distribution achieved by CED. As the CED of chemotherapeutic agents targets the site of tumor invasion, this method may be effective without severe toxicity to other parts of the brain.

The present study showed that local application of chemotherapeutic agents into the brain parenchyma induced transient opening of the BBB. Systemic chemotherapy during this period of BBB disruption had synergistic effects resulting in prolonged survival of tumor-bearing rats. The present strategy may provide a new approach for glioma chemotherapy.

Conflict of interest

None declared.

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REVIEW ARTICLE

New insights into glioma classification based on isocitrate dehydrogenase 1 and 2 gene status

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Abstract In glioma, mutations in the isocitrate dehydrogenase 1 and 2 (*IDH1/2*) genes have been receiving attention. *IDH1/2* mutations are frequently found in grade II and III gliomas. These genetic alterations occur very early in gliomagenesis and strongly predict favorable outcome in patients with high-grade gliomas. Despite the evolution of studies on this topic, the underlying mechanism of the *IDH1/2* mutations remains unknown. Here, we briefly review the current knowledge of *IDH1/2* and discuss molecular diagnostics based on *IDH1/2* gene status.

Keywords *IDH1* · Glioblastoma · Astrocytoma · Oligodendroglioma · Pilocytic astrocytoma

Introduction

The accumulation of genetic alterations turns normal cells or cancer-initiating cells into malignant tumors. Some genetic aberrations such as mutations in *TP53* and *EGFR* amplification are common in many organs; on the other hand, there are several mutations that are specific to certain malignant tumors. Recently, mutations have been discovered in the isocitrate dehydrogenase 1 (*IDH1*) and 2 (*IDH2*) genes that are only found in glioma [1, 2] and acute myeloid leukemia [1, 3], with a few exceptions [4–6]. The underlying mechanisms of these mutations are still unclear; however, they have already had a large impact on concepts of glioma. In this article, we briefly review the current knowledge of *IDH1* and its potential role in glioma classification.

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The discovery and function of the *IDH1* mutation in glioma

Recently, large-scale genomic analyses of malignant glioma have provided new insights [7–9]. In particular, Parsons et al. [7] sequenced 20,661 protein-coding genes from 22 glioblastoma tumor samples and found mutations in *IDH1*. *IDH1* mutations were detected in 12% of primary glioblastoma patients, especially relatively young glioblastoma patients, and most secondary glioblastoma patients (5 of 6 patients) [7]. Of note, glioblastoma patients with *IDH1* mutation show prolonged overall survival compared with patients without the *IDH1* mutation (median survival, 3.8 vs. 1.1 years, respectively). The *IDH1* mutation is also frequently observed in grade II and III gliomas and is a prognostically favorable factor in grade III glioma [1, 2, 10, 11].

The *IDH* genes encode three distinct IDH enzymes (IDH1, IDH2, and IDH3). Among these genes, the mutated form of IDH expressed in glioma mostly affects *IDH1* (only 4% of the mutations affect *IDH2* and none affects *IDH3*) [1, 12]. Mutations in *IDH1* and *2* are usually mutually exclusive, but 0.5% of *IDH*-mutated glioma patients carry mutations in both genes [12]. Regarding the normal functions of these genes, both catalyze the oxidative decarboxylation of isocitrate to alpha-ketoglutarate, resulting in the reduction of $NADP^+$ to NADPH [13]. However, their mutated forms were reported to display two opposing functions: the induction of hypoxia-inducible factor 1 alpha (loss of function) [13] and the conversion of alpha-ketoglutarate to 2-hydroxyglutarate (gain of function) [14].

Previous studies have also clarified the structural and biochemical activity of mutated *IDH1* [14, 15] and the slow-growing character of glioma cells carrying the *IDH1* mutation [16, 17]. Investigations of the mechanism of *IDH1/2* mutation in glioma are still ongoing, and much remains to be elucidated.

Molecular classification and *IDH1* gene status in glioma

Molecular diagnostics can identify subsets of tumors with similar molecular backgrounds; therefore, it is useful for predicting patient outcome and treatment response [18, 19]. *IDH1* mutation is an early event of gliomagenesis [20]; thus; gliomas can be divided into two distinct groups, the mutated *IDH1* group (the *IDH*-dependent pathway) and the wild-type *IDH1* group (the *IDH*-independent pathway) [21]. Low-grade gliomas (diffuse astrocytoma, oligodendroglioma, and oligoastrocytoma), grade III gliomas (anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma), and secondary glioblastomas were reported to belong to the *IDH*-dependent pathway. In contrast, pilocytic astrocytoma and primary glioblastoma were categorized as belonging to the *IDH*-independent pathway [21, 22]. However, a summary of current reports about the *IDH* mutation in glioma indicates that each distinct pathway includes grade I to IV gliomas, as described in Fig. 1. Here, we provide a detailed discussion about each grade of glioma based on their *IDH1* gene status.

Glioblastoma and IDH1 gene status

According to the World Health Organization (WHO) classification of tumors of the central nervous system [23], glioblastomas are divided into two types according to their clinical course. Those that involve a preceding lower-grade glioma are defined as secondary glioblastomas and those which do not are defined as primary glioblastomas. *IDH1* mutations are observed in 50–88% of secondary glioblastomas but in only 3.0–8.0% of primary glioblastomas [1, 2, 24–29]. Therefore, the *IDH1* mutation is a useful marker for distinguishing secondary glioblastomas, which are categorized as belonging to the IDH-dependent pathway, from primary glioblastomas, which belong to the IDH-independent pathway [27]. However, it is problematic that some secondary glioblastomas do not carry *IDH1* mutations and some primary glioblastomas do. Nobusawa et al. suggested that in the former cases, the glioma was actually a primary glioblastoma but was misdiagnosed as a lower-grade glioma. In the latter cases, the primary glioblastoma patients carrying *IDH1* mutations might have had preceding lower-grade gliomas that were not discovered because they were clinically silent [27]; this was because they matched the profile for secondary glioblastomas, i.e., a young age, frequent *TP53* mutation, and a lack of *EGFR* amplification [25, 27]. However, these explanations do not account for all cases. The same report described seven cases of grade III glioma and one of grade II glioma that progressed to secondary glioblastoma without *IDH1*

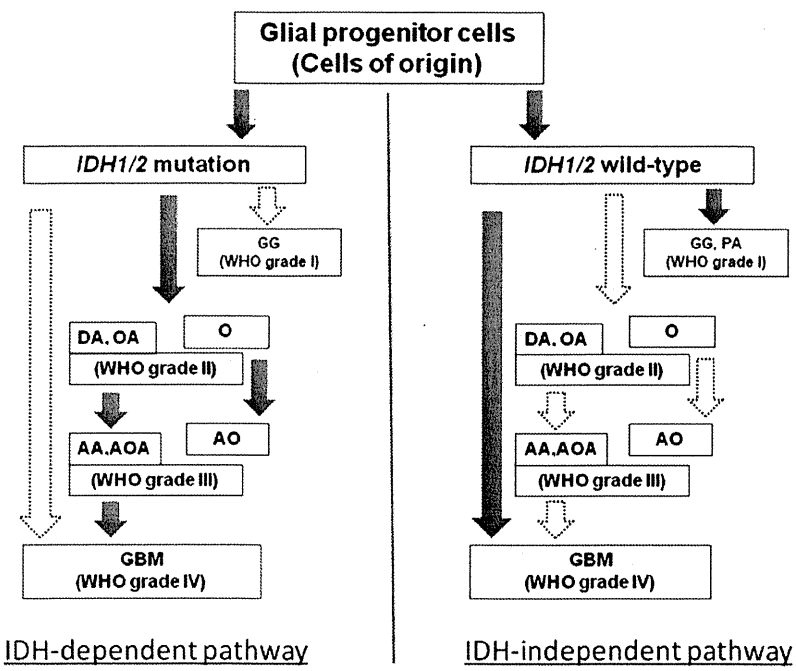

Fig. 1 Summary of glioma classification based on isocitrate dehydrogenase (*IDH*) gene status. Both the IDH-independent (*right*) and IDH-dependent (*left*) pathways include grade I–IV gliomas. The main pathways are indicated by *dark thick arrows*; possible alternative pathways are indicated by *clear dotted arrows*. *GG*, ganglioglioma; *PA*, pilocytic astrocytoma; *DA*, diffuse astrocytoma; *O*, oligodendroglioma; *OA*, oligoastrocytoma; *AA*, anaplastic astrocytoma; *AO*, anaplastic astrocytoma; *AOA*, anaplastic oligoastrocytoma; *GBM*, glioblastoma

mutation [27]. In addition, we experienced six cases of grade III glioma and two cases of grade II diffuse astrocytoma without *IDH1* mutation that progressed to secondary glioblastoma without *IDH1* mutation (unpublished data). These findings imply that a preceding lower-grade glioma without *IDH1* mutation can progress to secondary glioblastoma without *IDH1* mutation; therefore, a few secondary glioblastomas might belong to the IDH-independent pathway.

