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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.

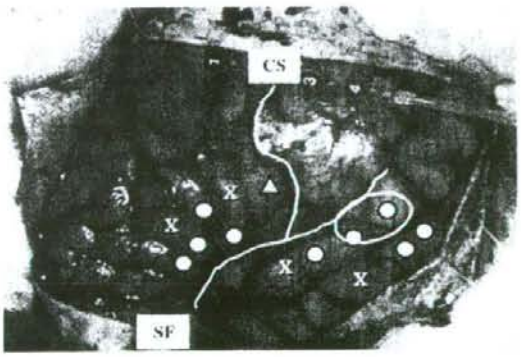

Fig. 1. *Case 1* – A 49-year-old woman with primary CNS malignant lymphoma. Intra-operative photograph of the brain map showing that the tumor is located under the Wernicke's area. ○ Speech arrest, △ dysarthria, × no response, *CS* central sulcus, *SF* Sylvian fissure

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

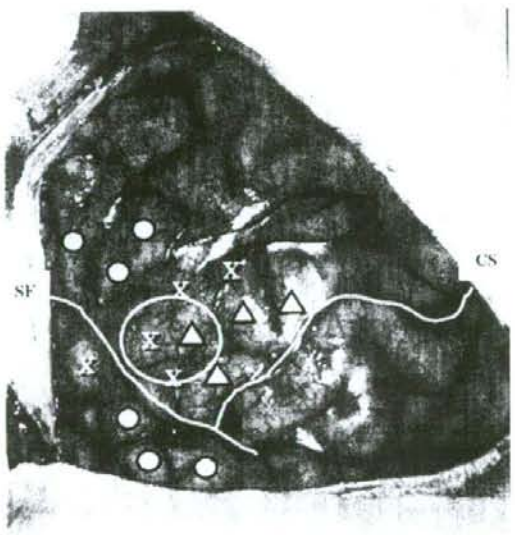

Fig. 2. *Case 2* – A 31-year-old woman with low-grade astrocytoma. Intra-operative photograph of the brain map showing that the tumor is located within the tongue motor area. ○ Speech arrest, △ dysarthria, × no response, *CS* central sulcus, *SF* Sylvian fissure

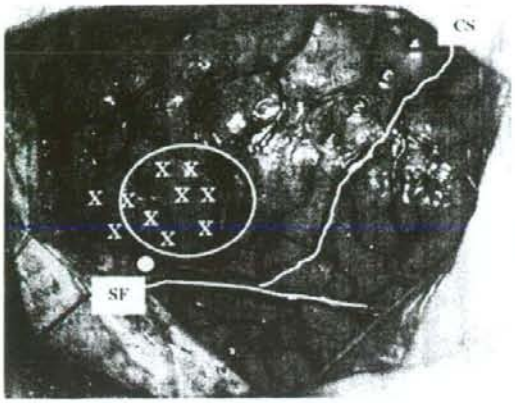

Fig. 3. *Case 3* – A 52-year-old man with frontal glioblastoma multiforme. Intra-operative photograph of the brain map showing that the Broca's area is located on the inside of the Sylvian fissure. ○ Speech arrest, △ dysarthria, × no response, *CS* central sulcus, *SF* Sylvian fissure

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.

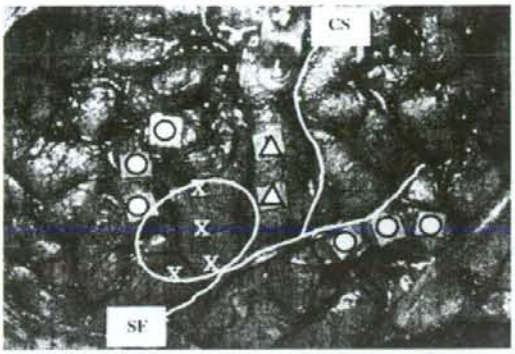

Fig. 4. *Case 4* – A 55-year-old man with oligodendroglioma. Intra-operative photograph of the brain map showing that the tumor is located under the Broca area. ○ Speech arrest, △ dysarthria, × no response, *CS* central sulcus, *SF* Sylvian fissure

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.

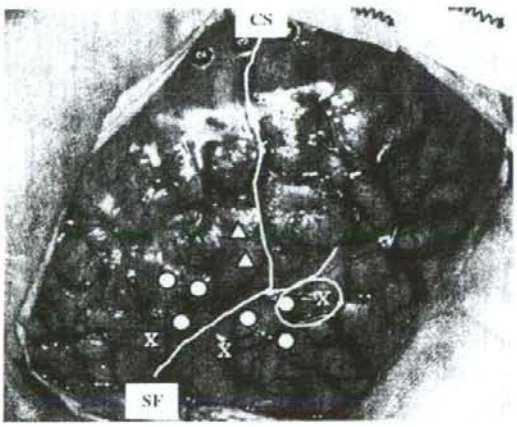

Fig. 5. *Case 5* – A 44-year-old woman with cavernous angioma. Intra-operative photograph of the brain map showing that the tumor is located under the Wernicke area. ○ Speech arrest, △ dysarthria, × no response, *CS* central sulcus, *SF* Sylvian fissure

