生検)後、3日以降14日以内である。
7) 登録時年齢が20歳以上69歳以下である。
8) ECOGによるperformance status(PS)0, 1, 2もしくは腫瘍による神経症状のみに起因するPS 3のいずれかである。
9) 星細胞腫Grade 3・4に対して初回治療例である。
10) 他のがん種に対する治療も含め、放射線治療・化学療法いずれの既往もない。
11) 下記のすべての条件を満たす。

白血球	≧3,000/mm^3
ヘモグロビン	≧8.0g/dl
血小板数	≧100,000/mm^3
GOT	≦ 100 IU
GPT	≦ 100 IU
クレアチニン	≦1.5mg/dl

12) 試験参加について患者本人から文書で同意が得られている。ただし、神経症状によって患者本人の署名が困難である場合、同意の確認を患者本人の定める代筆者の署名によって行ってもよい。

2. 除外基準

1) 活動性の重複がん(同時性重複がんおよび無病期間が5年以内の異時性重複がん。ただし局所治療により治癒と判断されるcarcinoma in situ(上皮内癌)または粘膜内癌相当の病変は活動性の重複がんに含めない)
2) 治療が必要な髄膜炎および肺炎を合併。
3) 妊娠中・妊娠中の可能性がある・授乳中の女性。
4) 精神病または精神症状を合併しており試験への参加が困難と判断される。
5) インスリンの継続的使用により治療中またはコントロール不良の糖尿病を合併。
6) 3ヶ月以内の心筋梗塞の既往、もしくは不安定狭心症を有する。
7) 肺線維症もしくは間質性肺炎の既往を有する。

対象患者が適格基準をすべて満たし、除外基準のいずれにも該当しないことを確認し、データセンターに連絡する。連絡を受けたデータセンターでは、

施設、組織診断(grade 3かgrade 4か)、年齢(60歳未満か60歳以上か)、術後3日以内に撮影されたMRIで残存腫瘍があるかないかの4点を割付調整因子としてランダム割付を行う。

3. プロトコール治療(Fig.2)

JCOGデータセンターに登録された症例はランダム割付され、A群としては、放射線照射第1日目および36日目にACNU 80mg/m^{2}を静脈内投与し、さらに8週ごとに同様の化学療法を12コース行う。B群では、放射線照射第1日目および第36日目より10日間procarbazine 80mg/m^{2}を経口投与し、服用8日目にACNU 80mg/m^{2}を静脈内投与する。これもその後8週ごとに12コース繰り返す。放射線治療はCTによる3次元治療計画に基づいて行い、摘出腔および残存腫瘍に2cmのマージンをつけた領域に60Gy、MRIのT2強調画像+2cmの領域に50Gyの照射を行う。ただしマージンについては、脳幹、視神経、網膜の耐容線量を優先し、縮小可としている。

4. エンドポイント

本試験は、ランダム化第II/III相試験として実施される。即ち、procarbazineを先行投与しACNUを静脈内投与する治療法について、第II相試験が行われていないため、ランダム割付後、B群56例について6ヶ月生存割合をprimary endpoint、有害事象発生割合をsecondary endpointとして解析する。この際、6ヶ月生存の閾値80%、期待値は90%と設定し、α=0.1, β=0.2として予定症例数を算出した。

第II相レベルを通過した場合、そのまま第III相試験に移行する。第III相でのprimary endpointは生存期間、secondary endpointは無増悪生存期間、奏効割合、完全奏効割合、有害事象とした。ここでは、第II相段階対象集団におけるgrade 3とgrade 4の症例数比を2:3と仮定し、ACNU群の2年生存割合をgrade 3, 4でそれぞれ50%, 20%と予想する。期待されるACNU・procarbazine併用群の生存期間がハザード比で1/1.35以下(2年生存割合で星細胞腫grade 3およびgrade 4でそれぞれ59.8%, 30.4%以上)であるかどうかを検出する優越性試験デザインとした場合、登録5年、追跡2年、α=0.05(片側)、検出力75%とすると必要症例数は合計284例、10%程度の不適格例を想定して、両群合計310例を予定登録数とした。

本試験プロトコールは、2004年3月にJCOG委員会の承認を受け、倫理審査委員会を通過した施設より順次登録が開始された。同年6月に第1例目の登録がなされ、その後若干予想を下回るペースであるが、2005年12月には70症例を突破した。

【おわりに】

原発性脳腫瘍の発生率は、10万人に11~12人とされ、その内、今回対象とした星細胞腫grade 3およびgrade 4は14%を占めるに過ぎない。このような希少疾患に対する臨床研究では、多施設共同試験が必須であるが、今まで国内の脳腫瘍治療分野では、そのような基盤が構築されておらず、エビデンスとなり得る研究結果に乏しかった。今回、JCOG脳腫瘍グループでの臨床試験が開始されたことにより、質の高いデータ管理のもとでの臨床研究が実施されることになり、今後の脳神経外科領域で臨床研究の方向づけとなるものと期待される。

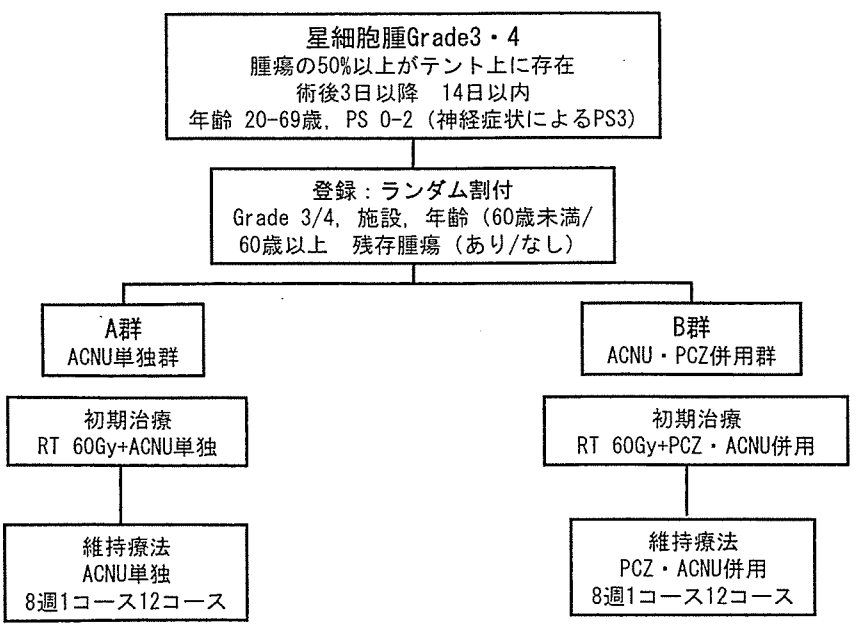

Fig.2
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Randomized Controlled Trial on Malignant Brain Tumors

—Activities of the Japan Clinical Oncology Group-Brain Tumor Study Group—

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Abstract

The Japan Clinical Oncology Group (JCOG)-Brain Tumor Study Group was organized with the support of the Health and Labour Sciences Research Grants of the Ministry of Health, Labour and Welfare. The group is now preparing a multi-institutional randomized controlled phase II/III study of chemoradiotherapy using ACNU versus procarbazine and ACNU for astrocytoma grades 3 and 4. The overall survival and response rates will be compared between the patients treated with ACNU and those treated with ACNU plus procarbazine. This study, under the surveillance of the JCOG, aims to set a standard protocol for treating patients with malignant glioma. Moreover, the study will establish a proper methodology for performing randomized studies in the field of neuro-oncology.

