II. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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III. 研究成果の刊行物・別刷

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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 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

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

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

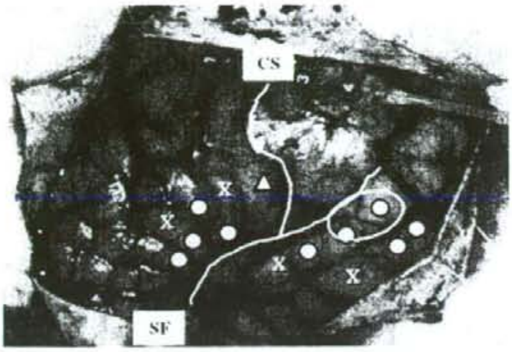

Fig. 1. *Case 1* – A 49-year-old woman with primary CNS malignant lymphoma. Intra-operative photograph of the brain map showing that the tumor is located under the Wernicke's area. ○ Speech arrest, Δ dysarthria, × no response, *CS* central sulcus, *SF* Sylvian fissure

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.

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

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, Δ dysarthria, × no response, *CS* central sulcus, *SF* Sylvian fissure

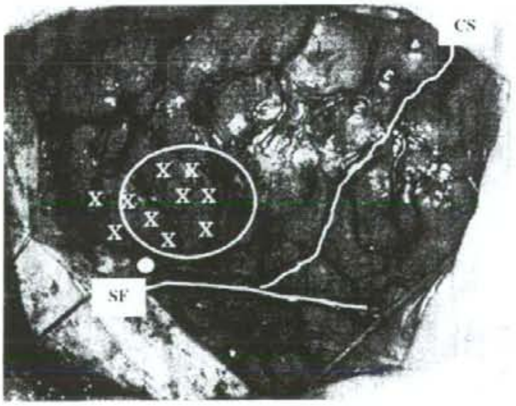

Fig. 3. *Case 3* – A 52-year-old man with frontal glioblastoma multiforme. Intra-operative photograph of the brain map showing that the Broca's area is located on the inside of the Sylvian fissure. ○ Speech arrest, Δ dysarthria, × no response, *CS* central sulcus, *SF* Sylvian fissure

failed to identify a frontal language area. His inferior frontal gyrus was swollen. We exposed the inner surface 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.

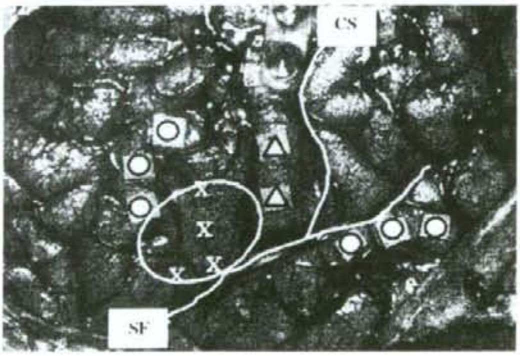

Fig. 4. *Case 4* – A 55-year-old man with oligodendroglioma. Intra-operative photograph of the brain map showing that the tumor is located under the Broca area. ○ Speech arrest, Δ dysarthria, × no response, *CS* central sulcus, *SF* Sylvian fissure

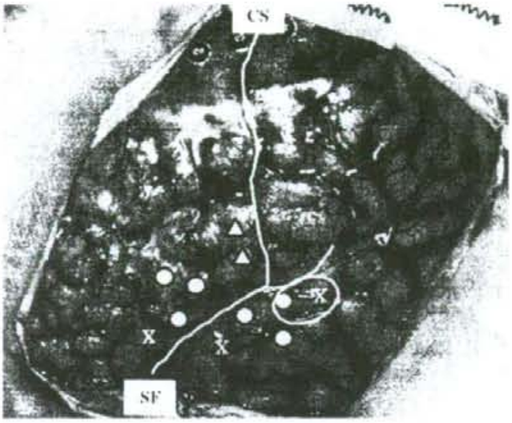

Fig. 5. *Case 5* – A 44-year-old woman with cavernous angioma. Intra-operative photograph of the brain map showing that the tumor is located under the Wernicke area. ○ Speech arrest, Δ dysarthria, × no response, *CS* central sulcus, *SF* Sylvian fissure

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.

