

Brain tumors in the mesial temporal lobe: long-term oncological outcome

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Object. Surgical treatment of brain tumors in the mesial temporal lobe (MTL) is a highly demanding procedure. Only a few studies describing the surgery of MTL tumors have been reported, and they have been focused on the operative techniques and immediate results of the surgery. The authors have analyzed the long-term oncological outcome in patients with MTL tumors.

Methods. Thirty-six patients with an MTL tumor were studied. The mean patient age at surgery was 32 years (range 13–62 years). The tumors were confined to the MTL (Schramm Type A) in 25 patients (69%). Extension of the tumor into the fusiform gyrus (Schramm Type C) and temporal stem (Schramm Type D) was observed in 4 and 7 patients (11 and 19%), respectively. There was a significant difference in the tumor size according to Schramm types ($p = 0.001$). Complete tumor resection was achieved in 26 patients (72%). All tumors were low-grade lesions except for 1 anaplastic astrocytoma.

Results. After a median follow-up period of 50.5 months, 7 patients showed progression of the disease. The actuarial progression-free survival rates were 97% in the 1st year, 84% in the 2nd year, and 80% in the 5th year. The degree of tumor resection was significantly related to the tumor control failure ($p < 0.001$) and malignant transformation of a low-grade tumor ($p < 0.001$). Univariate analyses using a Cox proportional hazards model showed that the following factors were significantly associated with a failure to control the tumor: 1) extent of the tumor (Schramm Type D; $p = 0.003$, relative risk [RR] 12.04); 2) size of the tumor ($p = 0.033$, RR 1.052/mm); 3) patient age at surgery ≥ 50 years ($p = 0.007$, RR 8.312); and 4) short duration of epilepsy (< 6 months; $p = 0.001$, RR 21.54).

Conclusions. Surgery is the principal treatment for MTL tumors, despite its technical difficulty. Complete tumor resection is strongly recommended for long-term tumor control. The MTL tumors are heterogeneous in their prognosis. Older age, short duration of epilepsy, and tumor size are all associated with poor outcome. Patients with these characteristics may have a more aggressive form of the disease than those with MTL tumors associated with chronic epilepsy. (DOI: 10.3171/2009.5.FOCUS09106)

KEY WORDS • brain tumor • mesial temporal lobe • outcome • prognosis

THE MTL is a relatively small structure, but is the most epileptogenic region of the human brain. It is hidden deep within the brain and has considerable anatomical complexity. Brain tumors arising from the MTL have been a formidable disease because of the difficulty of surgical removal and associated morbidity and mortality rates.

Brain tumors in the MTL have several distinct characteristics. First, the proportion of pathological characteristics of benign (low-grade) lesions is greater than for tumors in other locations in the brain. Many low-grade brain tumors, such as DNET and PXA, tend to be located in the temporal lobe, whereas malignant gliomas develop evenly in proportion to the volume of the brain. Second, the majority of patients with an MTL brain tumor present

with epileptic seizures, and many of them suffer from chronic drug-resistant epilepsy. Third, although the MTL is a complex structure, anatomical disconnection and en bloc resection of this region can be achieved by experienced surgeons and can result in low morbidity rates.

Following the seminal report on the surgery of limbic system tumors by Yaşargil et al.,²¹ advances in TLE surgery have improved the chance of a surgical cure for these tumors, with an acceptable level of complications.^{14,18} Schramm and Aliashkevich¹⁵ have described a practical classification of MTL tumors, allowing for preoperative surgical planning and objective evaluation of the outcome. However, the number of articles on brain tumors in the MTL is limited at present, and previous studies have focused on immediate surgical outcomes and complication rates.^{14,18,21} This narrow interest is partly attributed to the substantial technical difficulty of the operative procedures per se, and to the ongoing controversies concerning the optimal surgical approach. We analyzed the long-term surgical outcome in 36 patients with an MTL tumor, with emphasis on tumor control. Clinical

Abbreviations used in this paper: DNET = dysembryoplastic neuroepithelial tumor; MTL = mesial temporal lobe; PFS = progression-free survival; PXA = pleomorphic xanthoastrocytoma; RR = relative risk; TLE = temporal lobe epilepsy.

