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Original Article

Treatment in Patients with Malignant Glial Neoplasms：A Retrospective Analysis of Clinical Parameters, Therapy, and Outcome

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Abstract.

Objective: The purpose of this study was to evaluate the therapeutic impact of tumor resection in the treatment of malignant glial neoplasms and delineate the outcomes after a combined therapy.

Materials and Methods: A retrospective study was conducted (Jul 1996- Jun 2006) to compare the treatment results of stereotactic biopsy plus radiation therapy (69 patients) with those of surgical resection plus radiation therapy (44 patients). The clinical records were reviewed and analyzed regarding patient demographics, and treatment of choice, including surgery, radiotherapy, or a combination of both. Surgical indications and pretreatment performance status scores were also recorded. The treatment outcomes were analyzed in terms of survival time and performance status score.

Results: The resection group and the biopsy group did not differ in terms of age, pretreatment Karnofsky performance status (KPS), gender, duration of symptoms, presenting symptoms, tumor location, tumor size, and frequency of midline shift. Transient perioperative morbidity and mortality rates were 4.34% and 8.69%, respectively, in the biopsy group and 20.3% and 0%, respectively, in the resection group (P>0.05). This multivariate model identified age as the strongest pretreatment prognostic factor, and the KPS correlated significantly with age. The study indicates that patients with malignant gliomas who complete radiation therapy (doses > 50 Gy) after resection of tumor tissue mass survived longer than those who received biopsy alone, even after adjustment for the effects of clinical prognostic factors.

Conclusions: Surgical excision for maximum cytoreduction affords increased quality and duration of survival. In selected malignant gliomas, resection of the tumor mass followed by radiation therapy is associated with longer survival times than radiation therapy after biopsy alone.

Keywords **:** brain neoplasm, malignant glioma, prognostic factor, stereotactic biopsy

原著論文

惡性腦神經膠質瘤之處置經驗

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中文摘要

腦瘤的治療發展已有近百年的歷史，但是針對高惡性度神經膠質瘤(Malignant

glial neoplasms)迄今尚無治癒的方法，雖然各種療法包括手術及放射化療都在不斷努力研究突破中，目前尚無法治癒此類腫瘤。因此，治療的目的與目標是在建立組織學上的診斷，延長病人的生命，解除病人的痛苦，改善病人的神經機能障礙與生活品質。影響此類病患存活時間的因素牽涉較廣，其中包含年齡、臨床症狀表現(有無癲癇或神經缺損併發)，腫瘤位置，細胞型態及惡性度，和手術減壓根除程度，或放射治療的劑量等臨床因素。目前對於惡性神經膠質瘤的治療方法，大多數病例採手術切除，再加上術後放射線治療，有時再加上化學治療。我們總結本院從 1996 至 2006 年間收治 113 個惡性腦神經膠質瘤病例的臨床資料，針對診斷和治療的經驗作回朔性的比較與分析，分手術治療與保守立體定位切片診斷加放射治療等觀察群組，同時合併文獻回顧，總結惡性腦神經膠質瘤當前時效的診斷與治療。結果 69 例(60.83%)採保守立體定位切片檢查(stereotactic biopsy)合併放射治療，44 例(39.1%)行開顱手術治療(craniotomy with tumor resection)並加上放射治療，立體定位切片組有六例在術後一個月內死亡，三例神經功能惡化，而開顱切除組除了七例因腦瘤合併症無改善外，無死亡案例發生。結論：根據本院回朔性的案例分析顯示；手術後加上放射線治療之成效(存活時間)比單用手術或僅作立體定位切片加放射治療來的好，在病患狀況穩定前提下，應盡早掌握治療時機，進行手術及放射線治療。

關鍵字: 腦腫瘤、惡性神經膠質瘤、預後因素、立體定位切片

INTRODUCTION

The treatment of malignant gliomas remains a problem in that no contemporary treatments are curative; most therapies including surgery, radiotherapy, and chemotherapy are supposed to provide palliation before tumor recurrence and tumor-related death [1]. Many retrospective studies have reported that craniotomy and aggressive tumor resection prolongs survival in patients with high-grade gliomas [2-4]. However, others do not support the value of cytoreductive surgery in these tumors [5-8].

This retrospective study analyzed the benefit of tumor resection over biopsy in patients with high-grade glial neoplasms stratified for tumor grade and cell type, patient age and performance status, tumor location, and radiation therapy.