Recently, a new classification for glioblastomas was proposed based on integrated genomic analysis [8]. It was composed of four subsets: classical, mesenchymal, proneural, and neural. Each group displays specific molecular variations, and *IDH1* mutation is the main molecular variation of the proneural subtype. This new classification displayed close links with patient prognosis: the proneural type displayed the best prognosis, followed by the neural, mesenchymal, and classical types when all gliomas were analyzed, but the difference was not significant when only glioblastomas were analyzed. Interestingly, only the proneural subtype did not display altered survival or mortality during aggressive treatment, whereas the other three subtypes derived survival benefits from aggressive treatment.

Grade III glioma and IDH1 gene status

Grade III gliomas such as anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma carry *IDH1/2* mutations in 55–69.1% of cases [12, 26, 28, 29]. In this grade, patients with mutated *IDH1/2* survive significantly longer than patients with the wild-type *IDH1* [1, 2, 10, 26] (65 and 20 months, respectively [1]), and *IDH1* mutation is an independent favorable prognostic factor [11]. In terms of its molecular features, grade III glioma patients with mutated *IDH1/2* genes display *TP53* mutation [1, 28], 1p19q codeletion [10, 11, 26, 28, 30], and *MGMT* gene promoter methylation [10, 11, 24, 26]; on the other hand, patients with wild-type *IDH1* display an unmethylated *MGMT* gene [10, 11, 24, 26], *CDKN2A* homozygous deletion [1], loss of 10q (*PTEN*) [1, 10, 26, 28], and *EGFR* amplification [10, 26]. Because of their differing prognoses and distinct molecular backgrounds, Yan et al. [21] stated that grade III gliomas with and without *IDH1/2* mutation are distinct tumors. Hartmann et al. reported that patients with anaplastic astrocytomas expressing wild-type *IDH1* survive for a shorter period than glioblastoma patients with mutated *IDH1* but longer than glioblastoma patients with wild-type *IDH1*. They discussed an alternative classification that was closely associated with the clinical course of the disease, in which they used the term "anaplastic astrocytoma grade III" for anaplastic astrocytoma with mutated *IDH1* and the term "anaplastic astrocytoma grade IV" for anaplastic astrocytoma with wild-type *IDH1* [24].

Grade II diffuse glioma and IDH1 gene status

Among all grades of glioma, *IDH1/2* mutations are most frequently observed in grade II diffuse gliomas, such as diffuse astrocytoma, oligodendroglioma, and oligoastrocytoma, in which their incidence ranges from 71% to 86% [1, 12, 20, 29, 31]. Compared to its contribution to the improved prognosis of higher-grade gliomas [1, 2, 10, 11, 32], in grade II diffuse gliomas the *IDH1/2* mutation is a relatively controversial prognostic factor [26, 31, 33, 34]. Some reported grade II diffuse glioma patients with mutated *IDH1/2* demonstrated a better prognosis [26, 33, 34] although another study reported that *IDH1/2* mutations were not prognostic [31]. It was also reported that adult grade II diffuse astrocytoma patients expressing *IDH1/2* mutations presented with a more aggressive prognosis than pediatric counterparts that did not carry *IDH1/2* mutations [35]. This report indicated that even in the same grade II glioma, adult gliomas might be distinct from pediatric gliomas.

Currently, one of the key roles of *IDH1/2* gene status in grade II glioma is as a diagnostic marker. Because *IDH1/2* mutation is frequently observed in grade II diffuse gliomas, it enables us to distinguish grade II diffuse gliomas from other low-grade gliomas such as pilocytic astrocytoma, pleomorphic xanthoastrocytoma, and ependymoma, which rarely carry *IDH1/2* mutations [1, 20, 29].

About 20% of grade II diffuse glioma patients do not carry *IDH1/2* mutations. There are three possible explanations for the reporting of grade II diffuse glioma without *IDH1/2* mutations. First, it could have been the result of the timing of sampling. Watanabe et al. analyzed 51 glioma patients including those with low- and high-grade gliomas who underwent multiple biopsies. They found 9 patients without *IDH1* mutations at the first biopsy, but 2 of them were found to carry an *IDH1* mutation during the final biopsy [20]. The second possibility is misdiagnosis. Other gliomas such as pilocytic astrocytoma or ependymoma, which rarely carry *IDH1/2* mutations [1, 29], might be misdiagnosed as grade II diffuse gliomas with wild-type *IDH1/2*. There is no obvious histological or molecular distinction between grade II and III gliomas [36], and so *IDH1/2* wild-type grade III glioma could also be misdiagnosed as *IDH1/2* wild-type grade II glioma. The third possible explanation is an alternative classification. Grade II glioma patients expressing wild-type *IDH1/2* display the *TP53* mutation (wild-type *IDH1*:mutated *IDH1*, 2%:32%) and 1p19q codeletion (wild-type *IDH1/2*:mutated *IDH1/2*, 3%:37%) less frequently than patients carrying *IDH1/2* mutations [31]. Additionally, alterations in the *RB1* pathway were found in grade II diffuse gliomas expressing the

wild-type *IDH1/2*, providing a pathway distinct from that involving mutated *IDH1/2* [37]. As already mentioned, including our data, three cases of grade II glioma without *IDH1* mutation progressed to secondary glioblastoma without *IDH1* mutation. Therefore, a subset of grade II diffuse gliomas might belong to the IDH-independent pathway.

Grade I glioma and IDH1 gene status

The correlation between grade I glioma and *IDH1* gene status is not as strong as the correlations between *IDH1* gene status and other grades of glioma. Only 0–2% of pilocytic astrocytomas [1, 29, 38] carries *IDH1* mutations. The main molecular feature of pilocytic astrocytoma is alterations in the *BRAF* gene, which are observed in 66–70% of cases [38, 39]; thus, pilocytic astrocytoma is categorized as belonging to the *IDH*-independent pathway [21]. *IDH1/2* can be used in combination with *BRAF* as a sensitive and specific marker for differentiating pilocytic astrocytoma from grade II diffuse astrocytoma [38].

Ganglioglioma is reported to carry *IDH1/2* mutations in 8.2–38% of cases [2, 40]. In general, the presence of *IDH1/2* mutations in gliomas indicates a better prognosis. However, the presence of *IDH1* mutations in ganglioglioma is associated with a greater risk of recurrence, malignant transformation, and/or death [40]. Therefore, further investigations are needed to determine the underlying mechanism of *IDH1* mutation in ganglioglioma.

Pediatric high-grade glioma (pediatric HGG) and IDH1 gene status

There have been several reports of pediatric HGG patients displaying *IDH1* mutations [12, 29, 41], but compared to the frequency of *IDH1* mutations in adult HGG, they are relatively rare. Therefore, the contribution of *IDH1* mutation to pediatric HGG seems weaker than its contribution to adult HGG. Pollack et al. [41] examined 43 pediatric HGG patients and found 7 patients displaying *IDH1* mutations (16%), all of whom ranged from 14 to 21 years old. The mutated *IDH1* patients displayed significantly longer event-free and overall survival than the wild-type patients, all of whom were under 14 years of age. They concluded that older children achieve a more favorable prognosis. We experienced a 10-year-old female anaplastic oligodendroglioma patient with *IDH1* mutation (unpublished data). Currently, her progression-free survival is more than 24 months; regardless of age, pediatric HGG with *IDH1* mutation may present a favorable prognosis. Therefore, *IDH* gene status is a putative marker for differentiating patients with good prognoses from those with poor prognoses in pediatric HGG.

The paradox of *IDH1* mutation

Because the mutated form of *IDH1* induces both loss of function and gain of function [13, 14], a paradox emerged as to whether *IDH1* is a tumor suppressor gene or an oncogene [13, 14, 42]. Mutation in either a tumor suppressor gene or oncogene will logically lead to poorer prognosis; therefore, it is unclear why patients with mutated *IDH1* present with significantly prolonged survival compared with patients with wild-type *IDH1*. Currently, there are no answers to this question, but some groups have hypothesized that mutated *IDH* consumes NADPH and alpha-ketoglutarate, which normally rescue cells from oxidative stress, resulting in increased sensitivity to radiation therapy [43–45]. However, the proneural subtype of glioblastoma, which is characterized by *IDH1* mutation, was reported to derive no survival benefit from intensive therapy including radiation and chemotherapy.

There is no direct answer why 1p19q codeletion, *MGMT* methylation, a young age, and DNA promoter methylation occur significantly more frequently in the mutated *IDH1* group [46]. Interestingly, all these factors are known to be predictors of an improved prognosis [10, 47–49]. Therefore, one possible answer is that glioma patients with *IDH1* mutations live longer because better prognostic factors frequently occur in the mutated *IDH1* group. Further investigations are needed to clarify why favorable prognostic factors correlate with the mutated *IDH1* group.