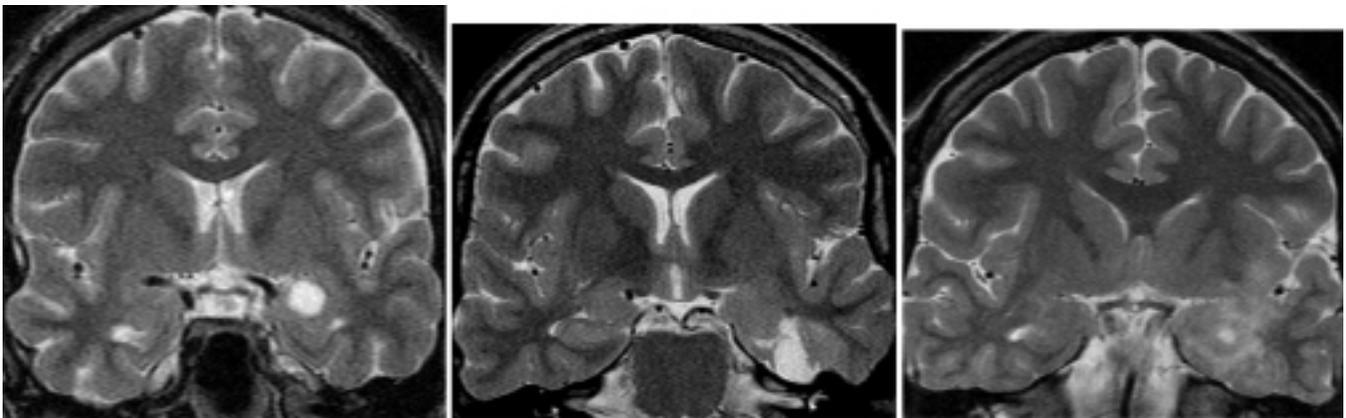


FIG. 1. Coronal images demonstrating the extent of MTL tumors classified according to Schramm and Aliashkevich (2008). *Left:* A Schramm Type A tumor restricted to the MTL, medial to the collateral or rhinal sulci; it is a DNET involving the left amygdala. *Center:* A Schramm Type C tumor affecting both the MTL and fusiform gyrus. It is a ganglioglioma involving both the parahippocampal gyrus and fusiform gyrus, crossing over to the collateral sulcus. *Right:* A Schramm Type D tumor invading the temporal lobe stem into the lateral basal ganglia or insular lobe. It is a ganglioglioma involving the MTL, temporal lobe stem, and insular lobe.

factors affecting the outcome were examined, with particular emphasis on the predictive value of the Schramm classification of this lesion.

Methods

Patient Population

We studied patients who had undergone surgery for an MTL tumor at the Seoul National University Hospital between January 1995 and December 2007. All patients were selected from the epilepsy surgery database. Only primary intraaxial tumors were included, and extraaxial tumors, such as meningiomas or schwannomas, were excluded. Patients who received initial resection at another institution were also excluded. The MTL is medial to the collateral or the rhinal sulci and includes the amygdala, hippocampus, uncus, and parahippocampal gyrus. Tumors arising from the fusiform gyrus without involvement of the MTL were excluded. Thirty-six patients with an intraaxial tumor in the MTL were included in our study. Twenty-three patients were male and 13 were female, and the mean age of these patients at surgery was 32 years (range 13–62 years). We retrospectively reviewed the clinical data of these individuals.

All patients presented with epileptic seizures. The seizures were drug-resistant in 20 patients but were adequately controlled with antiepileptic drugs in the other 16. The median age at seizure onset was 20.5 years (range 6–62 years), with a median duration of epilepsy of 3 years (range 1 month–48 years). No neurological deficits were observed at presentation in any patients.