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

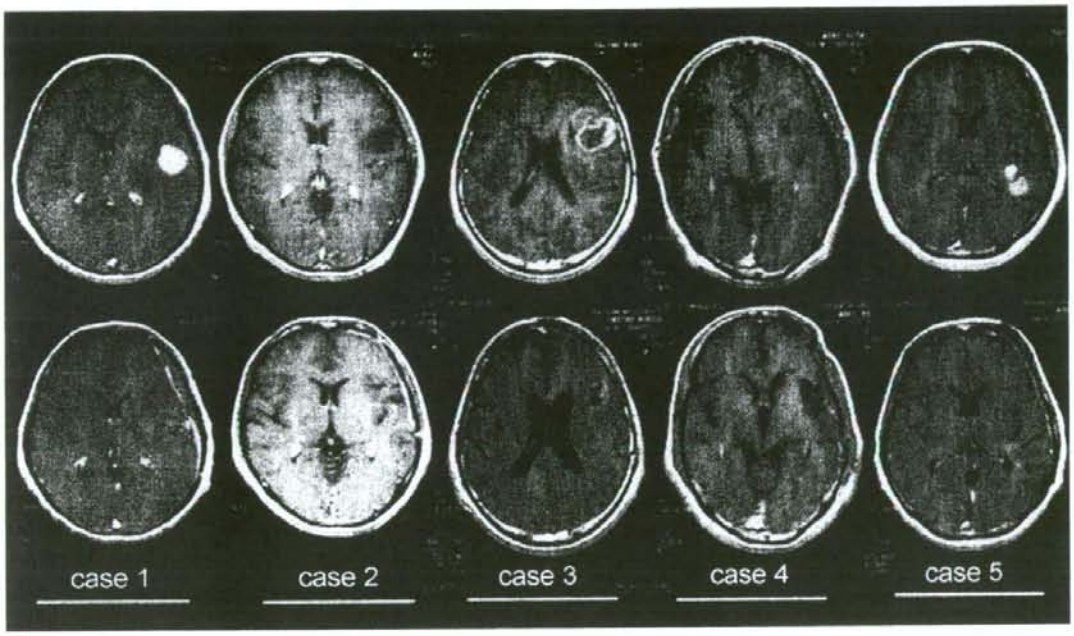

Fig. 6. Pre (*upper line*) – and post (*lower line*)-operative Gd-enhanced, T1-weighted magnetic resonance images obtained on the 5 patients. All tumors were removed almost totally

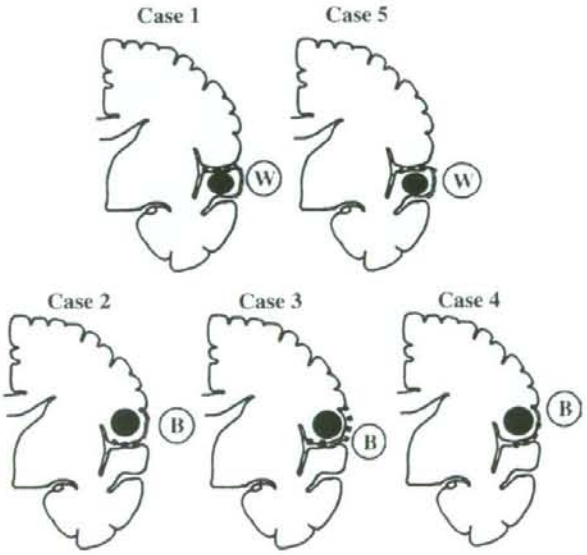

Fig. 7. Schematic drawing of the brain map of the 5 patients. *B* Broca's area, *W* Wernicke's area. The filled circles indicates the tumor. The dotted and gray lines encircle the functional- and non-functional areas, respectively

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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肺癌脳転移に対するゲフィチニブの効果

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Ⅰ．はじめに

ゲフィチニブ（イレッサ®）は，上皮成長因子受容体（EGFR）のチロシンキナーゼ（TK）を標的とする分子標的治療薬である．ゲフィチニブは，日本も参加したプラチナ製剤を含む前化学療法無効ないし再発進行非小細胞肺癌に対する第2相の国際共同試験（IDEAL1，2）で9～18％ほどの奏効率が報告され，特に日本人では27.5％の奏効率が認められたことを受け[9-18]，2002年7月に厚生労働省より手術不能または再発非小細胞肺癌に対してわが国において世界で初めて承認された．使用開始後，当初予想していなかった有害事象として致死的な急性肺傷害を起こす症例があり，薬害の話題として社会的問題となったが，他の抗癌剤で無効でも劇的な効果を示しその恩恵を受ける患者も多く，現在も肺癌治療において重要な薬物の一つとして使用されている．

転移性脳腫瘍は脳神経外科医が最も多く遭遇する脳腫瘍であり，原発巣としては肺癌が約半数を占める．現在の転移性脳腫瘍に対する治療としては，手術摘出あるいは放射線による治療の効果が広く認められ標準となっている．他方，抗癌剤治療についてはblood-brain-barrier（BBB）によって薬剤が浸透しにくいこともあり，効果は限られているのが現状である[32]．その中で，ゲフィチニブの登場以後，脳転移に対しての著効例が報告されるようになった．今回は，ゲフィチニブの特徴と現在までに得られている知見について触れた後，脳転移例に対する有効性について文献レビューを中心にまとめ，また脳神経外科領域に関連する話題としてグリオーマに対する治療の可能性についても，EGFRとの関係を中心に分子生物学的視点を含め概説する．

Ⅱ．EGFRおよびゲフィチニブの作用機序

EGFRは体内のさまざまな細胞で分化，増殖等において重要な働きをしているが，種々の悪性腫瘍細胞でも発現がみられ，腫瘍細胞における悪性化へ強く関与し，その過剰発現は予後不良因子である[33]．EGFRの構造は，細胞外領域，細胞膜貫