Key words: Japan Clinical Oncology Group, randomized controlled trial, malignant glioma, ACNU, procarbazine, O^6-methylguanine deoxyribonucleic acid-methyltransferase

Introduction

The Japan Clinical Oncology Group (JCOG) is a multi-institutional cooperative oncology group conducting clinical research for cancer and related problems.[2] JCOG consists of 13 oncology groups as of 2003. The Brain Tumor Study Group (JCOG-BTSG) was organized in April 2002 with support from the Health and Labour Research Grants of the Ministry of Health, Labour and Welfare in order to establish a standard therapy for malignant brain tumors.

This study describes a randomized controlled phase II/III study of chemoradiotherapy using ACNU versus procarbazine and ACNU for astrocytoma grades 3 and 4.

Materials and Methods

Patients with newly diagnosed supratentorial astrocytoma grade 3 or 4 will be enrolled and randomly divided into two groups. Patients in Group A will be treated with ACNU (80 mg/m^2 iv) during the postoperative radiotherapy (60 Gy local), whereas patients in Group B with procarbazine (80 mg/m^2 for 10 days per os) preceding and in addition to the administration of ACNU. Each regimen will be repeated every 8 weeks for 2 years if tolerated by the patients. The primary endpoint is the overall survival rate and the secondary endpoints are the response rate on magnetic resonance imaging and the frequency of adverse events. This study starts as a randomized phase II trial and proceeds to the phase III study if the efficacy of the Group B regimen in phase II warrants a study continuation.

The study protocol was developed under guidance of the JCOG and approved by the institutional review board of the institution to which each JCOG-BTSG member belongs. The study will be performed under surveillance by the JCOG.

Results

This study starts at the beginning of 2004. The expected number of patient enrollments is 310 in 5 years. The collected data will be monitored and statistical analyses carried out by the JCOG Data Center. The results will be evaluated by the Steering Committee.

Discussion

A standard therapy for malignant gliomas has not been established and various trials have been carried out. In most neurosurgical institutes in Japan, nimustine hydrochloride (ACNU) is administered in conjunction with conventional radiotherapy after surgical removal of the tumor. However, this common treatment regimen has never been scientifically justified by a randomized controlled study, and so should be considered "community standard."

The efficacy of ACNU in malignant glioma patients was evaluated in a group who received postoperative administration of ACNU in conjunction with radiation therapy and another group was received only radiation therapy.[4] This controlled study revealed an improved response rate for the patients treated with ACNU, however, no significant difference in overall survival was observed between the two groups.

ACNU is one of the most effective chemotherapeutic agents to date for malignant gliomas. ACNU passes through the intact blood-brain barrier and alkylates deoxyribonucleic acid (DNA) causing the anti-tumor effect. Most malignant gliomas nevertheless recur after ACNU chemotherapy and radiotherapy. Malignant gliomas frequently express high activities of O^6-methylguanine DNA-methyltransferase (MGMT), a DNA repair enzyme, which is considered to be one of the causes of the chemoresistance to ACNU. Procarbazine is another alkylating agent that yields O^6-alkylguanine.[3] If procarbazine is administered prior to ACNU as in our current

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protocol, we expect the abundant O^6-alkylguanine to deprive MGMT, leading to increased efficacy of ANCU.[5] A similar treatment protocol was applied using BCNU, procarbazine, and vincristine to 58 patients with recurrent glioblastoma and reported a high response rate of 29% (complete response 10.3%, partial response 19%).[1]

In order to establish a standard therapy for a certain clinical entity, strict randomized controlled studies are essential. Few such studies in the neuro-oncological field have been carried out in Japan. Brain tumor is one of the so-called orphan diseases. Hence, multi-institutional cooperation is essential to accomplish randomized trials that require a large number of patient enrollment. JCOG is a group of oncologists that conduct cooperative studies on various cancers in Japan. The BTSG was newly organized in JCOG and is now preparing this randomized trial in an unprecedented organized manner. Upon completion, this study should provide a scientific basis for the standard therapy for malignant gliomas. Moreover, we hope to establish a proper methodology for performing randomized studies in the field of neuro-oncology.

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Appendix: Members of the Japan Clinical Oncology Group-Brain Tumor Study Group

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Clinical Article

Surgical resection of tumors located in subcortex of language area

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Summary

Object. Although functional mapping facilitates the planning of surgery in and around eloquent areas, the resection of tumors adjacent to language areas remains challenging. In this report, we took notice that the language areas (Broca's and Wernicke's) present at the perisylvian fissure. We posit that if there is non-essential language area on the inner surface of the Sylvian fissure, safe tumor resection may be possible even if the tumor is located under the language cortex.

Methods. The study population consisted of 5 patients with intrinsic brain tumors (frontal glioma, $n=3$; temporal cavernous angioma, $n=1$; primary malignant central nervous system lymphoma, $n=1$) located in the perisylvian subcortex, in the language-dominant hemisphere. All patients underwent awake surgery and we performed intra-operative bipolar cortical functional language mapping. When the tumor was located under the language area, the Sylvian fissure was opened and the inner surface of the opercular cortex was exposed with the patient asleep, and additional functional mapping of that cortex was performed. This enabled us to remove the tumor from the non-functioning cortex.

In our series, 4 of 5 patients had not language function on the inner surface of the operculum. Only one patient, a 52-year-old man with frontal glioblastoma (Case 3) had language function on the inner surface of the frontal operculum.

Conclusion. We suggest that even perisylvian tumors located in the subcortex of the language area may be resectable via the nonfunctioning intrasylvian cortex by a transopercular approach without resultant language dysfunction.

Keywords: Functional mapping; language area; operculum; brain tumor.

Introduction

To minimize the risk of postoperative language deficits in patients scheduled for surgery near the perisylvian cortex in the dominant hemisphere, knowing the localization of language function is important for planning the cortical trajectory and the resection area. While reports on language cortical and subcortical mapping using awake craniotomy and/or a sub-dural grid are available [13, 14, 19], surgical resection under the eloquent cortices continues to present a high risk of neurological sequelae. Neuro-imaging functional techniques are in development and are beginning to be efficient for cortical sensorimotor mapping, but still lack sensitivity and specificity for language mapping, and remain difficult to give real-time data during surgery [16].