All patients received a diagnostic workup for the definition of epileptogenic zones, including brain MR imaging, FDG-PET, electroencephalography, and neuropsychological tests. These diagnostic workups were minimized and customized for tumor surgery in patients ≥ 50 years of age and with a short period of epilepsy. The MR images were obtained using a 1.5-T MR imaging unit, with a protocol that incorporated axial and coronal T2- and FLAIR-weighted images.

Tumor Characteristics

Twenty-seven patients (75%) had a tumor in the left temporal lobe, and 9 (25%) had a tumor in the right temporal lobe. We classified the tumors according to the scheme suggested by Schramm and Aliashkevich.¹⁵ Because we did not include tumors in the fusiform gyrus without involvement of the MTL, no Schramm Type B tumors (basal tumors in the fusiform gyrus) were included. Twenty-five tumors (69%) corresponded to Schramm Type A (MTL tumors involving the amygdala, hippocampus, uncus, or parahippocampal gyrus). Four tumors (11%) corresponded to Schramm Type C (tumors involving both the MTL and fusiform gyrus). Seven tumors (19%) that invaded the temporal stem and extended into the lateral basal ganglia or insular lobe were defined as Schramm Type D (Fig. 1). Tumor size was measured using both axial and coronal MR images, and the largest diameter was recorded. The mean tumor sizes were 22,

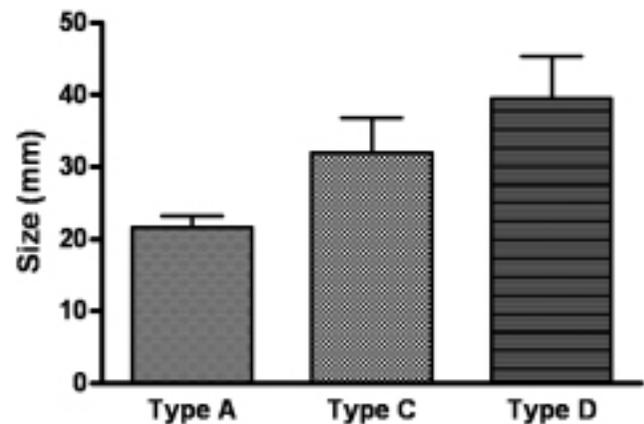


FIG. 2. Bar graph showing a comparison of tumor size with Schramm type. The mean tumor size of Schramm Type A was 22 mm, Type C was 32 mm, and Type D was 40 mm; the tumor size was significantly different between the groups ($p = 0.001$, Kruskal-Wallis test). Error bars indicate SEMs.