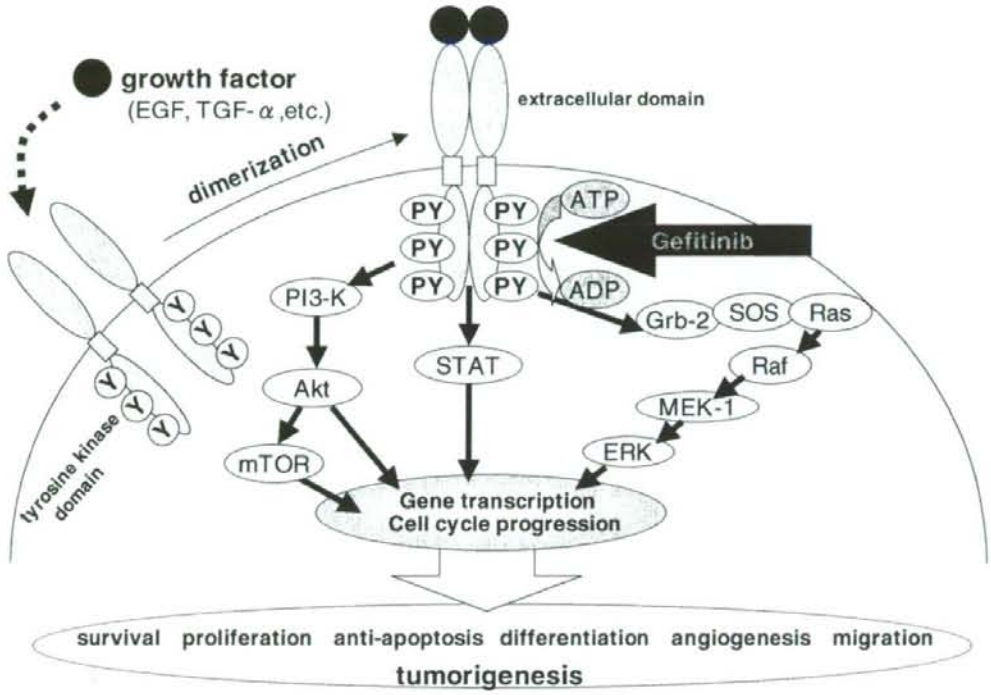

図1　EGFR活性化によるシグナル伝達とゲフィチニブ作用部位

リガンドであるEGF，TGFα等がEGFR細胞外領域に結合すると，EGFRや同じファミリーに属するerbB2/HER2，erbB3/HER3，erbB4/HER4とホモあるいはヘテロダイマーを形成し，細胞内領域のTKはお互いのチロシン残基をリン酸化して活性化される．腫瘍細胞では，EGFRがリガンド非依存性に恒常的に活性化され，RAS-MAPK経路，PI3K-Akt経路，STAT経路などに伝えられ，腫瘍細胞の増殖，アポトーシスの回避，血管新生，転移などに寄与し，悪性化に関与する．ゲフィチニブはEGFRの細胞内領域のTKにおけるATP結合を競合的に阻害することで抗腫瘍効果を発揮する．

通領域，およびTK部位を有する細胞内領域からなる．細胞外領域のリドカイン結合部位にEGFやTGFαなどのリガンドが結合すると，EGFR細胞内領域のTK部位にATPが結合し自己リン酸化して活性化され，RAS-MAPK経路，PI3K-AKT経路，STAT経路などにシグナルが伝わり，腫瘍細胞における増殖，浸潤・転移形成への関与，血管新生にかかわる分子発現やアポトーシス抑制に密接に働くと考えられている[1]．

ゲフィチニブはEGFR-TKの自己リン酸化部位へのATP結合を競合的に阻害し，以下へのシグナル伝達を阻害することで抗腫瘍効果を発揮する（**図1**）．EGFRのTK阻害薬という薬効のみで，非小細胞肺癌に対して大きな臨床効果が得られる可能性が示され，当初世界中で注目され大きな期待が寄せられた薬剤である．

Ⅲ．ゲフィチニブ使用の動向

IDEALにより肺癌で一定の効果が認められたものの，その後，プラチナ製剤を含む化学療法へのゲフィチニブの上乗せ効果があるかを検討した第3相試験で有意差が得られなかったこと[11, 12]，また既治療進行非小細胞癌に対してのプラセボと比較した試験（ISEL，日本人は含まれていない）で有意な生存期間の延長が得られなかったことを受け[35]，米国食品医薬品局（FDA）は2003年5月に標準的化学療法不応の進行非小細胞肺癌に対しての単独使用を一旦は承認していたが，2005年6月からは新規使用を原則禁止している．

製造販売元であるアストラゼネカ社は欧州医薬審査局（EMEA）への承認申請を取り下げた．しかし，ISELにおけるサブセット解析で東洋人での生存期間延長を認め，さらに後述するゲフィチニブ感受性EGFR遺伝子変異が東洋人に多いことが報告されるに至り，現在も日本を含むアジア諸国を中心に承認，使用されている．

日本でのゲフィチニブ使用開始後に社会問題となった急性肺障害，間質性肺炎発症については，発症率は5.8％でその死亡率は2.3％とされ，喫煙歴を有するもの，PS＞2，間質性肺炎合併症例，男性等が危険因子とされる．現在，ゲフィチニブの使用については安全に使用するためのガイドラインが日本肺癌学会から公表されている[37]．

Ⅳ．ゲフィチニブ感受性とEGFR変異との相関

ゲフィチニブの抗腫瘍効果については，当初EGFR発現量との相関が予想されたが，臨床試験における後ろ向き解析において否定された[4]．それらで明らかになったのは，非喫煙者，腺癌，女性，日本人といった患者群に奏効例が多いという臨床的特徴であった[9, 18]．

その後2004年春，米国でEGFRの遺伝子変異がゲフィチニブの感受性と強い相関があることを示唆する報告がなされ，大いに注目された[20, 26]．その遺伝子変異は，EGFRのTK領域をコードしているexon18～24のうち，最初の4つのexonの遺伝子領域に起こり，特にexon19の欠失変異とexon21の点突然変異の頻度が高いことが示されている．