Conclusion

We reviewed and discussed each grade of glioma according to *IDH1* gene status. The reported evidence suggests that each grade of glioma (grade I–IV) presents distinct clinical and molecular characteristics associated with *IDH1* gene status (Fig. 1). As discussed elsewhere, molecular alterations including *IDH1* gene status allow patients with similar genetic profiles to be identified; therefore, *IDH1* gene status could be useful for future clinical trials and classification purposes. It is still unknown how the *IDH1* mutation is correlated with glioma development or progression, and thus further investigation of this matter is necessary.

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術中MRIシステムを用いた脳腫瘍手術

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A New Intraoperative MRI System in Brain Tumor Surgery

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Summary: *Background of Study*: Extensive surgical removal of brain tumors lengthens life expectancy. As dynamic changes, such as brain shift, can occur during surgical procedures, intraoperative MRI is an important tool for safe and maximum resection of tumors. In July 2008, new operating room equipped with an intraoperative high-field MRI (1.5T) system, neuronavigation, and fluorescence diagnosis system opened at the author's institution, Yamagata University Hospital.

Methods: Preoperatively, 3.0T MR studies, including morphological study, multivoxel MR spectroscopy, tractography and functional MRI, were performed. If the tumor was located in or near an eloquent area, we performed MEP (motor evoked potential)/SEP (sensory evoked potential) monitoring and/or awake surgery using cortical and subcortical stimulation. Intraoperative MRI was performed after total resection or to obtain updated information on brain positioning during the removal of deep-seated tumors.

Results: Using this new suite, we have safely treated various brain tumors, including gliomas, metastatic brain tumors, meningiomas, and pituitary adenomas. Gross total removal was achieved in over 70% of malignant tumors. Intraoperative MR images contributed to improving the tumor resection rate and overall results.

Key Words: Intraoperative MRI system, Brain surgery
使用機種: Achieva 3.0T (Philips) Signa 1.5T (GE), Neuronavigation (Brain Lab)

はじめに

fMRIやDiffusion Tensor Imagingなどの新しい画像診断法の進歩により脳腫瘍手術の計画をより綿密に立てることが可能となった．運動誘発電位や覚醒下手術などのモニタリング・マッピングを用いて最大限の安全な摘出を図ることが浸潤性に発育し病理学的には全摘出が不可能と考えられる悪性神経膠腫にとってもoptimalな治療であると認識されるようになってきている．現在ナビゲーションシステムや超音波診断装置の併用による摘出率の向上が試みられているが，brain shiftや超音波診断装置の解像度の問題もあり，術中に正確に残存腫瘍，摘出率を把握することは困難である．2008年7月，当科で1.5テスラ術中MRIシステム（1.5T MRI (GE)，neuronavigation (Brain LAB)，術中蛍光診断・術中血管撮影機能FL400，FL800（KARL-STORZ）搭載手術顕微鏡（Leica），MRI・CT対応operation table (MAQUET)）を導入したので，新インテリジェント手術システムとその使用経験につき報告する．

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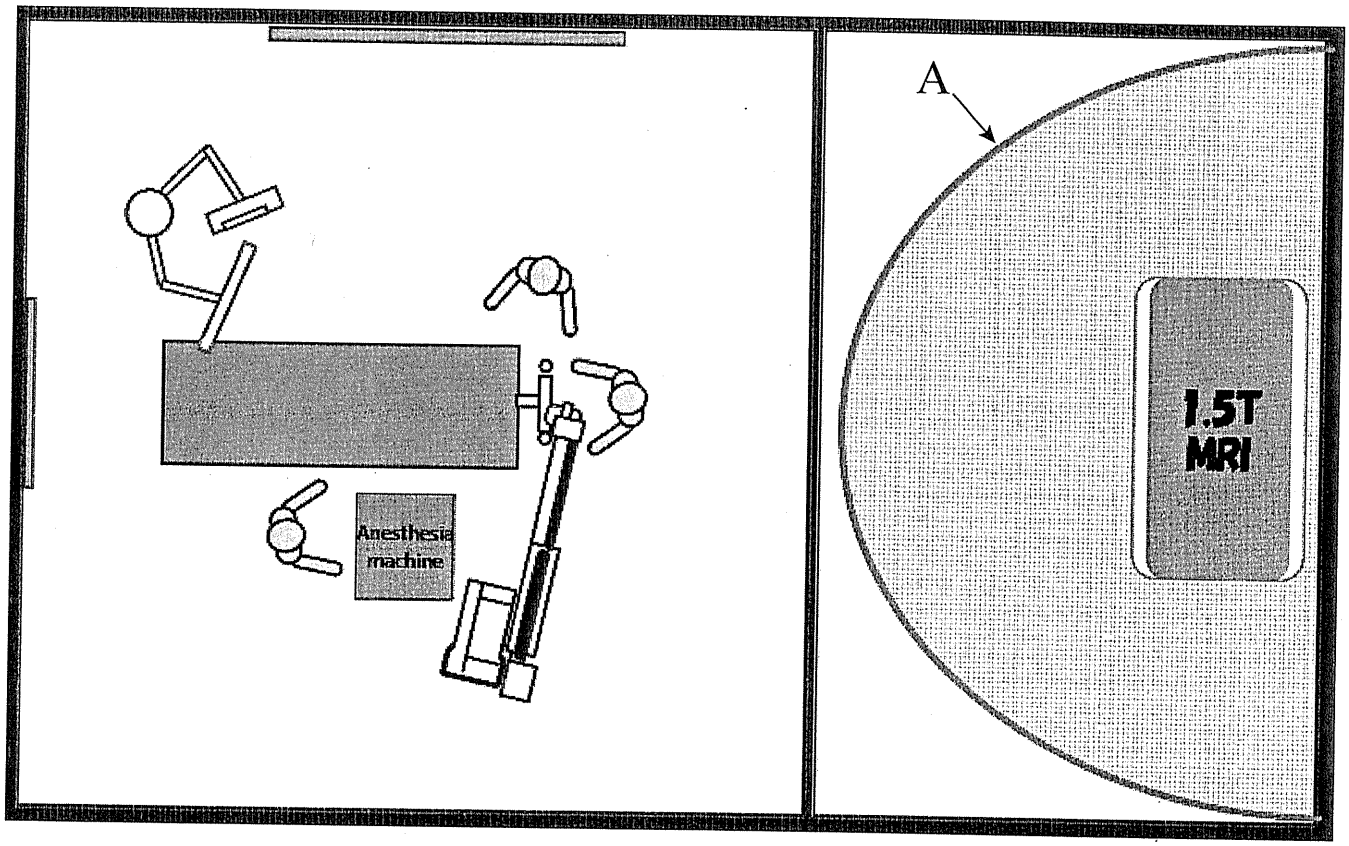

Fig. 1 Scheme of the new operation room. *line A* is 5-gauss line.