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CLINICAL MATERIALS AND METHODS

Patient Population

Between July, 1996, and June, 2006, 113 patients with malignant gliomas (68 males, 45 females) underwent surgical procedures performed at the Mackay Memorial Hospital. Patient ages ranged from 6 to 81 years (mean 42.4 years). Initial symptoms were seizures in 37 patients, neurological deficit in 65, and increased intracranial pressure (ICP) without deficit in 11. At surgery, 99 patients had neurological deficit, 12 had seizures only, and two had increased ICP (while receiving steroids). Tumor was found incidentally in one patient. Tumor location on computerized tomography (CT) and/or magnetic resonance (MR) imaging was: frontal in 21 patients, parietal in 15, temporal in 12, and occipital in 2; more than one lobe was involved in 36 patients, the thalamus/basal ganglia in 14, the corpus callosum in 6, the brain stem in five, and the third ventricle region in two.

Surgical Management

Stereotactic serial biopsy based on CT and MR

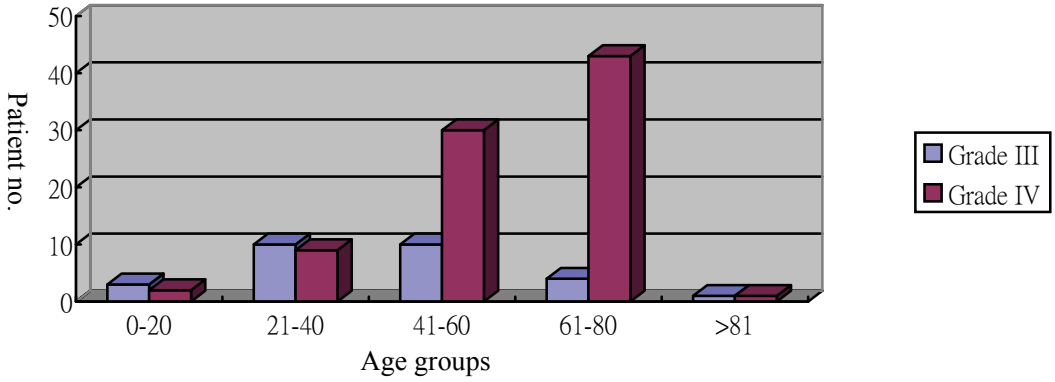

Figure 1. Graph showing number of patients with grade III and grade IV tumors for each decade of age (years) in 113 high-grade gliomas

imaging was performed on 69 patients as the sole surgical procedure. Serial tissue samples (10×1.5 mm) obtained from CT-defined hypodense and contrast-enhancing regions along a biopsy trajectory (one to nine specimens, average 3.68), were examined for tumor cell type and grade as described previously.

Resection of the tumor mass defined by contrast enhancement on CT and MR imaging was performed in 33 patients employing a volumetric stereotactic procedure described previously. The remaining 11 patients, harboring superficial lesions, underwent non-stereotactic open craniotomy, with gross total removal of the contrast-enhancing mass lesion.

Patient Selection

In the study groups, the option of a biopsy or resection procedure was offered to every patient. Resection was favored in lesions having a contrast-enhancing volume of greater than one-third the global lesional volume (contrast-enhanced area plus hypodensity). However, the higher risk of resection compared to biopsy and the modest benefit expected prompted many patients to choose biopsy instead of resection procedures.

Adjuvant Therapy

Fractionated external beam radiation therapy was administered over a 5-to 7-week period. Sixty patients received a dose of 60 Gy or greater, 26 received between 40-60 Gy, 14 received less than 40 Gy, and 13 refused radiation therapy or received no radiation because of rapid clinical deterioration. Forty-three patients entered various chemotherapy protocols.

Pathology

The grading system was employed according to the description by Daumas-Duport [2,9]. Tumor grade in astrocytomas and oligoastrocytomas was determined by the presence or absence of four criteria: nuclear abnormalities, mitosis, necrosis, and vascular endothelial proliferation; tumors were classified as grade III when two criteria were present and as grade IV when three or four criteria were present. There were 92 astrocytomas (19 grade III and 73 grade IV), 16 mixed oligoastrocytomas (9 grade III and 7 grade IV), and 5 malignant anaplastic oligodendrogliomas, corresponding to Smith grade D.