さらにこのEGFR遺伝子変異が非喫煙者，腺癌，女性，東洋人において高い頻度で認められ[17, 20, 26, 27]，先に見出されたゲフィチニブ奏効予測因子と相関し，それを支持するものであった．その遺伝子変異がゲフィチニブ感受性を強める機序としては，遺伝子変異をもったEGFRが，そのTKのATP結合部位に構造変化が生じる結果，EGFRが恒常的に活性化して悪性度が高まる一方，ゲフィチニブとの親和性が高まり，効腫瘍効果が高まると考えられている（**図2**）[10]．

この極めて重要な発見がなされた後，日本においてEGFR変異を有する未治療進行非小細胞肺癌に対する第2相臨床試験が行われ，約75％で腫瘍縮小効果が認められ[2, 14]，また肺癌術後再発の患者におけるゲフィチニブ治療患者の後ろ向き調査では，EGFR遺伝子変異患者群で生存期間の有意な延長が示された[23]．このように，EGFR-TK遺伝子変異は臨床における重要な感受性予測因子

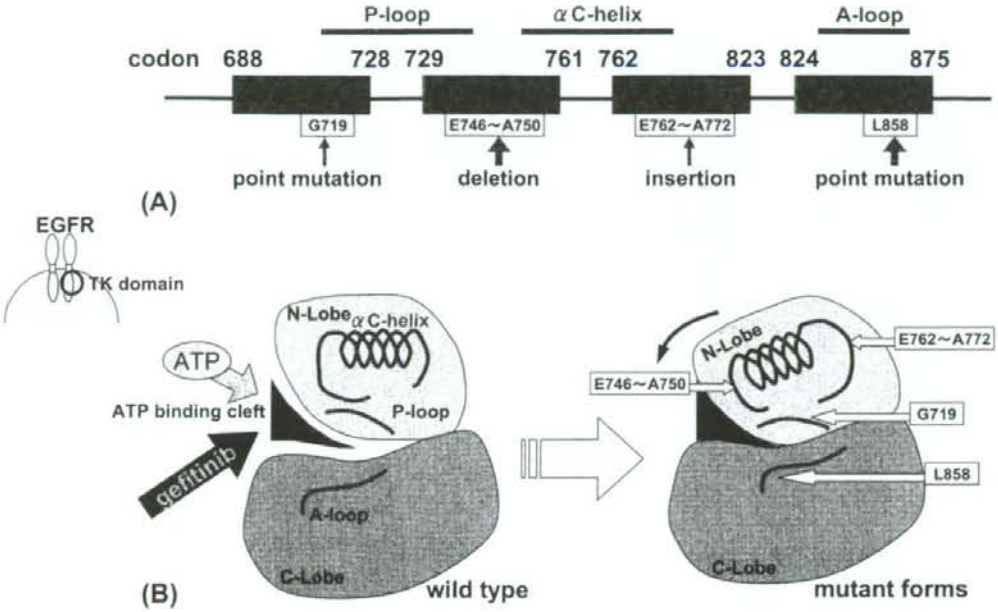

図2　ゲフィチニブ感受性腫瘍細胞におけるEGFR遺伝子変異の部位，およびそれによるTKタンパクの立体構造の変化（[10]を参考に作成）

EGFR-TK部位のタンパク構造は，2つの類球形のN-lobeとC-lobeから成り立っている（Bの左）．EGFR遺伝子変異は，この立体構造におけるN-lobeおよびC-lobeの一部に関係する最初の4つのexon内で起こる（A）．その結果，TKのタンパク立体構造がATP binding cleftを狭くする方向へ変化することで，EGFRが恒常的に活性化され悪性度が高まり，同時にゲフィチニブとの親和性が強くなり，抗腫瘍効果が高まると考えられている（Bの右）．

であることは間違いないと考えられている．ただし，それらが完全には一致せず，遺伝子変異がなくても感受性を示す例やその逆の例もわずかに存在することも付け加えておく．

その後，このEGFR遺伝子にさらに二次的な遺伝子変異が起こるとゲフィチニブに抵抗性をもたらすことが報告された[16, 28]．以上のように，臨床使用開始後，薬剤感受性と遺伝子変異との関係が詳細に研究され，明らかになってきたことはこの薬剤の特徴の一つであり，意義は大きい．

V．ゲフィチニブの肺癌脳転移に対する効果

ゲフィチニブの臨床使用が開始になって以降，脳転移例での腫瘍縮小効果が世界中から報告されている（図3），**表1**は，肺癌脳転移巣に対してのゲフィチニブ治療の効果についてのこれまでに報告されている主な調査である．

東洋からの報告が多いのは，前述のごとく東洋人であることが感受性因子の一つであり，ゲフィ

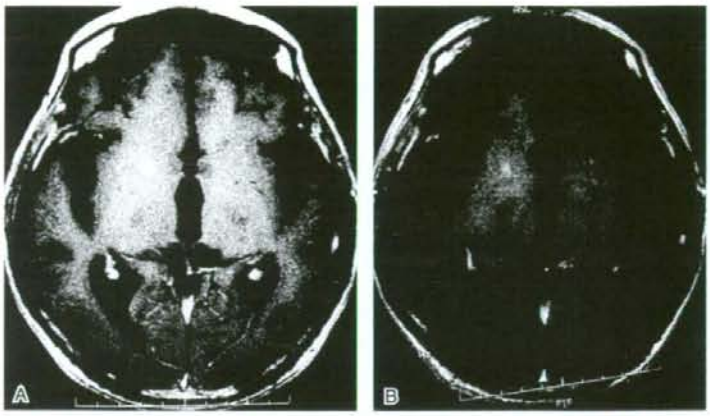

図3　脳転移巣に対してゲフィチニブが効果を示した患者のMRI所見（61歳男性，肺腺癌原発）
A：ゲフィチニブ治療直前のMRI．全脳放射線照射後に一旦縮小効果を示した後，最増大した右基底核病変を認める．
B：ゲフィチニブ治療開始後4ヵ月後のMRI．右基底核病変はほぼ消失している．