The supratemporal plane is divided into the three parts (planum polare, Heschl gyrus, planum temporale), and contains the primary and association auditory system and a part of Wernicke's area. However, the language function of the inner surface of the operculum, and the clinical presentation and treatment of patients with lesions in these areas have rarely been described.

Here we present the results of functional mapping and surgery undergone by 5 patients with tumors located in and around the subcortex of the language area. These

Table 1a. *Summary of the 5 patients*

Case	Age (yr), sex	Diagnosis	Tumor localization	Handedness	Language dominancy	Initial symptom
1	49 F	malignant lymphoma	lt. temporal	Rt.	Lt.	epilepsy
2	31 F	astrocytoma	lt. frontal	Rt.	Lt.	inicidental
3	52 M	glioblastoma	lt. frontal	Rt.	Lt.	hemiparesis
4	55 M	oligodendroglioma	lt. frontal	Rt.	Lt.	epilepsy
5	44 F	cavernous angioma	lt. temporal	Rt.	Lt.	transient paraphasia

Table 1b. *Summary of the severity of aphasia in the 5 patients*

Case	Overall SLTA severity		Auditory comprehension		Naming		Sentence repetition		Sentence reading aloud		Reading comprehension		Kana letter dictation		Sentence dictation	
	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post
1	10	10	7	9	16	18	3	5	4	5	7	9	10	8	5	5
2	10	10	10	10	20	20	5	4	5	5	10	10	10	10	5	5
3	5	9	1	1	14	14	3	4	5	5	1	1	6	8	1	1
4	10	10	9	8	18	18	4	4	5	5	10	10	10	10	5	5
5	10	10	10	10	20	20	4	4	5	5	8	8	10	10	5	5

lesions can be resected safely using functional mapping in patients undergoing awake surgery.

Methods

Subjects

There were 5 patients with intrinsic brain tumors (frontal glioma, $n=3$; temporal cavernous angioma, $n=1$; temporal primary central nervous system malignant lymphoma, $n=1$) located in the perisylvian subcortex in the language-dominant hemisphere. They were 2 men and 3 women; their median age was 46 years (range 31–55 years) (Table 1a).

Language evaluation

The Standard Language Test of Aphasia (SLTA) was used to evaluate language functions. The SLTA is the standardized test battery most commonly used to evaluate Japanese aphasic patients [20]. The aphasia severity ratings (0 = most severe, 10 = normal) are based on the 19 SLTA sub-scores; these were used as the primary language measure in the present study [8, 11]. The following seven subscores of the SLTA were also included in the analysis: auditory comprehension (to obey verbal commands) (out of 10); naming (out of 20); sentence repetition (out of 5); reading aloud short sentences (out of 10); dictation of Kana letters (out of 10); and dictation of short sentences (out of 5). Each patient was given the SLTA twice; the aphasia severity ratings before and after the operation (approximately 1 to 3 months after the surgery) are shown in Table 1b.

Intra-operative cortical functional mapping

To determine whether the lesions were located in the dominant hemisphere, patients underwent pre-operative functional MRI and/or intracarotid amytal testing (Wada test). During awake surgery, intra-operative cortical mapping for language was performed in all patients following the previous reports [1, 10, 14]. Intravenous anesthesia (propofol) was used during craniotomy. After creating a cranial opening large enough to expose most of the lateral temporal and inferior frontal lobe, propofol administration was discontinued and the patient was allowed to awaken. Silver-tip bipolar electrodes spaced approximately 5 mm from each other were placed on the exposed cortical surface. Stimulation parameters are set at 60 Hz, biphasic square wave pulses (1 msec/phase), with variable peak-to-peak current amplitude between 2 to 12 mA (peak-peak amplitude). To avoid eliciting local seizure phenomena or false negative or false positive results, a current below the after-discharge threshold was used so that depolarization was not propagated to the nearby cortex. Before mapping, 10 to 20 sites were selected and marked with small tags. Sites for stimulation mapping were randomly selected to cover all of the exposed frontal or temporal lobe cortex, including areas thought to contain sites essential for language function

and areas near and overlying the lesion site. Each patient was shown images of simple objects. Cortical stimulation, applied before the presentation of each image, was continued until there was a correct response or the next image was presented. Each pre-selected site was stimulated 3 to 4 times but never twice in succession. Sites where stimulation produced consistent speech arrest or anomia were considered essential language areas.

Case illustration

Case 1

This 49-year-old right-handed woman was in excellent health when she had her first generalized tonoclonic seizure. Preoperative MRI showed a round well-enhanced 2.5 cm lesion in the superior temporal gyrus. Intra-operative functional mapping of the essential speech cortex under awake surgery disclosed that the tumor was located just under the temporal language area. After exposing the posterior part of superior temporal plane by opening the Sylvian fissure, we performed intra-operative language mapping of the posterior part of the superior temporal plane. No language site was identified at that area. Unfortunately, we could not obtain an intra-operative pathological diagnosis, so we totally removed the lesion via a superior temporal plane cortical incision (Fig. 1). Postoperative histological diagnosis was primary CNS malignant lymphoma. This was treated with radio-chemotherapy as adjuvant therapy. Her postoperative SLTA score remained unchanged. She discharged from our hospital without any neurological deficits.

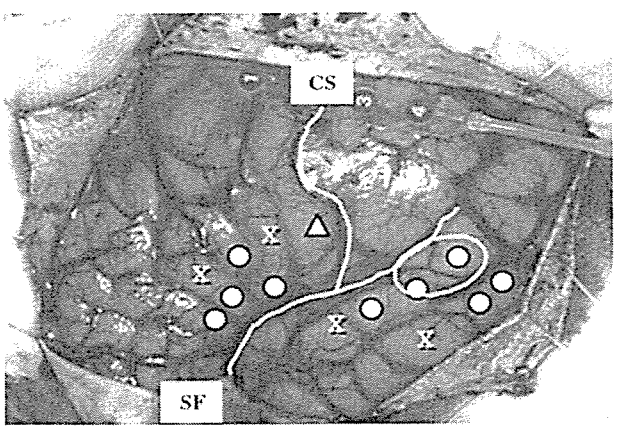

Fig. 1. *Case 1* – A 49-year-old woman with primary CNS malignant lymphoma. Intra-operative photograph of the brain map showing that the tumor is located under the Wernicke's area. ○ Speech arrest, △ dysarthria, × no response, *CS* central sulcus, *SF* Sylvian fissure

Case 2

This 31-year-old woman was in excellent health when she sustained a simple head injury. CT study incidentally disclosed an anomaly. Preoperative MRI revealed a round, non-enhancing, 3 cm lesion in the inferior frontal gyrus. With the patient awake, intra-operative cortical functional mapping of the essential speech cortex was performed. A frontal language area was identified; the tumor was located under the tongue motor area. We exposed the frontal operculum by opening the Sylvian fissure and performed intra-operative language mapping. No language function was identified at the inner surface of the posterior part of the frontal operculum; the tumor was removed from the non language area (Fig. 2). The histological diagnosis was low-grade astrocytoma. Although she suffered transient dysarthria, she fully recovered within several days.