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 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.

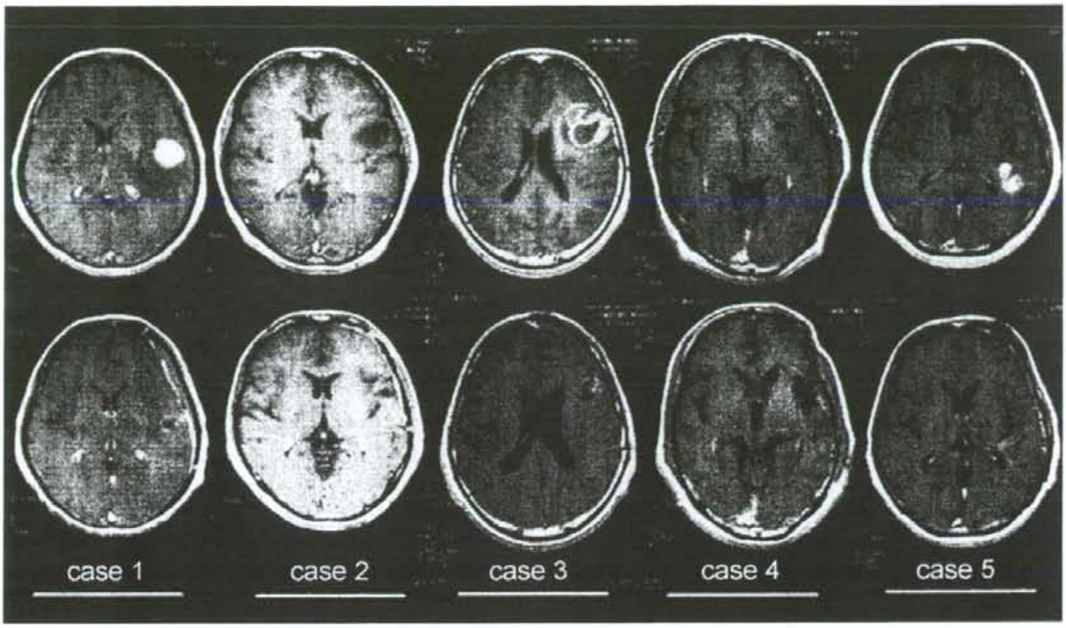

Fig. 6. Pre (*upper line*) – and post (*lower line*)-operative Gd-enhanced, T1-weighted magnetic resonance images obtained on the 5 patients. All tumors were removed almost totally

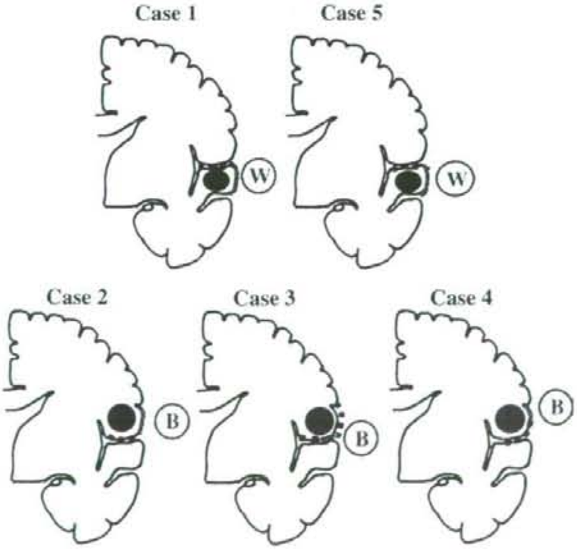

Fig. 7. Schematic drawing of the brain map of the 5 patients. *B* Broca's area, *W* Wernicke's area. The filled circles indicates the tumor. The dotted and gray lines encircle the functional- and non-functional areas, respectively

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剥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)．