表1　肺癌脳転移症例に対するゲフィチニブ治療の過去の報告例

著者，発表年	調査法	国	患者数（男/女）	腺癌（%）	奏効率	効果期間（月）*
Ceresoliら[5]，2004	前向き	伊	41(29/12)	23(56%)	10%	13.5
Hottaら[13]，2004	後ろ向き	日本	14(7/7)	12(86%)	43%	7.7
Nambaら[24]，2004	後ろ向き	日本	15(9/6)	11(73%)	60%	8.7
Shimatoら[34]，2005	後ろ向き	日本	8(6/2)	6(75%)	63%	12
Chiuら[6]，2005	前向き	台湾	76(40/36)	53(69.7%)	33%	5
Leeら[19]，2005	前向き	韓国	10**（NA）	10(100%)	70%	NA
Wuら[36]，2007	前向き	中国	40(22/18)	40(100%)	32%	9.0

NA: not available
* 効果期間：median progression-free survival，あるいは median duration of response
**全登録患者37例中，脳転移合併の患者数のみ表示

チニブが東洋の国々を中心に承認されていることを反映していると思われる．イタリアからの報告では奏効率が10％と東洋からの報告に比べ低い数字となっており，脳転移巣でも東洋人でより効きやすいことが想像される．

韓国のLeeらの報告は，患者群を非喫煙者かつ進行腺癌に限り，ゲフィチニブを第一選択肢として治療している臨床試験で注目されるが，臨床的奏効因子を満たす患者が大部分を占め，極めて高い奏効率となっている[19]．したがって治療対象を，奏効因子を満たす患者群に限れば，肺癌での報告と同様に脳転移においてもかなり高い奏効率

が得られる可能性があると思われる．さらに，脳転移巣においてもEGFR-TK領域の遺伝子変異がゲフィチニブ感受性に強く相関すると考えられ，効果予測因子として重要である[34]．効果の持続期間をみてみると，中央値で1年以下の報告が多く，一旦は効果を示してもやがては効かなくなることは肺癌に対する効果と同様であり，効果には限界がある．

また，この薬剤の延命効果については肺癌でも議論のあるところであるが，脳転移巣に対しての延命効果についても今のところ評価できる調査は報告されていない．興味深い症例報告としては，肺病変と同時に多発性脳転移で発症後，ゲフィチニブ治療のみで2年以上の間，脳転移巣の進行なく良好な経過をたどった症例や[22]，馬尾症状等で発症した脳脊髄髄膜播種に対しゲフィチニブ治療を行い，2週間で完全に神経症状が消失した症例の報告等がある[31]．ゲフィチニブは，神経症状の著明な改善とそれに伴うADL向上，さらに生存期間の延長効果をもたらす可能性を秘め，大きな恩恵を受ける患者もいることは確かである．

以上のようにゲフィチニブによる劇的奏効例がある一方で，抵抗性の症例や初期は奏効しても急激に抵抗性となる症例があるのも特徴である．肺癌治療で初期にゲフィチニブが奏効後に抵抗性となる場合，脳転移あるいは髄膜播種として進展する頻度が高いという報告もあり[25]，ゲフィチニブ治療の終末像として脳転移が現れることがあることも事実である．

ゲフィチニブによる脳転移あるいは髄膜播種に対する効果には，同薬のBBB透過性や髄液移行性も大きくかかわると考えられる．ゲフィチニブのBBB透過性は確認されていないが，分子量の小さな薬剤であり，有効例のほとんどは肺癌での使用量と同じ一日量250mgで継続されていることから，同量で脳転移巣や髄液腔へ十分に浸透する可能性が考えられる．一方で，髄膜播種合併例で，ゲフィチニブの十分な髄液移行と効果出現までに一日量1,000mg以上まで増量を必要とした症例の報告もあり[15]，症例によっては至適投与量が異なる可能性も考えられる．

脳転移巣に対する現在の標準的治療は放射線治療であり，現時点ではゲフィチニブを積極的治療の方法として使用することは難しく，過度に期待をするべきではない．しかし，非小細胞肺癌の脳転移例で放射線治療が困難な場合，治療歴や全身的な病状を考慮したうえで，QOL改善を期待してゲフィチニブを使用するという選択肢があることも知っておくべきであろう．その際には，急性肺傷害等の有害事象の危険性を十分認識し，また有効性を予測するうえで，患者背景やEGFR-TK領域の遺伝子変異の有無を検討することは重要であり，呼吸器専門医との協力が必要である．

Ⅵ．ゲフィチニブのグリオーマに対する治療の可能性

悪性グリオーマでもEGFR遺伝子過剰発現が高頻度で認められ，ゲフィチニブ治療の可能性が期待された．米国やイタリアではすでに再発悪性グリオーマ症例に対するゲフィチニブ治療の第2相臨床試験が行われ，腫瘍制御例はあったものの腫瘍縮小例はなく，6-month event free survivalが

13～14％，median overall survivalが24.6－39.4週と効果は限られたものであったと報告している[8,30]．これらの試験ではEGFRあるいは細胞外領域に関係する遺伝子変異であるEGFRvⅢの発現やEGFR遺伝子増幅等についても解析しているが，それらはゲフィチニブ効果とはまったく相関しなかった[30]．

その後，肺癌におけるEGFR-TK領域の遺伝子変異が発見されたのを受けグリオーマでも解析されているが，glioblastoma，anaplastic oligodendroglioma，low grade gliomaではそれらの遺伝子変異は認められず[3,21]，グリオーマにおけるEGFRの生物学的意義やその他の分子機序は肺癌におけるそれとは異なると考えられ，グリオーマではゲフィチニブによる効果を期待できない理由と考えられている．