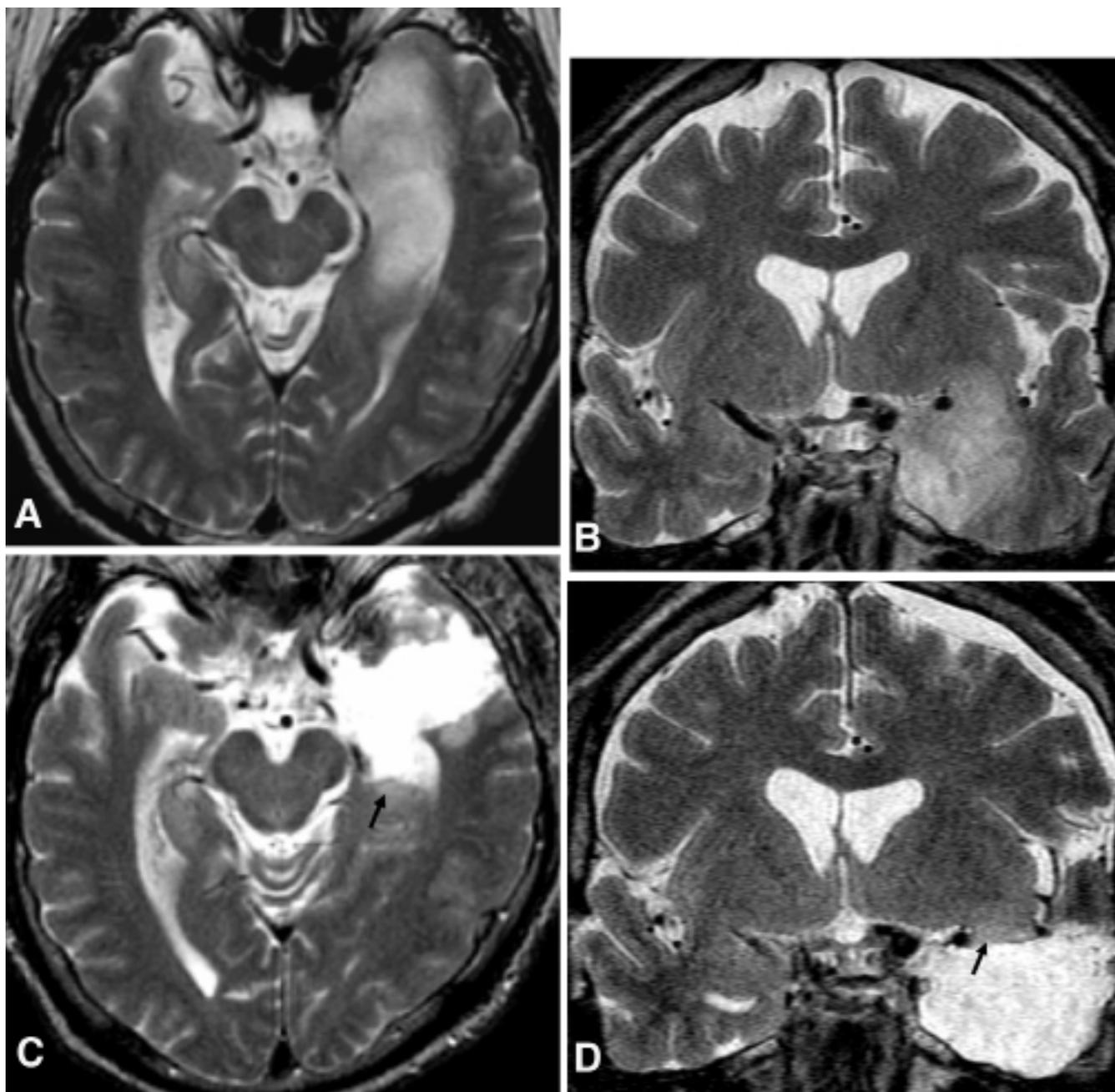


FIG. 3. Preoperative and postoperative MR images demonstrating a Schramm Type D oligodendroglioma in a 62-year-old man. A and B: Preoperative T2-weighted axial and coronal images. The tumor involves the MTL (amygdala, hippocampus, and fusiform gyrus) and extends into the temporal stem. C and D: Postoperative T2-weighted axial and coronal images. The resection was incomplete (subtotal resection). Small residual tumors are identified in the posterior hippocampal resection margin and in the temporal stem (arrows). The patient immediately received radiation therapy, but the tumor progressed 15 months after the operation.

32, and 40 mm for Schramm Types A, C, and D tumors, respectively, showing a significant difference in the tumor size according to the Schramm types ($p = 0.001$, Kruskal-Wallis test) (Fig. 2).

Surgical Approaches

Various surgical approaches were adopted for the radical resection of these tumors. Anterior temporal lo-

nectomy was the most common procedure (23 tumors, 64%), followed by temporal polar resection (lateral temporal resection < 3 cm in 8 tumors, 22%), transsylvian approach (4 tumors, 11%), and transsuperior temporal gyrus approach (1 tumor, 3%). The operative strategies for tumor-related TLE were described in our previous article.¹⁰ The primary concern was tumor control, especially in the patients with medically controlled epilepsy.