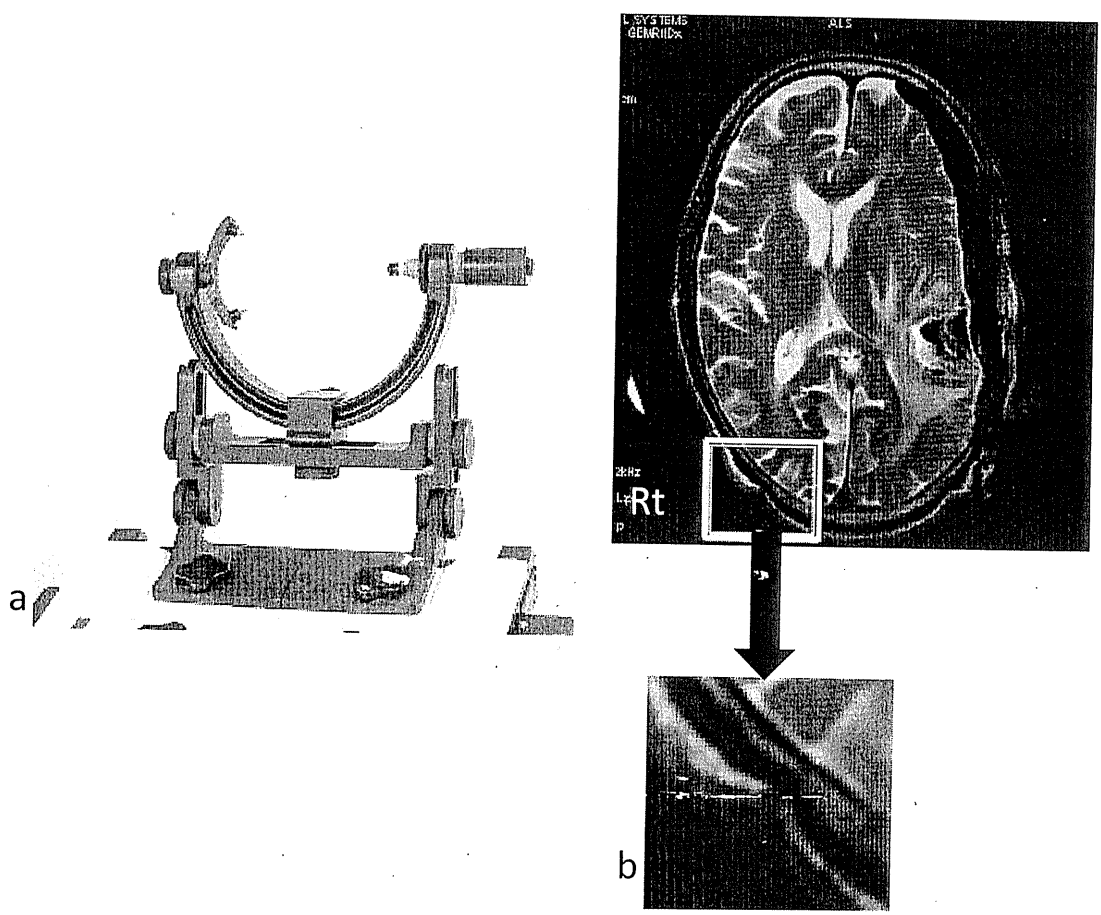

Fig. 2 **a**: Mayfield head clamp. **b**: MR image shows no artifact caused by head pin.

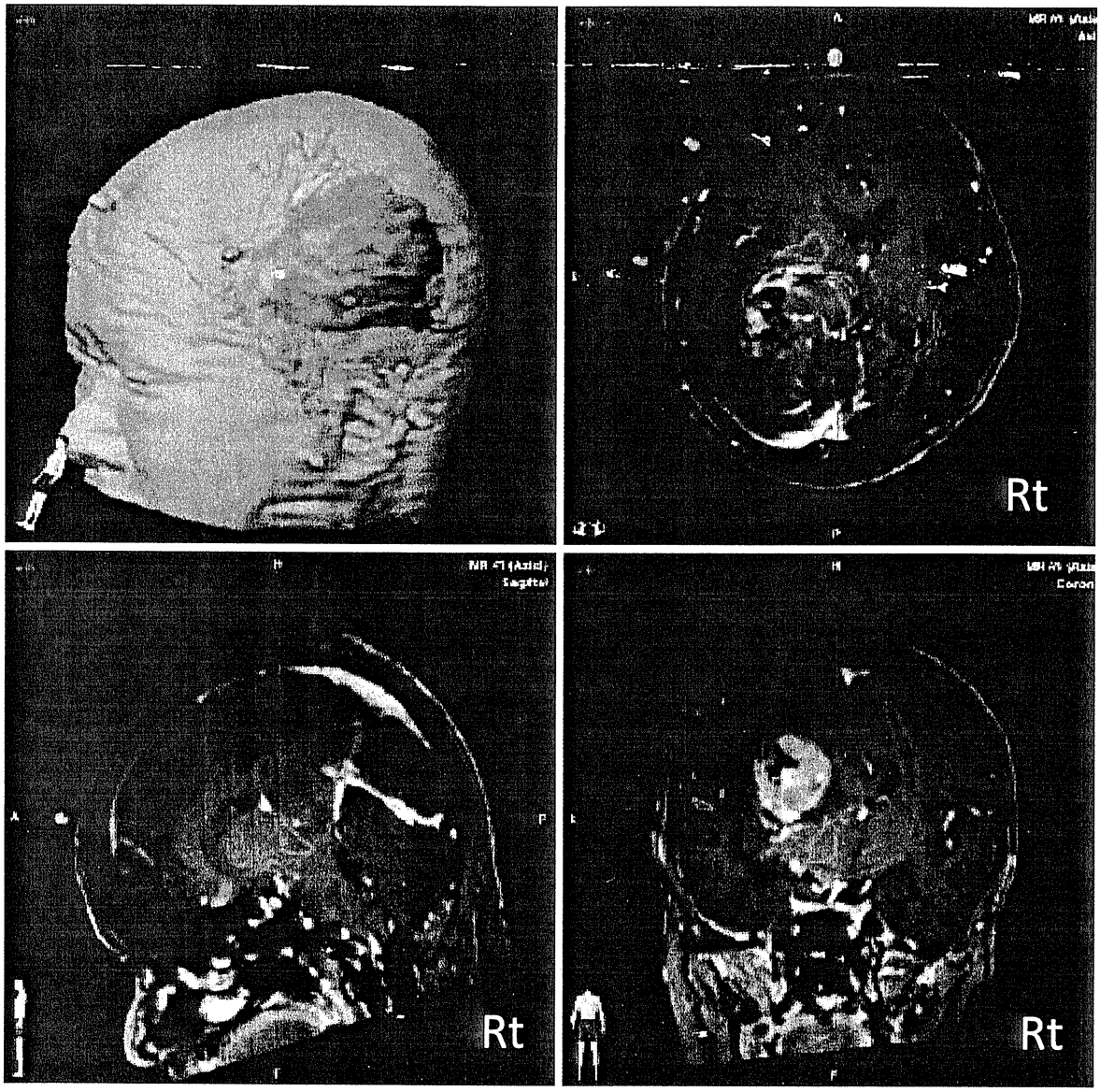

Fig. 3 T1-weighted images are displayed in axial, coronal and sagittal planes, as well as a 3-D rendering, depicting the three objects: tumor (*red*), fMRI (*yellow*), and pyramidal tract (*green*).

手術室システム

当院に導入された術中MRIシステムは，いわゆるtwin-erating theaterといわれる形で，手術室とMRI検査室が2の部屋に分かれている(**Fig. 1**)．このシステムの利点は，存の手術器具をそのまま使用し従来とほぼ同じ環境で手操作が可能，また手術患者の撮影を行っていないときに他の患者の検査が施行できるという経済的なメリットがる．しかしながら，MRIおよび手術室が一体となったシテムに比べ患者の移動距離が長くなるという不利な点もる．幸い当院では，麻酔科，その他co-medicalの理解と協によりこれまで問題なく安全かつ迅速な患者移動および査が行えている．MRIは1.5T(GE)の高磁場MRIが導入れ，高磁場MRIによる精細な画像とMRA，MRS，tracto-ıphyなどの撮影が可能である．Neuronavigation (Brain Lab)は，院内の画像サーバーと術中MRIの両方から画像を取り込むことができ，術中画像は数分でナビゲーションシステムに転送され，再レジストレーションなく患者がMRI終了し手術再開までにup-dateが完了する．2009年4月より，術前に3.0T MRIで撮影したデータを用いて，術中fMRI，tractographyを合成する機能も追加となった．頭部固定は，カーボンファイバー製のメイフィールド3点固定装置でCT，angiography，MRIに対応している．ピンはサファイヤ製でMRIでもアーチファクトがほとんど生じない(**Fig. 2**)．術中蛍光診断システムとしては，KARL-STORZのFL400, FL800が，顕微鏡に搭載され，5-アミノレブリン酸による腫瘍蛍光診断と，ICGを用いた蛍光血管撮影が可能である．5-ALAの蛍光診断には，蛍光診断装置（M&M VLD-1)を用いてスペクトル解析も行い，肉眼では認識困難