Case 3

This 52-year-old right-handed man was admitted to our hospital with aphasia and right-hand loss of power to grip. MRI showed a ring-like enhanced lesion in the frontal lobe. Intra-operative cortical language mapping failed to identify a frontal language area. His inferior frontal gyrus was swollen. We exposed the inner surface

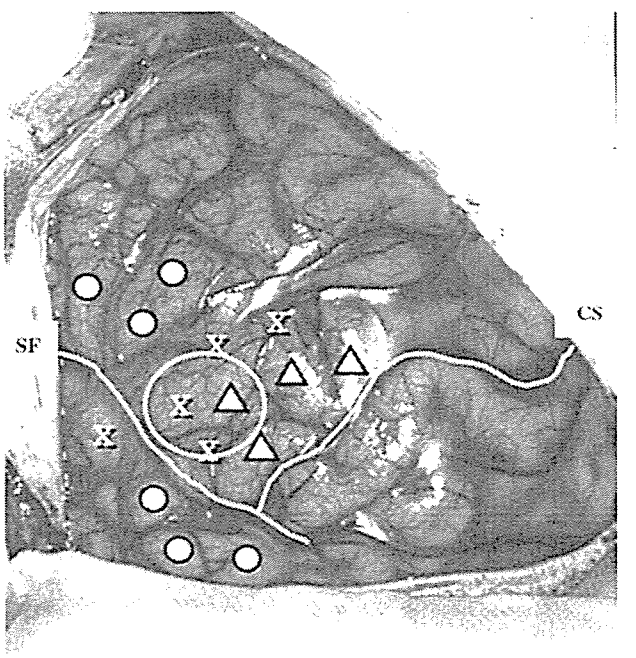

Fig. 2. *Case 2* – A 31-year-old woman with low-grade astrocytoma. Intra-operative photograph of the brain map showing that the tumor is located within the tongue motor area. ○ Speech arrest, △ dysarthria, × no response, *CS* central sulcus, *SF* Sylvian fissure

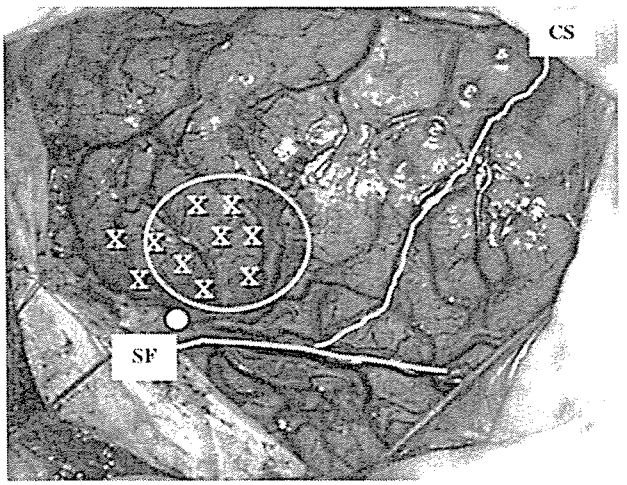

Fig. 3. *Case 3* – A 52-year-old man with frontal glioblastoma multiforme. Intra-operative photograph of the brain map showing that the Broca's area is located on the inside of the Sylvian fissure. ○ Speech arrest, △ dysarthria, × no response, *CS* central sulcus, *SF* Sylvian fissure

of the frontal operculum by opening the Sylvian fissure and performed intra-operative language mapping again. The essential language area, located on the inner surface of the frontal operculum, was compressed by a tumor and shifted into the Sylvian fissure. We resected the tumor through the non-language cortex (Fig. 3). The language area was replaced to the surface of inferior frontal gyrus. The histological diagnosis was glioblastoma multiforme. His overall SLTA severity had worsened immediately after the operation, whereas it recovered and improved 3 months after surgery (Table 1b).

Case 4

This 55-year-old-man was admitted our hospital with transient epileptic motor aphasia. T1- and T2-weighed MRI showed a low- and a high-intensity lesion in the inferior frontal gyrus, respectively, which was not enhanced by gadolinium. His pre-operative interictal SLTA score was normal. During awake surgery, intra-operative functional mapping identified a frontal language area. The tumor was located under the language area. We opened the Sylvian fissure and performed intra-operative language mapping at the inside of the Sylvian fissure again. Because no essential language area was identified on the inner surface of the frontal operculum, we resected the tumor through this non-language area (Fig. 4). The histological diagnosis was oligodendroglioma. His postoperative SLTA score was also normal.

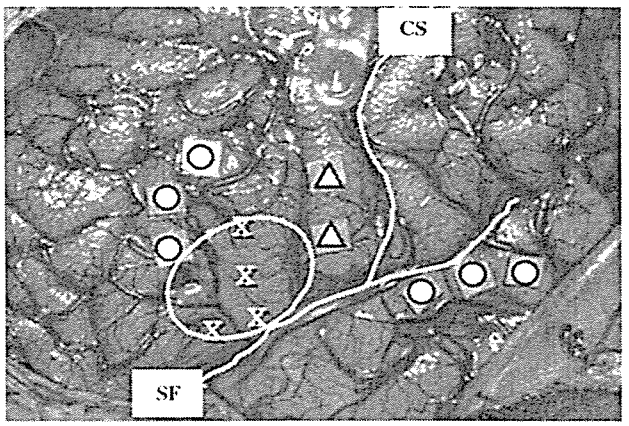

Fig. 4. *Case 4* – A 55-year-old man with oligodendroglioma. Intra-operative photograph of the brain map showing that the tumor is located under the Broca area. ○ Speech arrest, △ dysarthria, × no response, *CS* central sulcus, *SF* Sylvian fissure

Case 5

This 44-year-old woman visited our hospital complaining of transient paraphasia. T2-weighted MRI showed a mixed-intensity lesion with a hypo-intense rim in the left superior temporal gyrus. Awake craniotomy was performed. Intra-operative functional mapping revealed that the tumor was located under Wernicke's area. We opened the Sylvian fissure and performed intra-operative language mapping of the planum temporale. No language function was identified at that area. We resected the tumor through the non-language area on the splanum temporale (Fig. 5). The diagnosis was cavernous angioma. Her postoperative SLTA score was normal.