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 1 脳腫瘍に対する従来の摘出法

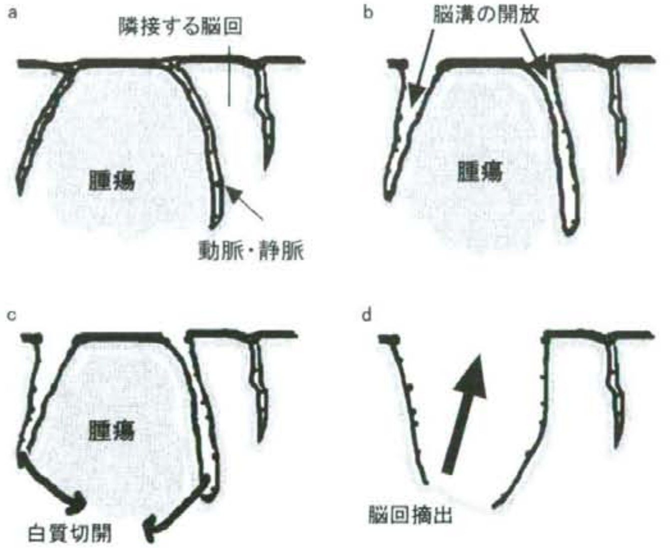

図 2 gyrectomy 法の手順

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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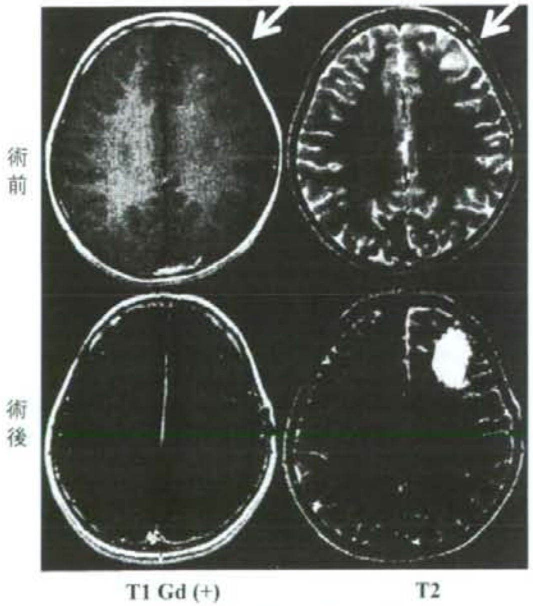

図 3 症例の術前・術後MRI
病変を含む脳回（矢印）を摘出している．

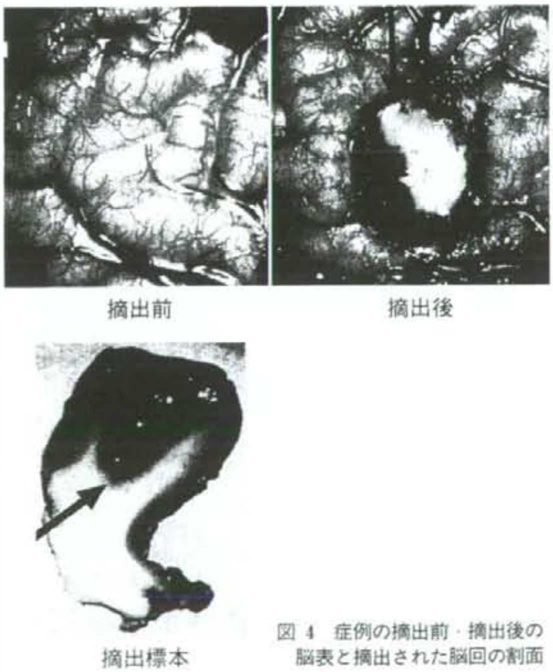

図 4 症例の摘出前・摘出後の脳表と摘出された脳回の割面

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Clinical Study

Initial experiences of palliative stereotactic radiosurgery for recurrent brain lymphomas

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Key words: chemotherapy, recurrent PCNSL, salvage treatment, SRS, symptomatic relief, toxicity