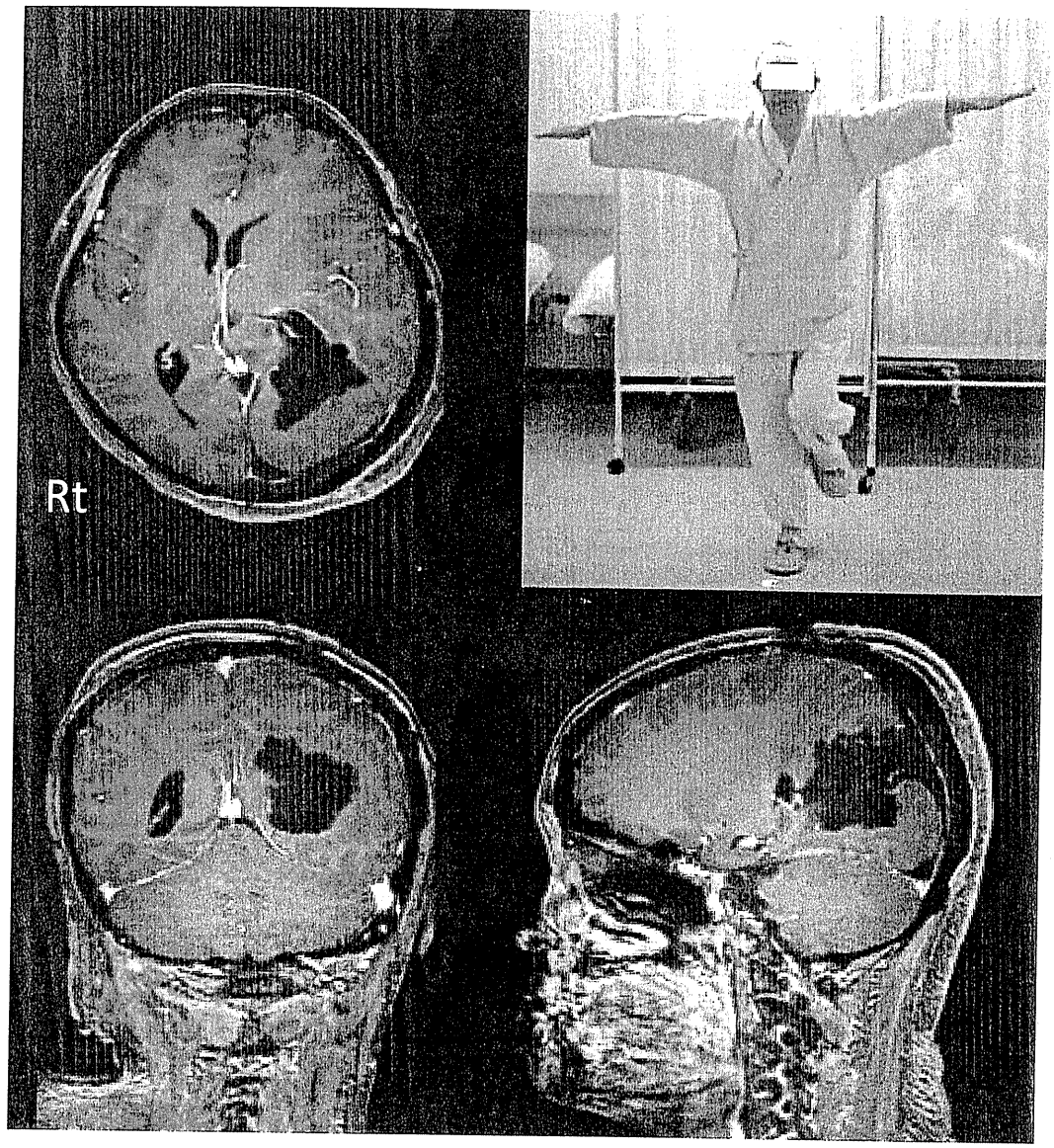

Fig. 4 Post-operative images show gross total removal of the tumor. Rt. motor weakness was improved after the operation.

な淡い蛍光を検出し腫瘍摘出度を向上させ局所再発率の低下を期待している.

対象と方法

2008年7月から2009年2月までに，32例の脳神経外科手術を施行した．内訳は，神経膠腫 14例，転移性脳腫瘍 3例，下垂体腺腫 7例，髄膜腫 3例，未破裂脳動脈瘤 3例，側頭葉てんかん（選択的海馬摘出術）2例，AVM 1例である．術中MRIシステムの最も良い適応は脳実質内腫瘍であるが，当科では腫瘍性病変以外の手術にも積極的に本システムを活用している．MRI検査は，DWI，T1, T2, FLAIR，造影3方向と脳動脈瘤・AVMではMRAも追加し，摘出率，虚血・出血病変などの有無の評価を行った．

症例呈示

症例1：54歳女性．Lt. parietal glioblastoma

右半身脱力と視野障害を主訴に来院した．MRIにてLt. parieto-occipitalに径5cmの腫瘍を認めた．Tractographyでは，錐体路は腫瘍により前方に圧排されていた.(**Fig. 3**) 開頭脳腫瘍摘出術を施行した．ナビゲーションにfMRIおよびtractographyデータを重ね，更にMEPによる運動モニタリングを併用し，腫瘍を全摘出した．術中MEPモニタリングで変化なく，MRIにて造影域の全摘出を確認して手術を終了した．術後，右片麻痺は消失した（**Fig. 4**）.

結　果

神経膠腫および転移性脳腫瘍17例の手術摘出率を示す.

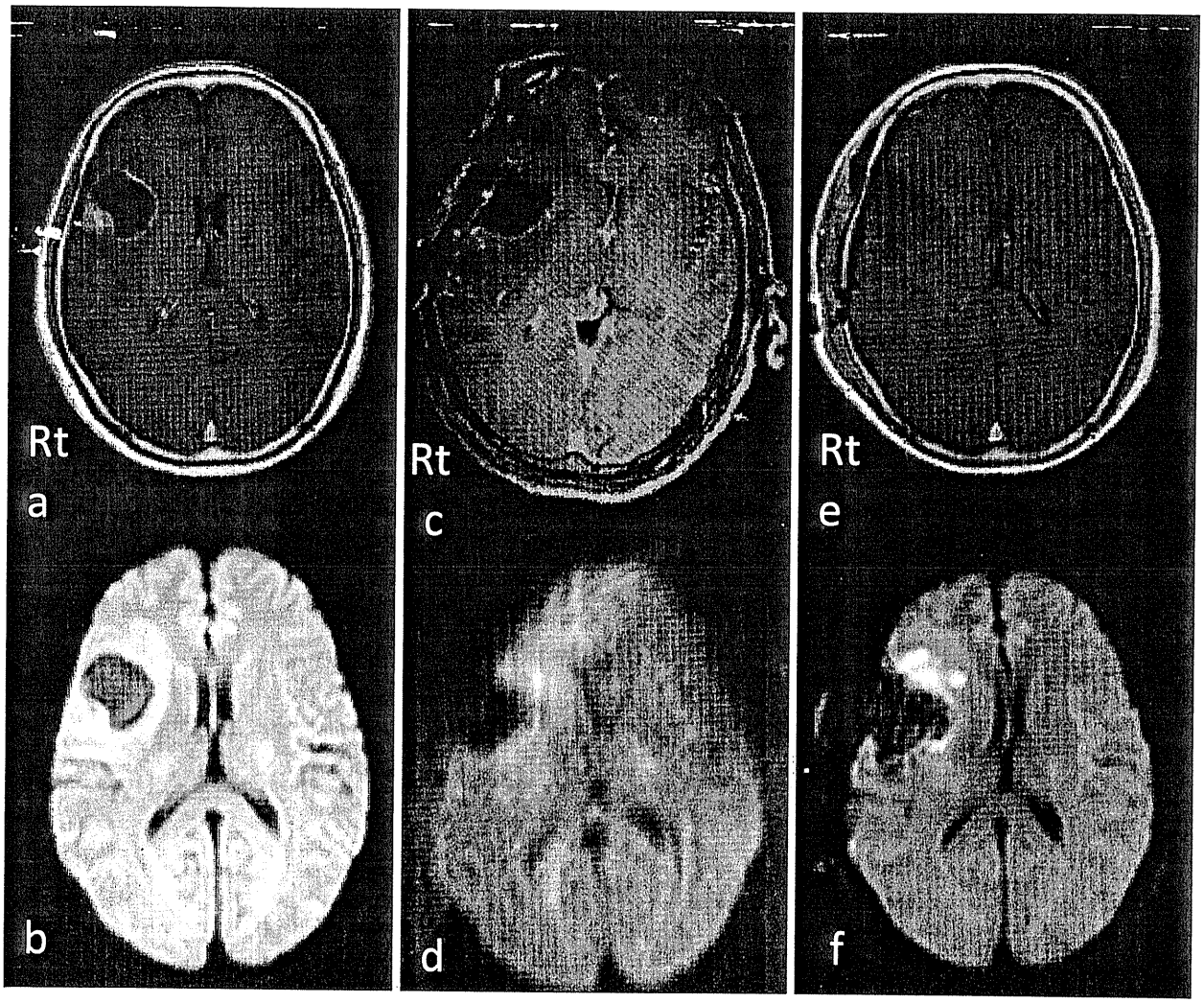

Fig. 5 Post-operative DW image revealed high signal area adjacent to the resection cavity (**e, f**). Intraoperative MR images do not show the abnormal intensity area (**c, d**). Preoperative MR images (**a, b**).