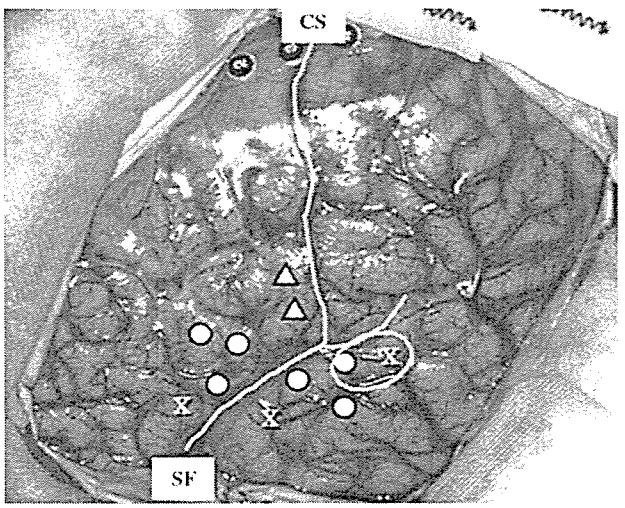

Fig. 5. *Case 5* – A 44-year-old woman with cavernous angioma. Intra-operative photograph of the brain map showing that the tumor is located under the Wernicke area. ○ Speech arrest, △ dysarthria, × no response, *CS* central sulcus, *SF* Sylvian fissure

Summary of cases

Pre- and postoperative MRI of the 5 patients are shown in Fig. 6. Quality of resection was systemically evaluated using immediate (within 72 hr after the operation) post-operative MRI. We were able to remove all tumors totally without permanent new neurological deficits and without exacerbation of the patients' aphasia. Schematic drawings presented in Fig. 7 identify the localization of the 5 tumors and the language areas. Of the 5 patients, only case 3, a patient with

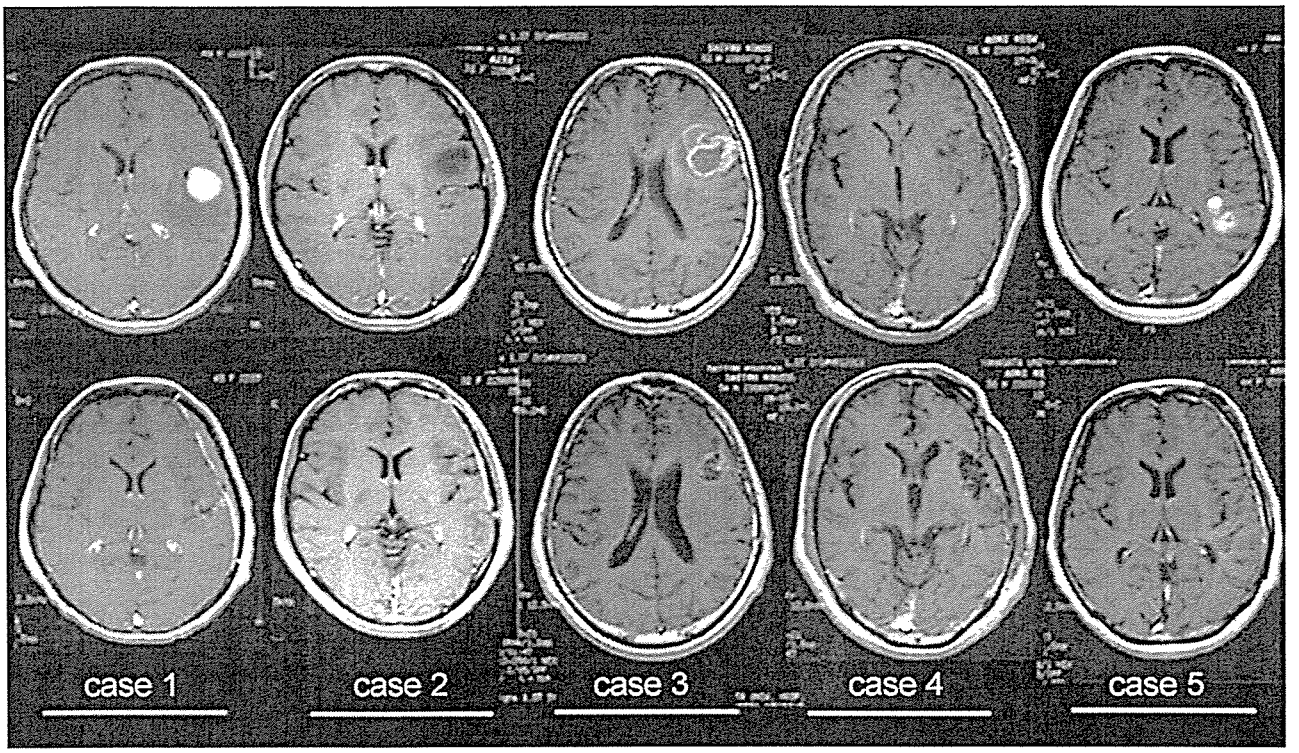

Fig. 6. Pre (*upper line*) – and post (*lower line*)-operative Gd-enhanced, T1-weighted magnetic resonance images obtained on the 5 patients. All tumors were removed almost totally

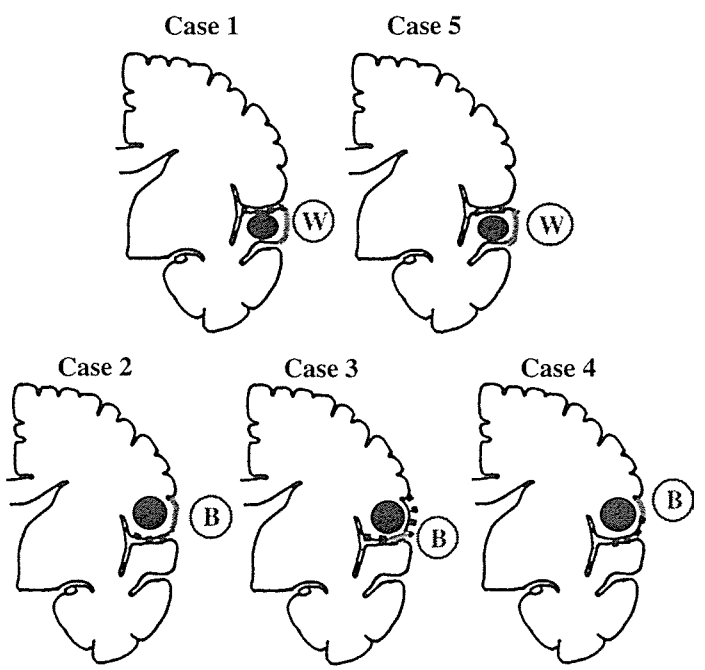

Fig. 7. Schematic drawing of the brain map of the 5 patients. *B* Broca's area, *W* Wernicke's area. The filled circles indicates the tumor. The dotted and gray lines encircle the functional- and non-functional areas, respectively

frontal glioblastoma manifested essential language function on the inner surface of the frontal or temporal operculum. This language area, located on the frontal operculum, appeared to be compressed and displaced by the tumor.