2005年には，臨床試験の結果から，EGFRvⅢとPTEN両者の発現がゲフィチニブ感受性に強く相関すると報告され，グリオーマに対してゲフィチニブ治療を考える際は，EGFRとその下流のシグナル伝達系を含めた因子を考える必要があることを示している．そして，新しい試みとしては，ゲフィチニブに加えてEGFR経路下流のmTOR（mammalian target of rapamycin）の阻害剤を用いる試みもされており，一定の効果が得られたことが報告されている[7,29]．

このようにグリオーマにおいてはゲフィチニブ単剤での分子標的治療には限界があると考えられ，関連する他の分子を同時に狙い撃つような戦略が必要と考えられる．

Ⅶ．おわりに

現在，脳転移に対しては放射線治療が中心となっているが，癌が全身疾患であることを考えれば脳を含めた全身的な効果を導いてくれる治療法が望まれる．これまでに報告されたゲフィチニブによる肺癌脳転移に対する効果は，脳転移に対する薬物治療の可能性を示してくれたと言える．今後は他の癌種も含め，脳転移巣への効果という視点からも抗腫瘍薬治療の研究が進められることを期待する．

ゲフィチニブの感受性と遺伝子変異との関連についての重要な発見は，薬物治療において「効く患者」をいかに選ぶかということの重要性を認識させられる．今後は，テーラーメイド治療の考え方が高まると考えられ，ゲフィチニブにおける成果は他の抗腫瘍薬治療の研究においても大いに参考となるであろう．

ゲフィチニブはまた，分子標的治療薬の可能性を示したと同時に，腫瘍生物学の見識を深めさらに問題点や課題も提示してくれたという点でも意味深い．他の分子標的治療を含め，今後のさらなる発展に期待し，注目していきたい．

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PAPER

Clinical significance of preoperative fibre-tracking to preserve the affected pyramidal tracts during resection of brain tumours in patients with preoperative motor weakness

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Objective: To clarify the clinical usefulness of preoperative fibre-tracking in affected pyramidal tracts for intraoperative monitoring during the removal of brain tumours from patients with motor weakness.

Methods: We operated on 10 patients with mild to moderate motor weakness caused by brain tumours located near the pyramidal tracts under local anaesthesia. Before surgery, we performed fibre-tracking imaging of the pyramidal tracts and then transferred this information to the neuronavigation system. During removal of the tumour, motor function was evaluated with motor evoked potentials elicited by cortical/subcortical electrical stimulation and with voluntary movement.

Results: In eight patients, the locations of the pyramidal tracts were estimated preoperatively by fibre-tracking; motor evoked potentials were elicited on the motor cortex and subcortex close to the predicted pyramidal tracts. In the remaining two patients, in which fibre-tracking of the pyramidal tracts revealed their disruption surrounding the tumour, cortical/subcortical electrical stimulation did not elicit responses clinically sufficient to monitor motor function. In all cases, voluntary movement with mild to moderate motor weakness was extensively evaluated during surgery and was successfully preserved postoperatively with appropriate tumour resection.

Conclusions: Preoperative fibre-tracking could predict the clinical usefulness of intraoperative electrical stimulation of the motor cortex and subcortical fibres (ie, pyramidal tracts) to preserve affected motor function during removal of brain tumours. In patients for whom fibre-tracking failed preoperatively, awake surgery is more appropriate to evaluate and preserve moderately impaired muscle strength.

A number of anatomo-functional evaluations of the pyramidal tracts have been developed to help preserve motor function while maximising the removal of brain tumours located in close proximity to the pyramidal tracts. Integrated functional neuronavigation and preoperative neuroimaging, such as functional MRI (fMRI), magnetoencephalography (MEG) and fibre-tracking, have been combined with intraoperative electrical stimulation to establish the clinical significance of the findings of each evaluation method.[1–6] Despite these developments in mapping and monitoring techniques, little is known about their clinical utility for patients suffering from motor weakness caused by brain tumours. As the tolerance of affected pyramidal tracts for surgical manipulation is weaker in comparison with that in patients without motor weakness, intraoperative evaluation plays a critical role in the surgeon's ability to maintain motor function. Decreased motor function itself, however, may affect the accuracy of intraoperative evaluation.

White matter fibre-tracking using diffusion tensor imaging is capable of visualising the integrity of white matter.[1 4 7–11] Although fibre-tracking of the pyramidal tracts does not always correlate with the degree of motor weakness, it does reflect the functional condition of the fibres.[10] To predict the clinical usefulness of intraoperative evaluation by presurgical non-invasive fibre-tracking imaging in patients with motor weakness, we compared the results of pyramidal tract fibre-tracking with the results of intraoperative direct electrical stimulation of the motor cortex and subcortical fibres (ie, pyramidal tracts) and spontaneous movements.

PATIENTS AND METHODS

Patients

We examined 10 patients, aged 28–67 years, who suffered from mild to moderate preoperative motor weakness due to brain tumours located close to the pyramidal tracts (table 1). The tumours included five cases of glioblastoma multiforme, three of anaplastic astrocytoma, one of diffuse astrocytoma and one cavernoma. All lesions were located within the language dominant frontal lobe; before operation, five patients had mild motor aphasia. In response to stimulation of the bilateral median and tibial nerves, scalp somatosensory evoked potentials (SEPs) were recorded in all patients. To evaluate cortical activity during voluntary movement, we evaluated finger/foot tapping during fMRI and MEG studies.