術中MRIにてGross total resection（GTR）は13例（76.5%）で得られた．術中MRI後に追加切除を加えた例は2例であった．脳梁を介して対側まで病変が及んでいた左前頭葉GBMと再発小脳GBMであり，摘出率の向上は得られたが，GTRまでは及ばなかった．術者がGTRと判断したにもかかわらず残存病変を認めた例はなかった．術中MRIの拡散強調画像にて，虚血病変を認めた症例はなかったが，術後MRIで腫瘍切断端にDWI高信号を認めた例が数例みられたことから，術中では手術操作から撮影までの時間が短く検出が困難であったと考えられた(**Fig. 5**)．出血に関しては，術翌日のCTにて摘出腔内に少量の出血を認めた鞍上部Gliomaにおいて，術中DWIにて同部位が高信号を呈していたことから，出血から撮像までの時間経過が影響するが，DWIにて術中の出血を検出できる可能性が示唆された(**Fig. 6**)．感染などの術中MRIに関連する合併症はこれまで認めていない．

考　察

術中MRIは，1993年ボストンのBrigham and Women's hospitalに世界に初めて導入され，その後世界各地で種々のシステムが開発され徐々に普及してきている[1)2)3)5)6)7)8)12)13)]．世界初のシステムは，0.3Tの低磁場MRIでコイルを縦に配置したDouble doughnut型といわれるもので，手術はコイルの間で行われ専用の手術器具を要するシステムである．日本でも同一システムが2000年に滋賀医科大学に日本初の術中MRIシステムとして導入された．同年，東京女子医科大学に導入されたシステムは，同じく低磁場MRIであるが，コイルを水平に配置し，手術を5ガウスラインより外側で行うことにより既存の手術機器がそのまま使用できるシステムである．また東京女子医科大学では，術中MRIだけではなく，ナビゲーションシステムおよび手術室情報管理システムを構築し，インテリジェント手術室という新たな概念を提唱した[15)16)]．2008年7月に稼働開始した当院

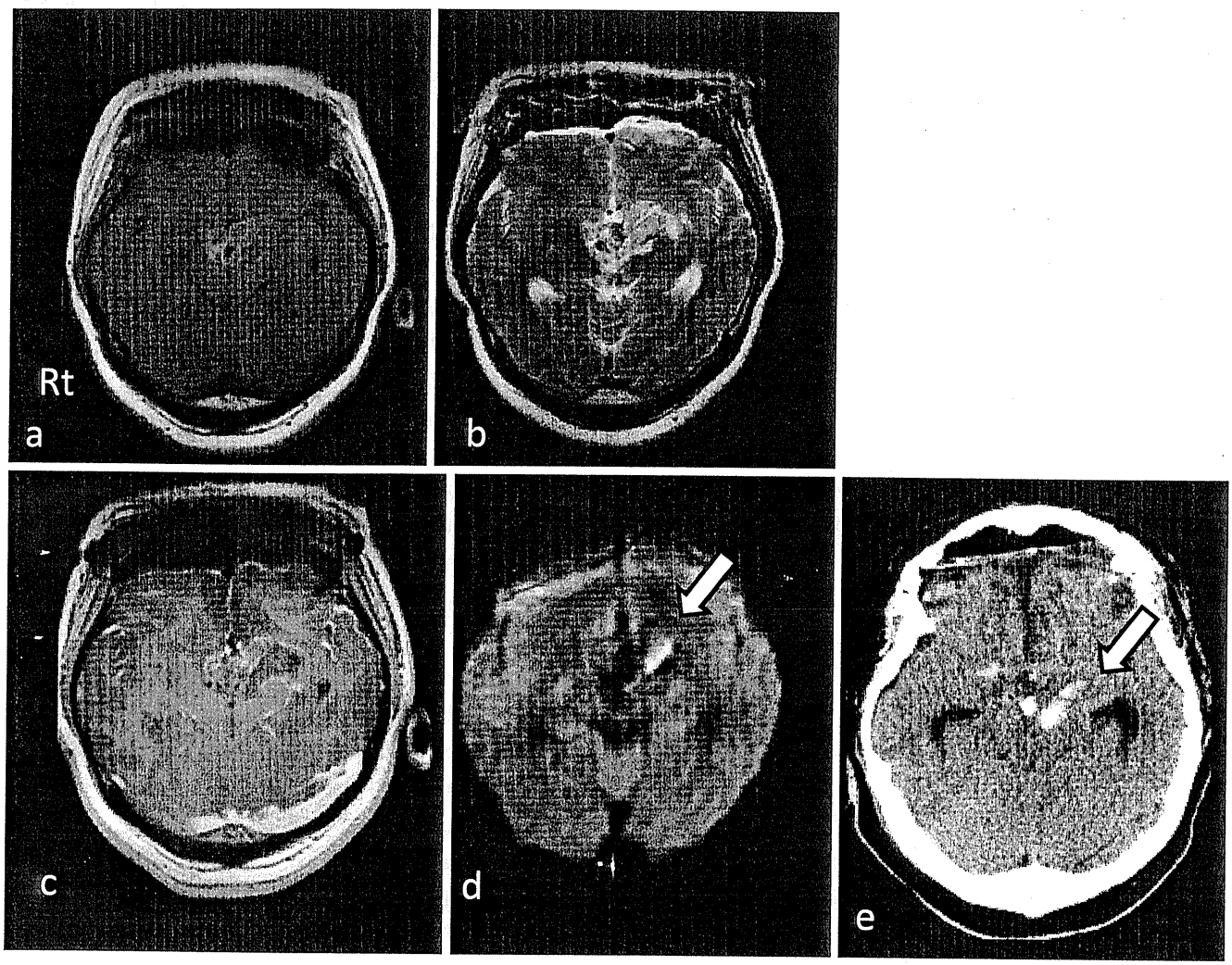

Fig. 6　Intraoperative MR images (**a**: T1-weighted, **b**: T2-weighted, **c**: T1 with Gadolinium, **d**: DWI). Intraoperative DW image shows intra-tumoral hemorrhage (**d**: *open arrow*). Post-operative CT shows the intra-tumoral hemorrhage (**e**: *open arrow*).

の新術中 MRI システムは国内 8 番目のものであり，高磁場 MRI システムとしては，2006 年の名古屋セントラル病院，東海大学についで日本で 3 番目となるものである[11)12)]．

術中 MRI システムが脳神経外科手術にもたらす利点としては，brain shift を up-date し手術中の navigation の精度を上げ安全に腫瘍摘出率を向上させうるということ，また術野内・外の術中の予想外のイベントを察知できることがあげられる[14)17)18)20)]．MRI による摘出率の判定を行うことにより，浸潤性に発育する glioma においても，手術摘出率が予後因子の 1 つであることが広く認められるようになり，術中 MRI システムを用いた摘出率向上は患者の予後向上に寄与するものと期待される[10)21)]．実際に 2005 年 Claus らは，術中 MRI を用いて腫瘍摘出を行った場合に glioma 患者の予後改善がみられたことを報告している[4)]．

術中 MRI は，すべての脳腫瘍手術に用いることが理想であるが，術中 MRI の必要度・貢献度は当然症例毎に異なる．また MRI のボアサイズ（患者撮影部位直径）による体位・頭位の制限もあり，現時点では全例に用いることは困難である．MRI のボアサイズ，コイル等の改良，頭部固定具，手術台の改良が必要である．

これまで悪性神経膠腫の摘出率の判定には，術後 48 時間以内の造影 T1 強調画像が用いられ，この判定に基づいた摘出率と予後との関係が検討されてきた．術中 MRI の自験例では，術中の trauma によっても造影剤漏出がみられることがあり，術中 MRI による残存腫瘍の判定に際して注意を要するものと考えている[9)]．特に，腫瘍が正常脳に覆われて，正常脳が庇になっている部位は顕微鏡の死角となりやすく腫瘍残存しやすい．また庇となっている正常脳を脳ベラなどで移動することにより trauma が生じやすくこの部位から造影剤が漏出する可能性がある．腫瘍切除端の造影域が残存腫瘍であるのか，挫滅された脳なのか判断に注意を要する．術中画像のみにとらわれることなく，術前画像で in-

ternal controlとなる脳溝・動静脈などと腫瘍境界との関係をしっかり把握することが，術中MRI・ナビゲーションシステムを用いた手術でも重要である．

極めて浸潤能の高い悪性神経膠腫に対して，病理組織学的な全摘出を完遂することは難しい．しかし，治療後の再発のほとんどが局所再発であることから[19]，MRI造影病変の辺縁に存在する腫瘍細胞が高密度に浸潤していると考えられる部位をより多く摘出することが重要であると考えられる．MRI造影病変は色調や硬さなどによりある程度鑑別できるが，造影域辺縁の浸潤部位の最大限の摘出を目指す場合，術中MRIおよび術中蛍光診断の貢献度は大きいと考える．術中MRIシステムによる摘出率，治療成績の変化について検討するとともに，放射線・化学療法をはじめとする後療法の改良・開拓も今後の重要な課題である．

結　語

2008年7月，当科で1.5テスラ術中MRIシステム（1.5T MRI（GE），neuronavigation（Brain LAB），術中蛍光診断・術中血管撮影機能FL400, FL800（KARL-STORZ）搭載手術顕微鏡（Leica），MRI・CT対応operation table（MAQUET））を導入した．本新システムを使用して安全に脳神経外科手術を施行し，悪性脳腫瘍の70%以上でGross total removalがなされた．今後，他の脳神経外科手術への応用と悪性脳腫瘍の予後改善に対する本システムの有用性を検討したいと考えている．