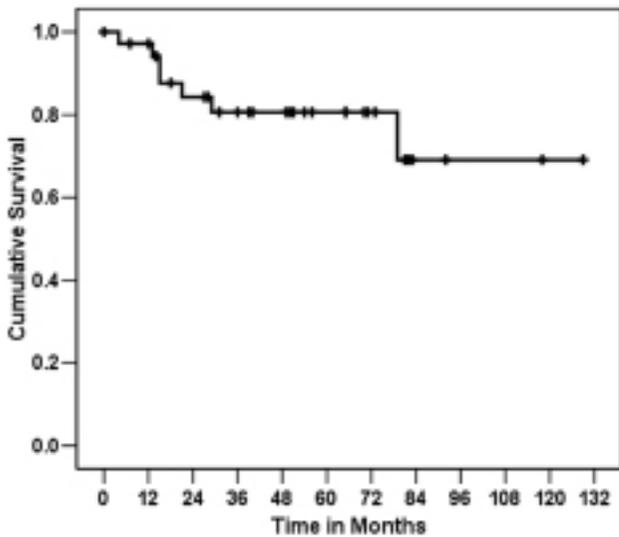


FIG. 4. Chart showing survival function of tumor control calculated with the Kaplan-Meier method. The actuarial PFS rates were 97% in the 1st year, 84% in the 2nd year, and 80% in the 5th year.

If the tumor involved the hippocampus, it was resected in all patients except 1, who refused hippocampectomy to preserve memory. Radical tumor resection was therefore attempted in all except this patient.

The extent of tumor removal was evaluated by postoperative MR imaging obtained within 3 months of the operation. Gross-total removal was achieved in 26 patients (72%). Removal was incomplete in 10 patients (28%); of these, 8 had subtotal resection (> 90% of tumor volume) and 2 had partial resection (50–90% of tumor volume) (Fig. 3).

Pathology and Adjuvant Treatment

Ganglioglioma was the most common tumor (13 lesions, 36%), followed by DNET (9 tumors, 25%), oligodendroglioma (6 tumors, 17%), and diffuse astrocytoma (5 tumors, 14%). Miscellaneous tumors included anaplas-

tic astrocytoma, choroid plexus papilloma, and PXA, with 1 case each. All lesions were low-grade tumors defined as WHO Grade I or II, except 1 anaplastic astrocytoma. The patient with this tumor received adjuvant chemotherapy and radiation therapy immediately after a subtotal resection. Another patient with a partially resected oligodendroglioma received postoperative radiation therapy.

Follow-Up and Statistical Analyses

The median follow-up period was 50.5 months (range 7–129 months). Neurological status was assessed in the outpatient clinic. Brain MR imaging was performed at regular intervals, ranging from 3 months to 1 year, according to the pathological diagnosis and the degree of tumor removal. Twenty-four patients (67%) are currently receiving follow-up care in the outpatient clinic. We have concentrated on assessing and analyzing the oncological outcome, because we have comprehensively dealt with the seizure outcome in patients with tumor-related TLE in our previous article.¹⁰

The PFS rate was calculated using the Kaplan-Meier method. A log-rank test was used for univariate analyses. A Cox proportional hazards model was applied for uni- and multivariate analyses. A nonparametric analysis (Kruskal-Wallis test) was applied to compare continuous variables between multiple groups. The level of significance was taken as 5%.

Results

To calculate the crude cumulative rate of tumor control, the end point was set when a recurrence was documented on the follow-up MR imaging or when the residual tumor had progressed (tumor volume increased > 25% in the follow-up MR imaging). The actuarial PFS rates were 97% in the 1st year, 84% in the 2nd year, and 80% in the 5th year (Fig. 4). Seven patients (19%) experienced tumor control failure (progression of the disease) during the follow-up period. The pathological findings in the tumors that were not controlled were ganglioglioma (3 cases), oli-