MRI data acquisition and diffusion tensor imaging (DTI) data processing for fibre-tracking and fibre-tractography reconstruction

Detailed methods for fibre-tracking have been described elsewhere.[8 10] Preoperative DTI and anatomical T1/T2 weighted volume imaging used a 3 T MR scanner (Trio; Siemens, Erlangen, Germany). T1 weighted volume data were obtained using a three dimensional magnetisation prepared rapid gradient echo (MPRAGE) sequence. T2 weighted volume data

Abbreviations: DTI, diffusion tensor imaging; fMRI, functional MRI; MEG, magnetoencephalography; MEP, motor evoked potential; MPRAGE, magnetisation prepared rapid gradient echo; ROI, region of interest; SEP, somatosensory evoked potential

Table 1 Clinical characteristics of the 10 patients

Patient No	Age (y)	Sex	Histological type	Location
1	67	M	Glioblastoma multiforme	Left fronto-parietal
2	58	F	Glioblastoma multiforme	Left fronto-insulo-temporo-parietal
3	53	M	Anaplastic astrocytoma	Left fronto-parietal
4	28	M	Glioblastoma multiforme	Left fronto-parietal
5	40	F	Glioblastoma multiforme	Left frontal
6	40	F	Cavernoma	Left fronto-parietal
7	48	M	Diffuse astrocytoma	Left fronto-parietal
8	56	M	Anaplastic astrocytoma	Left frontal
9	60	F	Anaplastic astrocytoma	Left fronto-insulo-temporal
10	50	M	Glioblastoma multiforme	Right fronto-parietal

were obtained using a three dimensional true fast imaging with steady precession sequence. DtiStudio software was used to perform fibre-tractography based on the fibre-assignment by continuous tracking method.[9 14] Fibre-tracking was initiated in both retrograde and orthograde directions according to the direction of the principal eigenvector in each voxel. Results that penetrated the manually segmented regions of interest (ROIs) were assigned to specific tracts. To reconstruct the pyramidal tract, two ROIs were segmented on axial $b = 0$ images: the first ROI at the cerebral peduncles and the second ROI at the precentral gyri.[9 15 16] If the pyramidal tracts were not detected between the two ROIs because of the presence of tumours, the hyperintensity area at the internal capsule on the $b = 0$ image was selected as the second ROI.[11]

Fibre-tractography data processing for navigation system

To convert tractography into a DICOM format dataset, three processing steps were applied. The first step was to change tractography to a voxel dataset. An 8 bit voxel dataset with binary contrast was created from the original tractography using DtiStudio, with the same matrix size as $b = 0$ images. In this voxelised tractography, marked voxels where fibre-tracts penetrate displayed the largest value, and other voxels the smallest ones.[15] The second step was to create merged images of tractography and $b = 0$ images with the same matrix size as the MPRAGE images. The 3-orthogonal coordinates of each voxel in MPRAGE and $b = 0$ images were obtained from the DICOM header information. Trilinear interpolation was applied for voxel value calculation. Merged images were generated from interpolated tractography and interpolated $b = 0$ images. The third step was to convert merged images into DICOM format, according to the MPRAGE header information. DICOM format tractography with the same imaging matrices as MPRAGE were obtained.

Preparation in the navigation system

The MPRAGE images, fast imaging with steady precession images and DICOM format tractography images were transferred to the navigation system (StealthStation TRIA plus, Medtronic Sofamor-Danek, Memphis, Tennessee, USA; or Vector Vision Compact Navigation System, Brain LAB AG Heimstetten, Germany) using Cranial 4.0/VV Cranial 7.5 software. We then applied non-rigid image fusion based on a mutual information algorithm using ImMerge/iPlan2.5 software. The day before the operation, we performed axial whole brain CT with a contiguous slice thickness of 1 mm and six independent scalp point markers for anatomical registration. The CT dataset was also input into the navigation system. CT, MPRAGE and DICOM format tractography were automatically registered; the anatomical registration points were verified to minimise navigation errors. As the differences in distortion between DTI and MPRAGE were within a few millimetres according to a phantom for the neuronavigation system, we determined that the spatial accuracy of the single shot echo planar sequence would be reliable; the potential error of the navigation due to image distortions would be limited to a few millimetres. At navigation setup, the accuracy of image registration was less than 2 mm. Fibre-tracking tractography

Table 2 Results of evaluation of motor function by preoperative and intraoperative assessments

Patient No	Motor weakness	MEG	fMRI	Scalp SEP	Fibre-tracking	MEPs (cortex)	MEPs (subcortex)	Awake surgery
1	Hand 4/5	x	x	x	x	o (unstable)	x	o
	Brachium 3/5	x	x	x	x	x	x	o
	Leg 2/5	x	x	x	x	x	x	o
2	Hand, brachium 1/5	x	x	x	x	x	x	o
	Leg 4/5	x	x	x	x	x	o (<1 cm)	o
3	Hand, brachium 3/5	o	o	o	o	o	o (<1 cm)	o
4	Hand 4/5	o	o	o	o	o	o (<1 cm)	o
5	Hand 4/5	NA	NA	o	o	o	o (<1 cm)	o
6	Hand 4/5	o	o	o	o	o	o (<1 cm)	o
7	Hand, brachium 4/5	NA	o	o	o	o	o (<1)	o
8	Hand 4/5	NA	NA	o	o	o	x (>2 cm)	o
9	Hand 4/5	o	NA	o	o	o	x (1 cm<<2 cm)	o
10	Hand 4/5	NA	o	o	o	o	x (1 cm<<2 cm)	o

fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; MEP, motor evoked potential; NA, not available; o, motor function detected; SEP, somatosensory evoked potentials; x, motor function was undetected. The distances between points of subcortical stimulation and the fibre-tracking pyramidal tracts are shown as less than 1 cm (<1 cm), between 1 and 2 cm (1 cm<<2 cm) or more than 2 cm (>2 cm).