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Comments

著者らは，本論文にて高磁場 MRI 等を備えた統合型手術室を用いた脳腫瘍治療について，その有用性について記載した．手術手技，および手術支援装置の進歩にともなって，浸潤性の高い腫瘍である glioma においても，手術摘出の重要性の指摘がされてきている．より安全にかつ摘出度をあげるために，著者らは統合型手術室において，種々の工夫を行っている．本論文は将来の手術室の方向性を示し，またこのような手術室をあらたに設置しつつある者にとって，参考となる記載に富んだ論文である．

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術中 MRI 等を組み合わせたインテリジェント手術システムについての報告である．摘出度を上げると共に術後の神経症状の悪化を防ぎ，手術成績を向上するために様々な努力がなされて来たが，その最先端が結集されている．術中 MRI は腫瘍の摘出度を知る以外にも合併症の有無についての check もできる点で有用であるが，そのコストと移動や撮影に時間を要することが問題である．High-grade glioma の多くでは蛍光システムで代用出来るが，low-grade glioma などの造影を受けない病変での有用性は現在のところ他に変わるものはないだろう．多くの病院ではこのようにすべてをそろえることは不可能であり，どの機器がどのような手術の時に有用なのかを今後検証して行って欲しい．

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5

中心溝近傍悪性神経膠腫の手術

Surgical resection of paracentral malignant gliomas

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■抄　録

はじめに：機能野およびその近傍に存在する腫瘍の手術は，最新の種々の modality を駆使しても未だ極めて難しい．手術の radicality と術後 morbidity をより正確に予測するため，術前プランニングおよび術中マッピング・モニタリングが極めて重要である．今回，中心溝近傍悪性神経膠腫につき，術前検査（MRI（FA 値），MEG（dipole moment: DM））と術中マッピング・モニタリング結果，術後神経症状との関係につき検討した．**対象**：中心溝近傍悪性神経膠腫 11 例．腫瘍局在は，前頭葉 5 例，前頭葉および頭頂葉 5 例，頭頂葉 1 例．病理診断は，膠芽腫 8 例，退形成乏突起膠腫 1 例，退形成上衣腫 1 例．術前 7 例に運動障害を認めた．術前の内包後脚の FA 値患側/健側比は 0.6-1.01 であり，MEG の DM 患側/健側比は 0.42-1.48 であった．**結果**：術後新たな運動障害出現は認めなかった．4 例で運動障害の改善を認めた．これらの術前 FA 値比は 0.7 以上であった．3 例で術前より見られた麻痺の悪化を認めた．2 例は上肢のみの悪化であり，1 例は上下肢とも悪化を認めた．上下肢ともに悪化を認めた例では，術中 MEP モニタリングで摘出前後の MEP 振幅は 30% まで低下した．術前の MEG DM 比が 1 以上を示していた．**考察**：術前の FA 値比や DM 比は，術後の運動障害の予測に有用である可能性が考えられた．

■ Abstract

BACKGROUND: In neurosurgery it is very important to achieve maximum resection with minimum morbidity. Towards this aim, developments in neuroimaging technology have enabled accurate preoperative evaluation of cerebral function and integrity. This study evaluated the preoperative condition of the pyramidal tract through measurements of fractional anisotropy value (FA) and the MEG dipole moment (DM). Preoperative and postoperative motor function were also evaluated. *METHODS:* This study consisted of 11 patients that presented with paracentral malignant gliomas (glioblastoma, $n=9$; anaplastic oligodendroglioma, $n=1$; anaplastic ependymoma, $n=1$). Preoperative studies at 3.0T included morphology and tractography. The FA value of the posterior limb of the internal capsule was estimated. The DM was estimated at N20m of somatosensory evoked fields elicited by median nerve stimulation. *RESULTS:* The preoperative FA ratio (affected/unaffected side) ranged from 0.6-1.01. The DM ratio (affected/unaffected side) ranged from 0.42

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-1.48. Preoperatively, 7 patients presented with motor weakness. Postoperatively, motor weakness was improved in 4 cases, and FA ratios were greater than 0.7. Motor weakness was aggravated in 3 patients: 2 exhibited only upper limb paresis and the other exhibited worsening hemiparesis and had a DM ratio greater than 1.0. Postoperatively, no new neurological deficits were observed in any of the patients. *CONCLUSION:* The preoperative FA and DM ratios could contribute to preoperative evaluation of the pyramidal tract and predict postoperative motor function.

Key words: Paracentral malignant glioma, MEG, Fractional anisotropy

はじめに

病理組織学的に全摘出が困難と考えられる悪性神経膠腫においても，手術摘出率が生命予後因子であることが認められるようになってきている [3, 6]. しかしながら，機能局在という特徴をもつ中枢神経において，最大限の摘出と脳機能の温存を両立することは極めて難しく大きな dilemma である. 特に機能野およびその近傍に存在する腫瘍の手術は，最新の種々の modality を駆使しても未だ極めて難しいものである. しかしながら，近年の画像診断技術の発展とモニタリング・マッピングの普及により，これまで摘出不能と考えられてきた部位の腫瘍の手術も積極的になされるようになってきている. これにより，中心前回に存在する腫瘍であっても摘出可能な場合が存在することも明らかとなってきた [4, 5]. 手術の radicality と術後 morbidity をより正確に予測してより安全で確実は手術を行うために術前プランニングおよび術中マッピング・モニタリングが極めて重要である. 今回我々は，中心溝近傍悪性神経膠腫において術前 MRI Functional anisotropy (FA) 値と MEG Dipole Moment: DM と術中マッピング・モニタリング結果，さらに術後神経症状との関係につき解析し，術前の FA 値および DM が機能予後予測に有用であるかを検討した.

対象と方法

中心溝近傍悪性神経膠腫 11 例を対象とした (Table 1). 年齢は, 25 ～ 79 歳（平均 55.7 歳）で，男性 9 例，女性 2 例である. 腫瘍局在は，前頭葉 5 例，前頭葉および頭頂葉 5 例，頭頂葉 1 例. 病理診断は，膠芽腫 9 例，退形成乏突起膠腫 1 例，退形成上衣腫 1 である. 術前 7 例に運動障害を認めた. 術前 MRI 検査には 3T MRI を用い，FA 値は内包後脚に ROI を設け患側/健側比を算出した (Fig. 1). MEG の正中神経刺激による Sensory evoked field（SEF）の DM の患側/健側比を算出した. 手術では，全例に MEP モニタリングを施行した. 優位半球の前頭葉に腫瘍が存在する 3 例

Table 1 Summary of cases with paracentral gliomas.

Case	age/sex	Location	Pathology	術前 FA 値比 (内包後脚)	MEG dipole moment 比	preop. Motor weakness	postop. Motor function
1	35/M	F	AO	1.003	0.616	none	no change
2	25/M	F	AE	1.023	0.477	upper 4	improve
3	66/M	F	GBM	0.797	0.523	upper 4	upper 3
4	49/M	F	GBM	0.604	1.482	upper 4/lower 4	upper 3/lower 3
5	64/M	F	GBM	0.921	0.88	upper 4/lower 4	upper 3/lower 4
6	75/F	F-P	GBM	1.014	0.913	upper 4/lower 4	improve
7	70/F	P-F	GBM w O	0.775	n.d	upper 3/lower 4	no change
8	57/M	P-F	GBM	0.904	0.425	none	no change
9	33/M	P-F	GBM	0.802	0.985	upper 4	improve
10	60/M	P-F	GBM	0.777	n.d	upper 3/lower 4	improve
11	79/M	P	GBM	0.915	0.624	none	no change