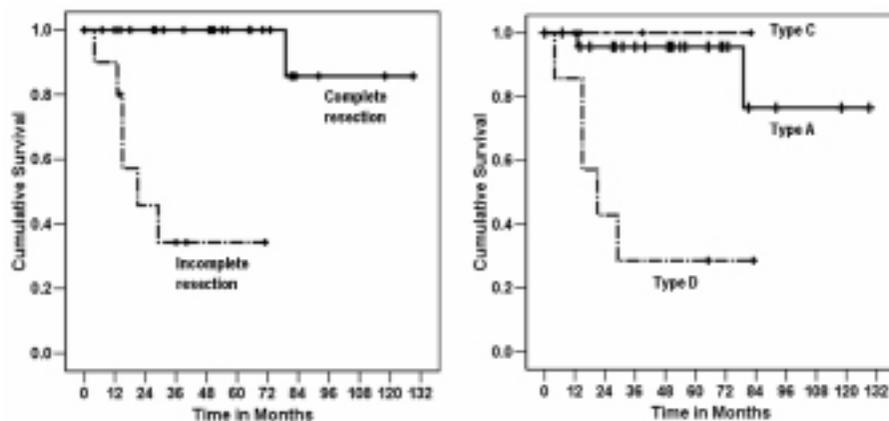


FIG. 5. Charts showing survival functions of tumor control according to the degree of surgical removal and the preoperative extent of the lesions. *Left:* Tumor control was significantly influenced by the degree of tumor removal ($p < 0.001$, log-rank test). *Right:* The extent of the tumors estimated by the Schramm types was also significantly associated with tumor control ($p = 0.001$, log-rank test). Ad hoc analysis revealed that Schramm Type D tumors were significantly more difficult to control than Schramm Types A and C tumors.

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TABLE 1: Correlations between the extent of the tumor, tumor size, incomplete resection, and tumor control failure

Factor	Statistics	Schramm Type D	Tumor Size	Incomplete Resection	Tumor Control Failure
Schramm Type D	Pearson coefficient (r value)	1	0.543	0.479	0.645
	p value		0.001	0.003	<0.001
tumor size	Pearson coefficient (r value)	0.543	1	0.518	0.363
	p value	0.001		0.001	0.030
incomplete resection	Pearson coefficient (r value)	0.479	0.518	1	0.636
	p value	0.003	0.001		<0.001
tumor control failure	Pearson coefficient (r value)	0.645	0.363	0.636	1
	p value	<0.001	0.030	<0.001	

godendroglioma (2), anaplastic astrocytoma (1), and PXA (1). Six of the 7 uncontrolled tumors were incompletely resected during the initial operation. One ganglioglioma recurred 6 years after complete removal of the tumor.

Kaplan-Meier survival functions showed that the tumor control was significantly affected by the degree of tumor resection ($p < 0.001$, log-rank test). The extent of the tumors estimated by the Schramm types was also significantly associated with tumor control ($p = 0.001$, log-rank test). Ad hoc analysis showed that Schramm Type D tumors were significantly more difficult to control than Schramm Types A and C lesions (Fig. 5). A Schramm Type D classification, larger tumor size, incomplete resection, and failure to control the tumor were all significantly correlated variables ($r > 0.3$ and $p < 0.05$ for all combinations; Pearson correlation) (Table 1).

Univariate analyses using a Cox proportional hazards model showed that among the various preoperative clinical variables, the extent of the tumor (Schramm Type D), its size, the patient's age at surgery, and shorter duration of epilepsy were all significantly associated with failure to control the tumor. Preoperative duration of epilepsy as a continuous variable was not a significant prognostic factor, but epilepsy lasting < 6 months was a strong negative factor ($p = 0.001$, RR 21.54; Cox regression analysis) (Table 2). Multivariate analyses using the same model re-

vealed no significant preoperative prognostic factors predicting tumor control failure.

Malignant progression (transformation) of a low-grade tumor occurred in 4 patients during the follow-up period. The actuarial malignant PFS in the 5th year was 88%. The initial pathological diagnoses in these patients were as follows: a low-grade ganglioglioma in 2, an oligodendroglioma in 1, and a PXA in 1 patient. Malignant transformation of the tumor was pathologically confirmed in 2 patients. The other 2 showed typical radiological features of malignant transformation (emergence of rim-enhancing masses or diffuse leptomeningeal seeding). The initial resection was incomplete in all these patients. The malignant PFS was significantly influenced by the degree of initial resection ($p < 0.001$, log-rank test) (Fig. 6).