Analysis Parameters

The following parameters were considered for statistical analysis: patient age, symptoms at onset, duration of symptoms, symptoms at surgery, prior history of brain glioma, preoperative Karnofsky Performance Scale (KPS) score, surgical procedure (stereotactic

Table 1. Median survival time and log-rank test of equality of survival distributions by tumor grade and other prognostic factors for 113 cases of high-grade gliomas

Variable	Grade III glioma			Grade IV glioma		
	No.of cases *	MST (wks)	Log-rank p value	No.of cases	MST (wks)	Log-rank p value §
Patient age(yrs)			0.0055			0.0001
0 to 20	3(1)	108.9		2(1)	50.0	
21 to 40	10(3)	NA	(0.30)	9(4)	66.9	(0.87)
41 to 60	10(2)	94.0		30(12)	38.9	
>60	5(1)	41.4		44(17)	16.4	
Symptoms at presentation						
Seizures	15(5)	NA		18(10)	51.6	
Increased ICP	3(2)	171.3	(0.04)	6(4)	33.1	(0.007)
Deficit	10(1)	29.4		60(19)	21.0	
Other	—			1(0)	—	
Symptoms at surgery			0.1221			0.1435
Seizures	8(2)	NA		3(2)	60.3	
Increased ICP	1(1)	NA	(0.007)	1(0)	NA	(0.81)
Deficit	19(4)	87.7		81(31)	29.0	
KPS score			0.0551			0.0004
> 90 %	9(3)	NA		5(1)	50.1	
71% to 90%	14(4)	171.3	(0.23)	45(19)	36.3	(0.42)
≤ 70%	5(1)	53.6		35(12)	16.6	
Tumor location			0.0181			0.0638
Cortical	8(3)	135.4		23(25)	44.3	
Subcortical	17(4)	50.8	(0.26)	54(20)	24.6	(0.0001)
Midline	1(0)	171.3		5(0)	15.6	
Brain stem	3(0)	27.7		2(0)	38.3	
Cell type			0.1939			0.0023
Oligodendroglioma	5(1)	NA		—	—	
Oligoastrocytoma	9(3)	135.4	(0.91)	7(5)	70.1	(0.06)
Astrocytoma	19(4)	82.3		73(27)	26.2	

MST=median survival time; NA=not attained (>50% of cases remain alive); ICP=intracranial pressure; KPS= Karnofsky Performance Scale

* Numbers in parentheses indicate patients undergoing resection

§ Numbers in parentheses indicate p value of Wilcoxon tests of equality of percentage of patients resected in each factor group

biopsy or resection), tumor location (cortical, subcortical, midline, or brain-stem), tumor cell type (astrocytoma, oligoastrocytoma, or oligodendroglioma), tumor grade (III or IV), and postoperative radiotherapy and dose. Quality of survival was assessed by serial KPS scores obtained over the follow-up period.

Table 2. Median survival time and log-rank test of equality of survival distributions for 102 newly diagnosed cortical and subcortical of high-grade gliomas

Variable	Grade III gliomas (25 cases)			Grade IV gliomas (77 cases)		
	No.of cases	MST (wks)	Log-rank p value	No.of cases	MST (wks)	Log-rank p value
RT			0.6203			<0.0001
None	1	—		10	4.1	
< 40 Gy	1	87.7		12	13.3	
40 to 59 Gy	10	171.3		14	37.1	
> 60 Gy	13	98.4		41	40.8	
Treatment groups			0.7462			0.0527
Resection + RT ≥ 50 Gy	7	98.3		25	50.0	
Resection + RT <50 Gy	1	—		8	31.1	
Biopsy+ RT ≥50 Gy	16	135.4		28	33.0	
Biopsy+ RT < 50 Gy	1	NA		16	6.7	

* Only cortical and subcortical locations are considered (midline and brain stem tumors are excluded). RT=radiation therapy; MST=median survival time; NA=not attained

Tumors that reached or involved the cortical surface were classified as " cortical"; "subcortical" lesions included those located in the deep white matter, basal ganglia, and thalamus. "Midline" lesions included those in the corpus callosum, third ventricle, septal area, and hypothalamus. Brain stem lesions comprised midbrain and pontine locations only. Follow-up information was provided by clinic records, referring physicians, and by telephone calls to patients and families.

Statistical Analysis

The reference point for this study was the date of current diagnostic surgical procedure. The endpoint was survival to death or date of last follow-up review. Survival curves and median survival time (MST) were estimated based on Kaplan and Meier's nonparametric method. Log-rank tests were used to assess the strength of association between survival time and each of the parameters as a single variable. To assess the short-term as well as long-term effect of surgical treatment on survival time, the Smirnov test was also used.