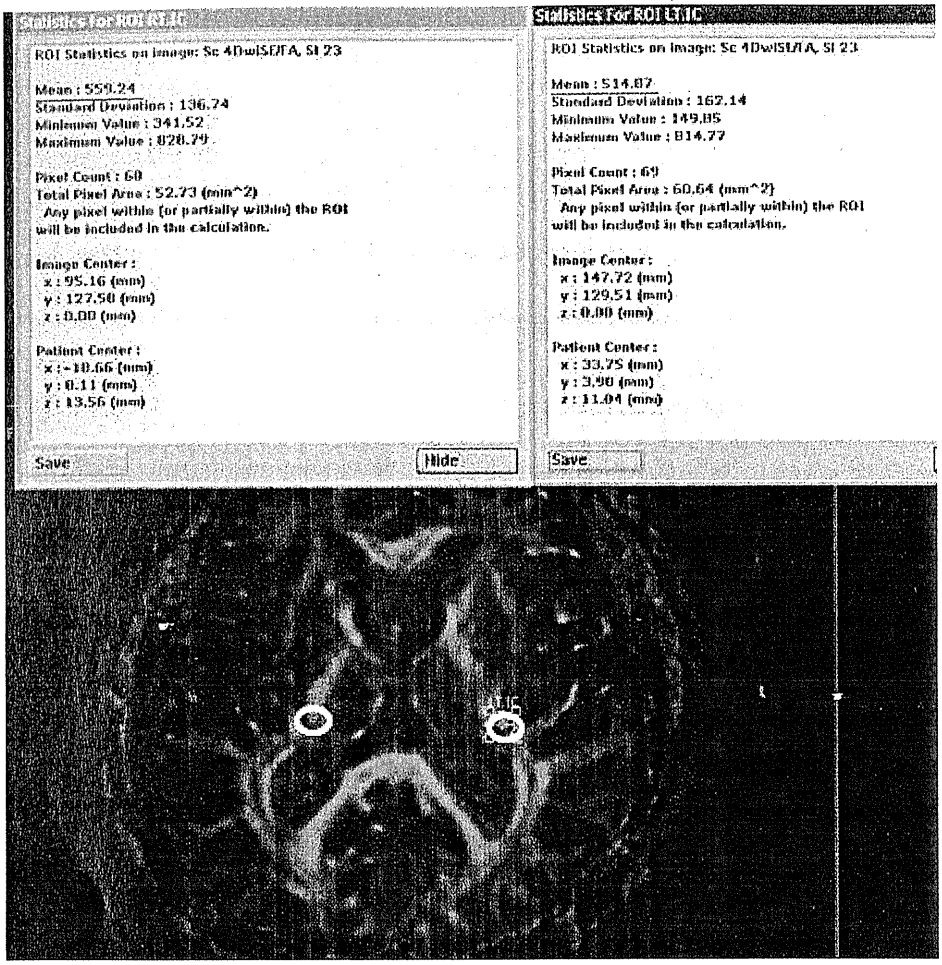

Fig. 1 MR workstation screen showing FA value of the selected ROI (circle).

Table 2 Treatment results of our 11 cases.

Case	age/sex	Pathology	PFS (M)	OS (M)
1	35/M	AO	23+	23+
2	25/M	AE	32+	32+
3	66/M	GBM	21+	21+
4	49/M	GBM	3	14
5	64/M	GBM	5	10+
6	75/F	GBM	4+	4+
7	70/F	GBM w O	12	23+
8	57/M	GBM	3	15
9	33/M	GBM	17+	17+
10	60/M	GBM	5	10
11	79/M	GBM	18	21+

+: 生存打ち切り

に覚醒下手術を施行した．Neuronavigation，5-アミノレブリン酸蛍光診断を併用して腫瘍摘出を行った．

結　果

11例でgross total resectionが可能であった．4例で運動障害の改善を認めた．2例で術前より見

Table 3 Results of MEP monitoring and functional outcome.

Case	age/sex	Location	Pathology	術前 FA 値	D-response ΔMEP (%)	preop. Motor weakness	postop. Motor function
3	66/M	F	GBM	0.797	50	upper 4/lower 5	upper 3/lower 5
4	49/M	F	GBM	0.604	30	upper 4/lower 4	upper 3/lower 3
5	64/M	F	GBM	0.921	37.5	upper 4/lower 4	upper 3/lower 4

られた麻痺の悪化を認めた．1 例は上肢のみの悪化であり，1 例は上下肢とも悪化を認めた．再発は，6 例に認められた．5 例は局所再発，1 例は播種であった．median OS は未到達である（Table 2）．

1）FA 値比，MEG DM と術後運動機能（Table 1）

腫瘍が中心前回に存在する 3 例で麻痺の悪化が認められ，これらの術前 FA 値比は 1.0 以下であった．中心後回に腫瘍が存在する例では，FA 値が 0.8 よりも低下していても麻痺の改善が見られた．上下肢ともに麻痺の悪化を認めた症例のみが術前の MEG DM 比が 1 以上を示しており，FA 値比も最も低値であった．頭頂葉に存在する腫瘍において，術前麻痺を呈する症例では SEF の同定ができず DM が計測できなかった．

2）MEP モニタリングと術後運動機能（Table 3）

摘出前後の硬膜外電極 MEP の振幅の変化を ΔMEP とすると，麻痺が生じた症例では，50% 以下に振幅が低下していた．上肢のみの悪化を認めた例では 50% まで低下，上下肢ともに悪化を認めた例では，30% まで低下していた（Table 3）．

考　察

中心溝近傍悪性神経膠腫 11 例において，術前の FA 値比，MEG DM 比，MEP モニタリングと術後の運動障害の関係について検討した．前頭葉腫瘍では術前より FA 値が低下している場合，術後運動機能の悪化を認めた．頭頂葉病変では術前 FA 値が低下していても麻痺の悪化はみられなかった．FA 値による錐体路障害の評価は，これまでも脳梗塞や脳腫瘍で試みられてきた．2005 年，Beppu らは，three-dimensional anisotropy (3-DAC) にて神経膠芽腫症例の錐体路の障害につき検討し，3-DAC が錐体路への腫瘍浸潤予測に有用であることを報告している [1]．今回の検討では，腫瘍の主座により同程度 FA 値の低下を認めても頭頂葉腫瘍よりも前頭葉腫瘍で麻痺の悪化が生じやすかった．これは解剖学的位置関係からも妥当であると考えられ，FA 値のみでは機能予後予測が困難であることを示している．Beppu らの検討においても術前の FA 値の低下の程度と術後運動機能障害の関連には統計学的な有意差が認められなかった．DTI, tractography は，錐体路と腫瘍の位置関係を把握し安全な手術を行うために有用である．しかし，FA 値の欠点として ROI の取り方により値が変化することがある．この問題は tractography についても同様であり，ROI の設定により描出される線維が大きく変化する，すなわち客観性，普遍性に乏しいという欠点がある．このため，ROI の設定と結果の解釈に注意を要し，今後より普遍的な定量方法の開拓が望まれる．

FA 値が白質の情報であるのに対して，MEG DM は皮質の状態を反映しているという相違がある．今回これらを組み合わせることで，腫瘍が脳に及ぼす影響を多面的に評価できる可能性があるのではないかと考え，FA 値に加え MEG DM 比についても検討した．MEG DM に関する報告としては，2002 年 Tsutada らが parkinson 病をはじめとする種々の病態において MEG　DM が大脳皮質活動の左右差を鋭敏に検出できる可能性を示している [7]．MEG においては，検査方法の原理より信号源と detector の距離や角度など物理的な変化により検査値が変化する．このため大きな腫瘍により中心溝に変移，ねじれなどを生じると皮質活動が変化したような結果を出してしまう可能性がある．また，中心後回に腫瘍が存在している場合には，case 7, 10 のように SEF が推定できない場合も生じる．2007 年 Willemse らは，中心溝周囲の病変により後脛骨神経から推定される SEF にどのような変化が現れるのか，latency, equivalent current dipole strength, root mean square, spatial distribution について 17 例の検討を行った [8]．その結果，患側で dipole strength が大きくなること，

また運動障害を有する例で，障害の無い例よりも大きくなることを報告している．我々の例でもCase 4でDMが患側で大きかった．患側の信号が大きくなるメカニズムとして，Willemseらは前頭葉から頭頂葉への抑制の解除の可能性について考察している．Case 4ではFA値も11例中最低値であり，腫瘍により周囲脳に破壊的な変化が生じてこれがFA値，DMに反映していた可能性も考えられるが，更なる症例の積み重ねが必要と考えている．

術中MEPの変化については，自験例の解析から硬膜外電極を用いたD-responseの振幅の変化を指標としている[2]．また摘出前後の振幅変化（ΔMEP）が50%低下までであれば独歩可能であるとの結果から，摘出の続行・中断は50%を指標に行ってきた．今回術後運動障害を生じた3例でも，振幅低下が50%の症例では上肢のみの運動障害悪化，30%まで低下を来した例では上下肢ともに悪化を生じた．ΔMEP 50%例では術後速やかに独歩可能であり，2例は，杖，装具などの使用により歩行が可能なレベルまで回復した．今回の結果からも術中MEPモニタリングで振幅50%の低下を一つの目安として摘出続行もしくは中止を検討するのが適当であると考えられた．術中モニタリングで術後の機能予後予測をしながら摘出範囲を決められることは，近年の脳神経外科手術の進歩の中でも最も大きなものの一つであると考える．

まとめ

より安全で確実な脳腫瘍手術のため，術前検査による手術プランニング，術中モニタリングは必須のものである．術前のFA値，MEG DMは中心溝近傍悪性神経膠腫の術後機能予後予測の一助となる可能性があると考えられた．

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