Three patients succumbed to the disease during the follow-up period: 1 had an anaplastic astrocytoma, in 1 the ganglioglioma had transformed into a glioblastoma, and 1 had a PXA that transformed with diffuse leptomeningeal seeding. The actuarial overall survival rate in the 5th year was 90%.

Discussion

The MTL is part of the limbic lobe and is characterized by a distinct cellular architecture and distinct

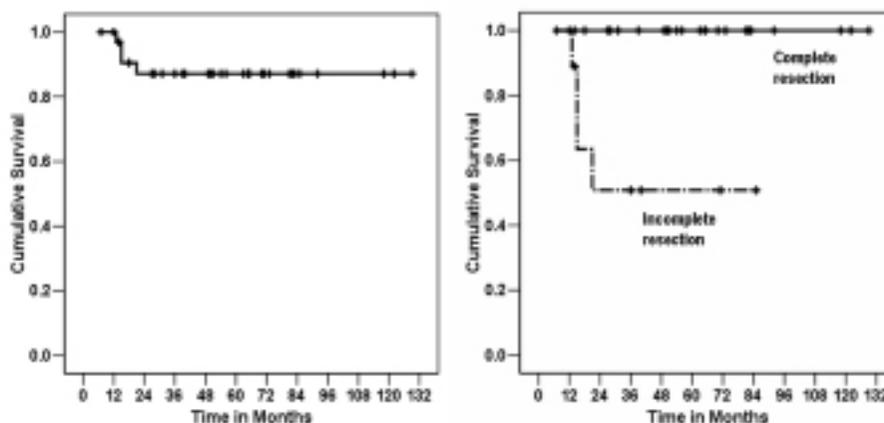


Fig. 6. Kaplan-Meier survival plots depicting malignant PFS, assessed in 35 patients with a low-grade tumor. *Left:* Malignant progression (transformation) of the tumor occurred in 4 patients; the actuarial malignant PFS in the 5th year was 88%. *Right:* The malignant PFS was also significantly influenced by the degree of tumor removal ($p < 0.001$, log-rank test).

TABLE 2: Relative risks for tumor control failure estimated with a Cox proportional hazards model*

Factor	Univariate Analysis			Multivariate Analysis		
	p Value	Crude RR	95% CI	p Value	Adjusted RR	95% CI
laterality (lt MTL)	0.704	0.727	0.140–3.772	NA	NA	NA
extent of tumor (Schramm Type D)	0.003	12.04	2.317–62.53	0.261	3.611	0.385–33.92
tumor size (mm)	0.033	1.052	1.004–1.101	0.643	0.985	0.926–1.049
age at op (continuous variable)	0.036	1.059	1.004–1.118	NA	NA	NA
age at op \geq 50 yrs	0.007	8.312	1.788–38.64	0.236	3.108	0.476–20.29
duration of epilepsy (continuous variable)	0.864	1.006	0.942–1.073	NA	NA	NA
duration of epilepsy < 6 mos	0.001	21.54	3.647–127.2	0.056	8.313	0.926–1.049

* NA = not assessed.

anatomical connections.²¹ Many kinds of brain tumors develop in the MTL. Low-grade brain tumors, such as ganglioglioma, DNET, and diffuse fibrillary astrocytoma, are the most common tumors of the MTL.¹⁴ The frequent occurrence of these low-grade brain tumors in the MTL, a relatively small region in the human brain, may be attributed to the presence of the subependymal plate lying along the temporal horn and the subgranular layer in the hippocampus, where uncommitted neuroglial progenitors exist through childhood to adulthood.⁵ Epileptic seizures are more common in low-grade tumors than in high-grade ones.¹⁹ Tumors of a mixed glioneuronal character, such as ganglioglioma and DNET, are frequently associated with cortical dysplasia, an epileptogenic developmental anomaly.¹³ Therefore, brain tumors are one of the main causes of TLE, and surgical outcome of the MTL tumors has been chiefly addressed in studies of TLE surgery.^{3,4}