RESULTS

Postoperative Mortality and Morbidity

Six deaths occurred within one month following 69 stereotactic biopsy procedures; one death was related to surgery, one to nonsurgical complications, and four to a rapidly deteriorating neurological course unrelated to stereotactic biopsy. Three patients had postoperative worsening of preoperative neurological deficit, transient in two and permanent in one.

There were no postoperative deaths among the 33 patients who underwent stereotactic resection or

among the 11 patients receiving nonstereotactic resection. Transient postoperative worsening of a preoperative deficit was noted in 7 patients, and a permanent postoperative deficit was noted in two patients.

Overall Survival

Median survival time was 30.1 weeks in 80 patients with grade IV gliomas; their 12-and 24-month survival rates were 27.1% and 9.7%, respectively. The 33 patients with grade III gliomas had a median survival of 87.7 weeks, with survival rates of 60.1% and 39.3% at 12 and 34 months, respectively.

Stratification Parameters

The survival distributions for the significant six prognostic factors were considered separately for grade III and grade IV patients and are summarized in Table 1. The number of patients in each clinical factor subgroup undergoing stereotactic resection is provided in order to study distribution similarities of patients undergoing biopsy versus resection.

Patient Age

The age distributions for patients with grade III and grade IV gliomas are illustrated in Figure 1. These four age groups were significantly different (log-rank test, $p < 0.0001$) and remained statistically significantly different for grade III as well as grade IV gliomas (p=0.0055 and 0.0001, respectively). As shown in Table 1, the proportion of patients undergoing biopsy alone in each of the age groups was not statistically different (Wilcoxon test, p=0.30 for grade III and p=0.87 for grade IV).

Symptoms

Patients presenting with seizures survived significantly longer than those presenting with increased ICP or progressive neurological deficit, both in grade III patients (MST not yet attained, 171 weeks, and 29 weeks, respectively; log-rank test, p=0.0023) and in grade IV patients (MST 52 weeks, 33 weeks, and 21 weeks, respectively; log-rank test, p=0.0007).

As indicated in Table 1, for patients undergoing biopsy and resection, Wilcoxon test showed p=0.04 for grade III tumors and p=0.007 for grade IV tumors in relation to symptoms at presentation; Wilcoxon tests showed p=0.07 for grade III tumors and 0.81 for grade IV tumors in relation to symptoms at surgery.

Karnofsky Performance Scale

Preoperative KPS score was strongly correlated with survival in patients with grade IV tumors (p=0.0004), but not in those with grade III tumors (p=0.0551), As shown in Table 1, the proportions of patients undergoing biopsy and resection were similar among the three KPS groups for grade III and IV (p=0.23 and 0.42, respectively).

Tumor Grade and Cell Type

Differences in survival rates for grade IV astrocytomas, grade IV oligoastrocytomas, grade III astrocytomas, grade III oligoastrocytomas, and malignant oligodendrogliomas were statistically significant ($p< 0.0001$). In addition, considering grade III and grade IV tumors separately, differences in survival rates according to cell type were significant in grade IV tumors (p=0.0023), but not in grade III tumors (p= 0.1939). The proportions of patients undergoing biopsy and resection in each cell type group, provided in Table 1, were not statistically different (Wicoxon test, p=0.91 for grade III and p=0.06 for grade IV).

Tumor Location

In grade IV gliomas, a cortical location was associated with the longest survival (MST 44.3 weeks), and a midline location (MST 15.6 weeks) with the shortest (p=0.0638). In grade III gliomas, deep hemispheric and cortical locations were associated with the longest survival (MST 171.3 weeks and 135.4 weeks, respectively) and brain-stem and midline locations with the shortest (MST 50.8 weeks and 27.7 weeks, respectively) (p=0.0181). As shown in Table 1, resec-

tions were rarely performed for midline and brainstem lesions. Therefore, the following analysis of survival after biopsy versus resection concerns only those 102 patients with lesions in cortical and subcortical locations.

Survival Following Resection and Biopsy

Considering all grade III and grade IV patients as a group, patients who underwent resection survived longer (MST 51.1 weeks) than those who had a stereotactic biopsy (MST 29 weeks). This differenc was not statistically significant with the log-rank test (p=0.21), which tends to emphasize long-term differences, but was significant with the Smirnov test (p=0.0008), which emphasizes short-term differences. In grade III glioma patients, difference in survival between biopsy (MST 98.2 weeks) and resection (MST 135.4 weeks) groups were not significant (log-rank test, p=0.66; Smirnov test, p=0.3413). However, grade IV patients who received tumor resection survived longer (MST 44 weeks) than those undergoing biopsy (MST 19 weeks) (log-rank test, p=0.0036; Smirnov test, p<0.0001).