Summary

In Kyoto University Hospital, stereotactic radiosurgery (SRS) has been performed for its rapid palliative effect in patients with recurrent primary central nervous system lymphoma (PCNSL), often in combination with salvage chemotherapy. In the present study, the treatment outcome and toxicity of SRS for recurrent PCNSL was retrospectively evaluated. Between March 1998 and June 2004, 17 histologically proven recurrent PCNSLs in nine patients were treated with linac-based stereotactic radiosurgery. All patients had developed intracranial recurrences after initial treatment including external beam radiation therapy (EBRT). The prescribed dose was 10.0–16.0 (median 12.0) Gy. Seven of nine patients received systemic chemotherapy around the time of SRS. The target volume was 0.4–24.5 ml (median 3.5 ml). Initial tumor response could be evaluated in 15 of 17 lesions. Among them, radiological complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) was observed in 3, 10, 2, and 0 lesions, respectively. One-year overall survival rate and relapse-free survival rate after first SRS was 58% and 22%, respectively. Improvement of symptoms was observed in six patients. The time from SRS to symptomatic relief was 1–57 days (median 3 days). No ≥ grade 2 acute toxicities related to SRS were observed. In conclusion, linac-based SRS with a prescription dose of 10–12 Gy for recurrent PCNSL is useful for palliation, especially considering the short time, rapid tumor response, and low treatment toxicity.

Introduction

Primary central nervous system lymphoma (PCNSL) is a rare brain tumor entity, which accounts for 0.5–1.5% of primary intracranial neoplasms in immunocompetent individuals [1]. The natural course of untreated PCNSL is highly aggressive and fatal, with a median survival time of approximately 1.5–4 months from the time of diagnosis [2–4].

Usually, PCNSL is treated with external beam radiotherapy (EBRT) and/or chemotherapy as an initial treatment, since the radio- and chemosensitivity of PCNSL seems to be as high as that of nodal or extranodal malignant lymphomas that occur in the body. Various combined regimens such as EBRT alone [5,6], EBRT followed by CHOP-like chemotherapy [7,8], high dose intravenous methotrexate alone [9], and high dose methotrexate followed by EBRT [10–12] have been employed, showing a median survival time of 12–30 months [4–12].

Although rapid and complete tumor regression is commonly seen in most cases of PCNSL, intracranial recurrence is often observed even within the previous radiation field. Failure after initial treatment was reported in 35–60% of adequately treated patients with PCNSL [6,13–15].

The prognosis of intracranial recurrent PCNSL seems to be dismal. The median survival time has been reported to be only 2–4 months from the time of recurrence without any treatment. Patients with intracranial recurrent PCNSL may be able to be salvaged with systemic chemotherapy, and possibly with radiotherapy. Several previous reports have shown the effect of these salvage therapies on patient prognosis. Median survival time was reported to be 10–16.5 months [14–16].

The use of conventional EBRT for recurrent PCNSL is often limited in consideration of the tolerance dose of brain parenchyma. In most cases, a large volume of brain parenchyma has been irradiated as a major part of the standard initial therapy. On the other hand, stereotactic radiosurgery (SRS), which has been widely used in the treatment of various brain tumors, may be a treatment option for recurrent PCNSL. Stereotactic irradiation minimizes the irradiated volume of surrounding normal brain parenchyma. This technique delivers an effective radiation dose to the recurrent tumor without severe neurological toxicity, even when the recurrent tumor is located within the field of previous EBRT. However, the microscopic tumor infiltration is not covered by SRS alone.

In our institute, SRS has been performed for its rapid palliative effect in patients with recurrent PCNSL, often in combination with salvage chemotherapy. In the present study, the treatment outcome and toxicity of SRS for recurrent PCNSL was retrospectively evaluated.

Methods and Materials

Patient Background

Between March 1998 and June 2004, 17 histologically proven recurrent PCNSLs in nine patients were treated with linac-based stereotactic radiosurgery at Kyoto University Hospital. There were five male and four female patients and their age was 51–79 (median 66) years old at the time of the first SRS.

All patients had developed intracranial recurrences after initial treatment, including EBRT. The primary tumor lesions had received 37.8–56.0 (median 54.0) Gy using a daily dose of 1.5–2.0 Gy, in which a whole brain irradiation dose of 33.0–48.6 (median 41.4) Gy had been followed by local boost irradiation. The interval between previous EBRT and the first SRS was 6.6–50.4 (median 16.6) months.