Discussion

Although functional mapping facilitates the planning of surgery in and around eloquent areas, the resection of tumors adjacent to language areas remains challenging. Ojemann and his associates reported that the essential language area localized to a focal areas of dominant hemisphere cortex of approximately 1 cm^2 [14, 15]. And the exact location of these sites in the left dominant hemisphere was found to vary substantially across the patient population. Haglund and colleagues reported that a margin of 7 to 10 mm around the language areas resulted in significantly fewer permanent postoperative linguistic deficits [9]. Recently, Duffau and colleagues noted no higher rate of definitive language worsening despite a resection coming in contact with the language sites (but higher rate of transient postoperative aphasia) [4]. Whittle IR *et al.* reported the incidence of iatrogenic dysphasia without intra-operative brain mapping is not dissimilar to that described after resection during use of awake craniotomy and intra-operative language testing [21]. They suggested that a large prospective study would be required to assess the usefulness of intra-operative language testing. Recently, Duffau H *et al.* reported that successful resection of a left insular cavernous angioma using intra-operative language mapping [5]. And Berger MS *et al.* mentioned that to maximize the extent of tumor resection while minimizing permanent language deficits, and recommended the using of cortical stimulation mapping [2]. Although this might be still controversial, we believe intra-operative language mapping is necessary to avoid surgical morbidity.

In this report, we took note that the language areas (Broca's and Wernicke's area) present at the perisylvian fissure. We posit that if there is non-essential language area on the inner surface of the Sylvian fissure, safe tumor resection may be possible even if the tumor is located under the language cortex. We operated on 3 patients with frontal gliomas without new neurological deficit except case 3 who experienced worsening of his aphasia transiently. But, his aphasia was improved 3 months after surgery.

The functional imaging studies allow detection of all the areas implicated in the realization of a task, but not the essential structures in these networks. There has been some work on the importance of the left frontal operculm for syntactic processing [6], and this region is activated during functional imaging studies of language. The functional imaging studies detected the distribution of 'essential' and 'participating' neuronal activity. But, the distribution of 'participating' neurons is substantially different to the focal, lateralized 'essential' sites identified by stimulation mapping for language. Noninvasive functional imaging modalities are an aid to the neurosurgeon, but the golden standard is still believed to be intra-operative monitoring. The evolution of better presurgical functional brain mapping techniques such as magnetic source imaging (MSI), fMRI, and probabilistic Diffuion Tensor imaging/fiber tracking methods will allow an estimation of the anatomical and functional cortex [7, 12]. These techniques may have the potential to promote functional neuronavigation as to an alternative to awake surgery.

The supratemporal plane of the temporal lobe in humans and subhuman primates contains the cortical representation of the primary and association auditory system and forms a part of Wernicke's area. However, the clinical presentation and treatment of patients with lesions in these areas have rarely been described. Silbergeld *et al.* who performed intra-operative cortical mapping during awake surgery on 2 patients subjected to resection of left-hemisphere Heschl gyrus gliomas, reported that neither patient manifested postoperative deficits [18]. Of 3 patients with non-dominant hemisphere Heschl's gyrus gliomas operated on by Russell and Golfinos [17], one presented with postoperative difficulty with music comprehension and production. In this report, we operated on 2 patients with left planum temporale tumors. We only examined language function intra-operatively. However, none of our 2 patients complained of auditory dysfunction and auditory change upon cortical stimulation. And we could remove the tumors without language dysfunction via non-functioning planum temporale cortex.

In our series, 4 of 5 patients had no essential language area on the inner surface of the operculum. Only one patient, a 52-year-old man with a frontal glioblastoma (Case 3) had language function on the inner surface of the frontal operculum. Duffau and colleagues reported 3 cases of inferior frontal gyrus (F3) glioma operated on without neurological deficits. They speculated that total F3 infiltration by glioma, thus a functional reorganization due to brain plasticity would explain the lack of deficit [3]. However, from intra-operative findings, after tumor removal, language cortex replaced on to the surface of the inferior frontal gyrus. We could not detect

essential language area on the medial area of the essential language area, and so we speculated his language area was compressed and displaced, rather than that there was reorganization of a new language area.

In conclusion, we posit that there is non-essential language area on the inner surface of the Sylvian fissure. While studies on larger patient populations are necessary, we can remove the perisylvian tumors through overlying non-language cortex. We propose our (opercular) approach may be useful in patients requiring the resection of perisylvian tumors.

Conclusions

Of 5 patients with tumors in the perisylvian cortex, only one, a patient with a frontal glioblastoma, manifested essential language function on the inner surface of the frontal operculum. In this exceptional case, the language cortex was compressed by the tumor and displaced to the inside of the Sylvian fissure. Based on the functional mapping data we obtained, we suggest that even tumors located in the subcortex of the language area may be resectable through the nonfunctioning opercular cortex without inducing postoperative language dysfunction.

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Comment

This is an interesting study that emphasizes the value of intra-operative stimulation in awake patients during the resection of lesions adjacent to eloquent cortex. The authors hypothesize that even in the presence of lesions which seem unresectable because of location near Broca's or Wernicke's area, in selected cases a complete resection may be possible when the tumor is approached through a trans-opercular route of non-functional intrasylvian tissue on the inner' surface of the operculum.

In our opinion, however, awake craniotomy, while still regarded as the reference standard of surgery in eloquent cortex, should be considered an interim solution until the advent of better and more powerful functional imaging modalities that help us visualize functionally important brain tissue. We have experience with language MEG (magneto-encephalography) for over 5 years in about 120 cases operated upon for gliomas in the vicinity of Broca' and Wernicke's area with functional neuronavigation. From our experience we conclude that this may well be an alternative to intra-operative awake stimulation.

The evolution of better presurgical functional brain mapping techniques and probabilistic Diffusion Tensor Imaging/fibertracking methods will allow an estimation of the anatomical and functional cortex hitherto norknown. These techniques may have the potential to promote functional neuronavigation as to a true alternative to awake craniotomies.

More correlative studies will be warranted in the future to prove that these new techniques are as safe as the proven and tested method of intra-operative electrical stimulation.