Several authors have described the surgical outcomes of MTL tumors from an oncological perspective.^{14,18,20} These studies have included a substantial number of malignant brain tumors, such as anaplastic astrocytomas, glioblastomas, and metastatic tumors, broadening the interest from epilepsy surgery to include oncology. Despite the heterogeneity of the pathological entities, MTL tumors can be viewed as a group by neurosurgeons for the following reasons. First, the pathological findings and tumor grade cannot be accurately predicted preoperatively, and resection is the initial treatment most resorted to for MTL tumors. Second, most brain tumors are more or less resistant to adjuvant therapies, and resection is currently the principal treatment. Third, MTL tumors, especially those with the pathological characteristics of low-grade lesions, tend to be restricted to the anatomical boundary of the temporal lobe, and complete removal of them is possible in many cases. Last, in many cases, in toto temporal lobe resection is required for seizure control. Therefore, complete resection is an important goal for the treatment of MTL tumors. Most brain tumors tend to progress eventually following incomplete resection. Although some authors have reported that DNETs remain quiescent following incomplete removal, in a previous study we have reported 2 cases of recurrence of DNET arising from the lateral temporal lobe.¹⁰ The completeness of tumor removal is known to be a major prognostic factor for both low- and high-grade gliomas in many studies.^{9,11,17}

All of our patients except 1 had a low-grade brain tumor (WHO Grade I or II), whereas previous MTL tumor studies included a greater proportion of malignant tumors (22–44%).^{14,18,20} The homogeneity of our cases allows us to analyze long-term outcomes. However, there is still inherent heterogeneity in the low-grade pathological findings, with prognostic implications. Therefore, we focused on the PFS rather than overall survival, because PFS reflects the direct influence of surgery rather than the overall survival, which may be affected by subsequent treatment and the biological behavior of the tumor.

Analyses of the PFS and relevant preoperative prognostic factors in this study revealed 2 distinct facts. First, the extent of an MTL tumor was a significant risk factor for the progression of the disease. Schramm and Aliashkevich¹⁵ proposed the classification of mesiobasal temporal lobe tumors based on the MR imaging study of hundreds of cases. Tumor size and the proportion of those with malignant histological findings increased according to the Schramm types.¹⁴ Schramm Type D tumors that extend beyond the MTL into the diencephalon, insular lobe, and temporal neocortex represent more aggressive disease. Complete resection of these tumors is difficult and precarious in many cases.¹⁴ We found that Schramm Type D tumors were associated with incomplete resection and subsequent progression.

Second, a patient age \geq 50 years with a duration of epilepsy < 6 months was associated with a poor prognosis. This finding amply reflects the heterogeneity of the study population, which included patients with chronic epilepsy as well as those with simple tumors. It has been proposed that brain tumors associated with chronic epilepsy have a better prognosis than tumors in patients without epilepsy.^{8,12} Some authors have suggested that this phenomenon is related to different tumor histopathological characteristics.¹⁶ However, this phenomenon may reflect a selection bias, because chronic epilepsy lasting for years without significant disease progression is de facto evidence of a slowly growing benign lesion. Patient age is a more reliable prognostic factor in neurooncology. Gliomas behave more malignantly with increasing patient age, both quantitatively and qualitatively. In the pediatric population, the majority of gliomas are low-grade tumors, and even glioblastomas have a better prognosis than those of adulthood.^{2,6} Young age is also associated with a longer

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survival in patients with low-grade gliomas.^{1,7} Therefore, as for MTL tumors, older patients with a short symptom duration may experience a more aggressive form of the disease associated with a larger and more infiltrative tumor, although the initial pathological examination might show the presence of a low-grade tumor.

Conclusions

Surgery is the principal treatment for MTL tumors, despite its technical difficulty. Complete tumor removal is strongly recommended for long-term tumor control. Older patient age, short symptomatic duration, large tumor size, and tumor invasion beyond the MTL are associated with poor outcome. Patients with these characteristics may experience a more aggressive disease than MTL tumors associated with chronic epilepsy.

Disclosure

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