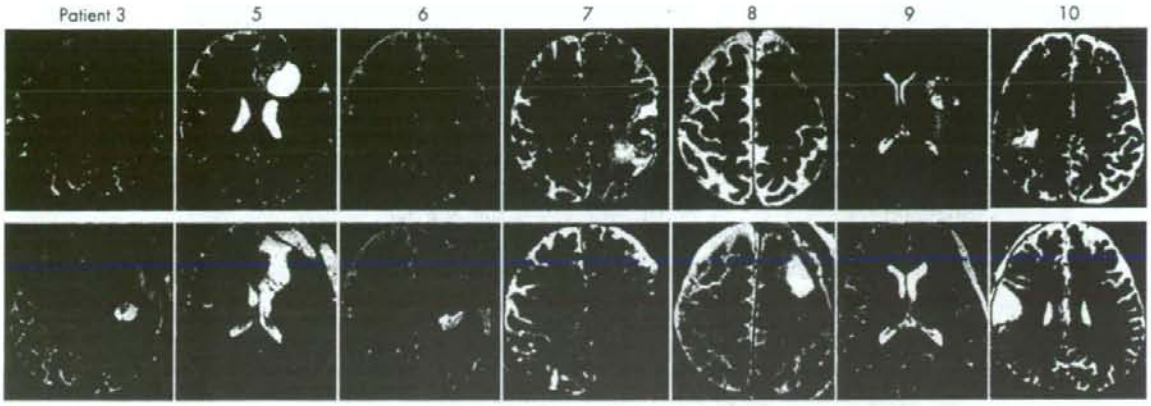

Figure 1 Upper: preoperative T2 weighted MRI in patient Nos 3, 5, 6, 7, 8, 9 and 10, with brain tumours showing a hyperintense area that is close to the pyramidal tracts (red), identified by fibre-tracking. Lower: postoperative T2 weighted MRI demonstrated the extent of tumour removal. Postoperative fibre-tracking in patient Nos 3, 6 and 9 revealed preservation of the pyramidal tracts (red).

of the pyramidal tracts between the cerebral peduncle and the precentral gyrus was successful in 50 surgically treated brain tumour patients without motor weakness (data not shown).

Intraoperative electrical stimulation

The bilateral abductor pollicis brevis, biceps brachialis, deltoid, gastrocnemius, quadriceps femoris and tibialis anterior muscles were chosen for electromyogram recording using neurological monitoring (Epoch XP, Axon Systems, New York, USA). After induction, general anaesthesia was maintained by intravenous infusion with propofol for craniotomy. Muscle relaxants were administered only for intubation and were not continued during surgery. The highest N20–P20 phase reversal of cortical SEPs was recorded using 4×5 subdural electrodes to identify the central sulcus. If SEPs were not sufficient to define the central sulcus, intraoperative visual inspection of the sulci combined with neuronavigation was used to orient the anatomy. After discontinuing the propofol infusion, patients awoke without further deficits.

To monitor motor function of the corticospinal tracts electrophysiologically, we first stimulated the precentral gyrus to identify a positive control motor evoked potential (MEP) and the intensity appropriate to stimulate subcortical fibres. The intensity of cortical stimulation was increased from 5 mA to a maximum of 25 mA. If afterdischarges were induced, we repeated the test at the same intensity or using a 1 mA lower

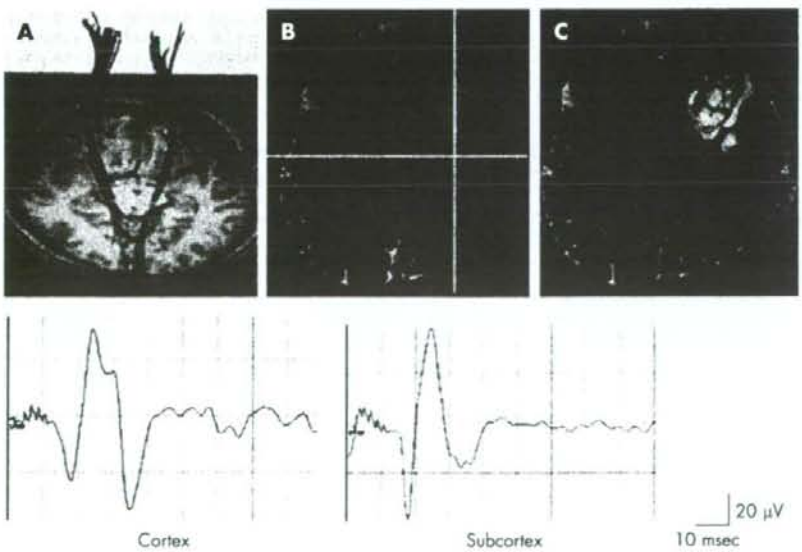

Figure 2 Patient No 4 had a left fronto-parietal glioblastoma multiforme. (A) Preoperative fibre-tracking identified symmetrical pyramidal tracts (red lines) from the cortex to the cerebral peduncles. (B) Brain T2 weighted MRI revealed a hyperintense area in close proximity to the left pyramidal tract, identified by fibre-tracking (red). Cortical stimulation of the left precentral gyrus, which had been defined by a somatosensory evoked potential, elicited a motor evoked potential (MEP) in the right abductor pollicis brevis muscle (Cortex). During removal of the tumour, subcortical stimulation elicited MEPs at the bottom of the tumour (intersection of the yellow lines in the intraoperative navigation image), 1 cm from the edge of the predicted pyramidal tract (red) (Subcortex). To avoid causing additional neurological deficits, no further removal was performed. (C) Postoperative T2 weighted MRI demonstrated preservation of the pyramidal tracts identified by fibre-tracking (red).