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イラストークリニカルテクニック

皮質てんかんに対する gyrectomy

▣ はじめに

てんかん焦点の切除の眼目は確実な焦点の切除と周囲脳の損傷を避けることである．このために，グリオーマなどの髄内腫瘍摘出法として我々が開発した gyrectomy 法を応用しているので紹介する．

gyrectomy 法

従来，髄内腫瘍の摘出は，図1のごとく，腫瘍に対し subpial にアプローチし，超音波メスや腫瘍鉗子を用いて piece by piece に摘出を進めることが一般的であった．この方法では脳溝内を走行する血管や隣接する脳回の思わぬ損傷や腫瘍の残存を招きかねない．gyrectomy 法は，腫瘍を含み摘出を予定する脳回と周囲の脳回との間の脳溝を開放し，脳溝内の血管や周囲脳回を損傷することなく，腫瘍を含む脳回を一塊として摘出する方法であり，従来の方法の問題を克服することが可能な手技である．

脳溝の開放は摘出する脳回の全周のくも膜を鋏を用いて鋭的に切離しながら，脳表の静脈を隣接する脳回側に寄せていく．くも膜に適度な張力をかけながら，脳溝内を走行する動脈周囲を剝離しながら動脈の走行の把握を進め，摘出する脳回を栄養する動脈を確認したら，その動脈のみを凝固切離する．全周にわたってこれらの操作を脳溝底部まで進めると，摘出する脳回は隣接する脳回と完全に孤立する．最後に脳溝底の深さで脳回を凝固切開し，白質に到達しこれを切離し脳回ごと一塊に摘出する．既に動脈が処理されているため，ほとんど無血下に白質切開を進めることができる．また，腫瘍が底部に残存していても無血下なので視認しやすく，追加切除も容易である(図2)．

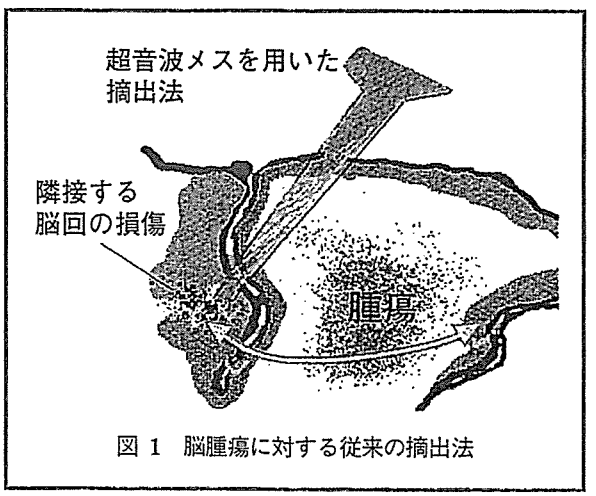

図 1　脳腫瘍に対する従来の摘出法

皮質てんかんへの応用

皮質形成異常，結節性硬化症，限局したグリオーマなどで難治てんかんの症例が gyrectomy のよい適応である．これらの病変のように皮質と白質の境界が不鮮明な症例においても確実な摘出が可能であるばかりでなく，隣接する正常な脳回が保護されるため，新たな焦点形成の予防にもなり得，病変の完全な摘出と発作消失の両面で治癒が期待できる．当科では10例の皮質形成性異常病変に対し gyrectomy による焦点切除を行い，全例 Engel の class Ⅰであった．

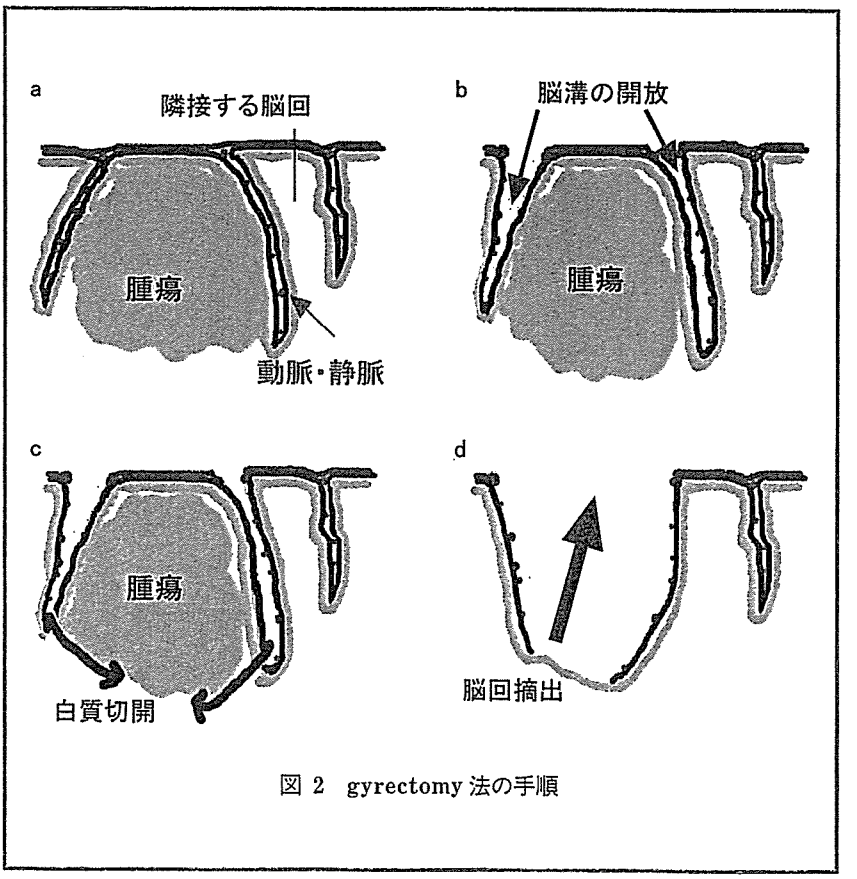

図 2　gyrectomy 法の手順

0289-0585/06/¥500/論文/JCLS

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症 例

9歳女児．6歳時から複雑部分発作と右を向く向反発作と，それに続く全身痙攣発作が出現しだす．フェニトイン200 mg/日，カルバマゼピン400 mg/日，フェノバルビタール500 mg/日を服用していたが，発作は1日に数回は出現していた．MRIにて異常を指摘され当科に紹介となった．皮質脳波記録下に，病変をgyrectomy法にて一塊として摘出した．摘出標本の病理診断は結節性硬化症に認められる皮質結節であった．術後は発作は一度も出現せず11年が経過している（図3，4）．

■ ま と め

gyrectomy法の利点は，1）周囲の脳回および同部を栄養する動脈の不用意な損傷がない，2）腫瘍栄養動脈の選択的で確実な処理を行えるため，無血野での操作が可能となる，3）脳溝底が同定できるため，脳回底部での切除線の決定が容易である，などである．

手術においてはマイクロサージャリーの技術を駆使することには言を俟たないが，摘出脳回の同定，範囲の決定，動脈の処理などには，術前・術中の機能マッピングや術中モニタリング技術の積極的な応用が安全性・確実性をより高めるためには重要である．