Treatment

Corticosteroids were administered to all patients before SRS. Seven of the nine patients received systemic chemotherapy around SRS, including VEPA (vincristin, cyclophosphamide, prednisolone, adriamycin) and DeVIC (dexamethasone, etoposide, ifosfamide, carboplatin) regimens.

All patients underwent SRS using 6 MV X-ray beams generated by Clinac-2300c linear accelerator (Varian Inc., Palo Alto, CA). Treatment planning was carried out using the X-Knife system (Radionics Inc., Burlington, MA), following a 3 mm-slice contrast-enhanced CT scan and MR-CT fusion if necessary. The contrast-enhanced tumor lesions and critical structures, such as eyes, brain stem and optic nerves, were delineated. Planned target volume (PTV) was determined as the contrast-enhanced tumor with a 2–3 mm margin. Four to six beam arcs were arranged first automatically and then manually, so that the optimal dose distribution could be achieved, considering both the doses of PTV and critical structures. Irradiation was carried out in a single fraction. The prescription dose varied according to the tumor size and location. The mean prescribed dose (80% isodose) to PTV was 10.0–16.0 (median 12.0) Gy. One lesion was treated by the combination of two isocenters.

At the time of the first SRS, the number of treated tumors was one for seven patients and two for two patients. Two of the nine patients received multiple SRS sessions at the diagnosis of intracranial distant recurrences following preceding SRS; one patient received the second SRS 27 months after the first SRS, and the other received four sessions of SRS to six tumors during seven months for repeated intracranial distant recurrences.

Outcome evaluation

The patients were followed up with MRI/CT studies. Initial tumor response was evaluated within two months after SRS. In the assessment of the initial tumor response, complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD) was defined as complete disappearance of the tumor, a ≥ 50% reduction in the tumor volume, a ≥ 25% increase in the tumor volume, and non-CR/PR and non-PD, respectively.

Intracranial relapse-free survival and overall survival times were calculated from the day of the first SRS using the Kaplan–Meier method. Toxicity was judged by NCI-CTC version 2 criteria.

Neurological status of the patients was evaluated by regular interviews and physical examinations, and scored according to the RTOG functional neurological scale [17].

Results

Treatment parameters

The target volume was 0.4–24.5 (median 3.5) ml. The collimator size used was 12.5–40 (median 30) mm in diameter, and the total beam arc was 160–410 (median 395) in degree. The coverage rate of the prescription dose to PTV was 92–100 (median 99)%. The minimal and maximal tumor dose was 5.5–17.7 (median 9.1) Gy and 12.5–20.3 (median 15.2) Gy, respectively. Major treatment parameters for the 17 tumors are summarized in Table 1. In all cases, the doses to eyes, optic nerves and brain stem did not exceed 12 Gy.

Initial tumor response and local regrowth after SRS

Initial tumor response could be evaluated in 15 of 17 lesions. Among them, radiological CR, PR, SD and PD were observed in 3, 10, 2 and 0 lesions, respectively, as listed in Table 2. The overall response rate (CR plus PR) was 87%. There was no relationship between the initial tumor response and the SRS parameters, including prescription dose, minimal dose, target volume, and the coverage rate. In Figure 1, an example of CR is shown.

Local tumor regrowth was seen in one lesion, which had received a prescription dose of 12.0 Gy and a minimal dose of 6.4 Gy. It was initially judged PR, but increased in size 2.4 months after SRS.

Pattern of recurrence after SRS and survival

One patient remained disease-free for 20.3 months, one patient developed local regrowth 2.4 months after SRS, and seven patients developed intracranial distant recurrences 0.7–27.2 (median 3.1) months after the first SRS. Recurrences after the first SRS were salvaged by further SRS in two patients, and by systemic chemotherapy in three patients.

One-year overall survival rate and one-year intracranial relapse-free survival rate was 58% and 22%, respectively, as shown in Figure 2. Median overall survival time and median intracranial relapse-free survival time was 7.7 months and 3.7 months, respectively. No relationship between the SRS parameters and survival was observed in the present study. However, the median overall survival time in patients with peri-SRS chemotherapy was significantly longer than that in patients