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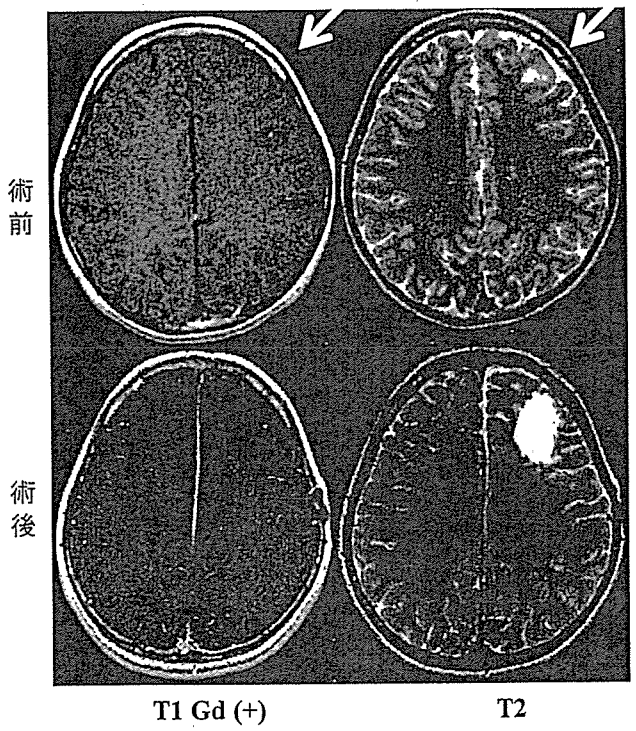

図3 症例の術前・術後MRI
病変を含む脳回（矢印）を摘出している．

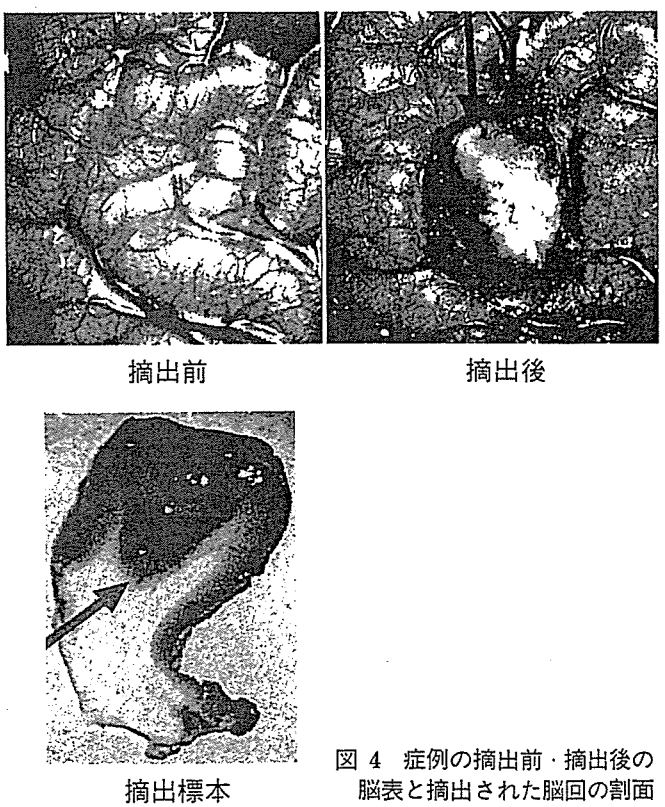

図4 症例の摘出前・摘出後の脳表と摘出された脳回の割面

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Ischemic complications associated with resection of opercular glioma

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Object. Opercular glioma inferolateral to the hand/digit sensorimotor area can be resected safely using a neuronavigation system and functional brain mapping techniques. However, the surgery can still sometimes cause postoperative ischemic complications, the character of which remains unclear. The authors of this study investigated the occurrence of infarction associated with resection of opercular glioma and the arterial supply to this region.

Methods. The study involved 11 consecutive patients with gliomas located in the opercular region around the orofacial primary motor and somatosensory cortices but not involving either the hand/digit area or the insula, who had been treated in their department after 1997. Both pre- and postoperative diffusion-weighted magnetic resonance (MR) imaging was performed in the nine consecutive patients after 1998 to detect ischemic complications. All patients underwent open surgery for maximum tumor resection. Postoperative MR imaging identified infarction beneath the resection cavity in all patients. Permanent motor deficits associated with infarction involving the descending motor pathway developed in two patients. Cadaveric angiography showed that the distributing arteries to the corona radiata were the long insular arteries and/or medullary arteries from the opercular and cortical segments of the middle cerebral artery.

Conclusions. Subcortical resection around the upper limiting sulcus of the posterior region of the insula and wide resection in the anteroposterior and cephalocaudal directions of the opercular region were considered to be risk factors of the critical infarction. Surgeons should be aware that resection of opercular glioma can disrupt the blood supply of the corona radiata, and carries the risk of permanent motor deficits.

KEY WORDS • **infarction** • **complication** • **glioma** • **descending motor pathway** • **operculum** • **diffusion-weighted imaging**

PRECISE localization of a glioma in the frontoparietal opercular region inferolateral to the hand/digit sensorimotor area is now possible using various methods including functional brain mapping techniques, neuronavigation systems, intraoperative MR imaging, and photodynamic diagnosis using various photosensitizers. Therefore, gliomas in this location, even in the dominant hemisphere, can be totally resected without causing permanent neurological deficits.[5,9,11,12] During such procedures, surgical techniques for opercular glioma have concentrated on the identification and preservation of the cortical and subcortical functions.[5,11,12] However, little is known about the ischemic complications that can occur after the resection of an opercular glioma.

Diffusion-weighted MR imaging, which reflects the degree of water diffusion in vivo, is an invaluable tool for the diagnosis of acute stroke and other types of brain injury.[14] Several potential applications of DW MR imaging in patients with gliomas have been recently investigated, mainly for the evaluation of tumor cellularity.[7,8,16,21] Recently, postoperative DW MR imaging has been proposed as a routine study to identify ischemic complications after resection of the glioma.[15] Diffusion-weighted MR imaging detected abnormalities after resection in approximately two thirds of newly diagnosed gliomas. At our institution, postoperative MR imaging including DW imaging has been performed for nearly 10 years as one of the examinations used to determine the postoperative state of patients after tumor removal and has disclosed evidence of postoperative ischemic complications.

In the present study we investigated the postoperative ischemic complications and DW MR imaging findings in 11 patients with pure opercular gliomas surgically treated during the past 9 years. Microangiography studies of cadavers were also analyzed to identify the blood supply for the corona radiata. Finally, referring to the results of the microangiographic analysis, we tried to determine the risk factors for critical infarction at the corona radiata that were likely to result in permanent motor deficits.

Abbreviations used in this paper: DW = diffusion-weighted; GBM = glioblastoma multiforme; MCA = middle cerebral artery; MR = magnetic resonance.