Radiation Therapy

For the following treatment groups: resection and radiation dose of 50 Gy or greater or lesser, patients who received radiation doses between 40 and 59 Gy survived the longest (p<0.0001); those with radiation doses 60 Gy or over did not have significantly longer survival (Table 2). Patients with resected cortical and subcortical grade IV gliomas and radiation doses of 50 Gy or greater survived longer (MST 50.6 weeks) than those treated with irradiation (doses >50 Gy) following stereotactic biopsy (MST 33 weeks) (log-rank test, p=0.0527; Smirnov test, p=0.0326). Mean survival time in patients with subcortical grade IV gliomas receiving less than 50 Gy was 5.7 weeks in the biopsy group and 26 weeks in the resection group.

The study indicates that patients with malignant gliomas who completed radiation therapy (doses > 50 Gy) after resection of tumor tissue mass survived longer than those who received biopsy alone, even after adjustment for the effects of clinical prognostic factors.

DISCUSSION

There are several variables that affect survival in patients with gliomas: the tumor histology and proliferative capacity, the patient's age and performance (e.g. Karnofsky score), the extent of surgery, and the doses of radiation therapy or chemotherapy [10,11].

In the present series, patients lived longer following resection of the contrast-enhancing mass than those undergoing biopsy only for cortical and subcortical grade III and grade IV gliomas combined and for grade IV gliomas considered alone.

Reduction of tumor burden is theoretically supportable from a cytokinetic point of view, and aggressive resection for glial tumors should be associated with longer survival times [12-14].

Wood et al. [15] found significantly longer survival when postoperative CT scans revealed no residual contrast-enhanced tumor mass was correlated with time to tumor progression and prognosis; others did not.

High-grade gliomas comprise a mass of solid tumor tissue surrounded by parenchyma infiltrated by isolated tumor cells (which usually cannot be resected). In many grade IV gliomas, the apparent tumor tissue mass that can be resected represents a significant proportion of the global lesional volume (tumor tissue and infiltrated parenchyma). However, no significant difference in survival in grade III glioma patients undergoing resection or biopsy was noted because the small number of grade III patients in our data set provided little power to detect moderate differences. In addition, grade III gliomas tend to comprise a volume of edematous parenchyma infiltrated by isolated tumor cells with relatively small zone(s) of solid tumor tissue---a minor component of the global lesional volume, resection of which is probably cyto-

kinetically insignificant.

Clinical Factors

Some clinical factors associated with survival of patients with malignant gliomas have been well established in previous publications and confirmed by multivariate survival analyses [16,17]. These were considered in this study when comparing survival in biopsy and resection patients.

Tumor Grade

Survival in patients with brain gliomas was strongly associated with tumor grade in this series. However, uniformity in the classification schemes should be emphasized. The numerical grading scheme proposed by Daumas-Duport [2] presents distinctly different survival curves for each of the four grade classifications and excellent concordance in grade interpretation between independent pathologists. The Daumas-Duport system was selected for the present study, which considered grade III and grade IV survival data separately.

Patient Age

Age independently affected survival in these patients with glial neoplasms. The median survival rates of younger patients were longer than those of older patients with a similar tumor type. As noted in other multivariate analyses, young adults (20 to 40 years of age) survived longer; patients over 60 years old had the shortest survival. In the present series, the number of patients undergoing biopsy and resection was similar in each of these age groups.

Karnofsky Performance Scale

In the present series, preoperative Karnofsky Performance Scale status was an important and independent prognostic factor in the study model. Several other studies confirm these findings [18]. However, no significant differences in KPS scores existed between the biopsy and resection patient groups in our series.

Preoperative Symptoms

Neurological symptoms and signs affecting patients with glial neoplasms reflect the location of the tumor rather than the specific tumor histology [19]. The occurrence of seizures as the first symptom was significantly associated with longer survival after adjustment for the effects of the other covariates in the study model. However, other studies considered seizures to be dependent on other covariates, such as long duration of preoperative symptoms, tumor cell types (e.g. oligodendroglioma), and cortical location. In the present study, the distribution of patients treated by resection and biopsy within the preoperative symptom groups was not significantly different.

Tumor Location

Some authors believe that superficial tumors, more amenable to extirpation, are associated with longer survival than deep-seated lesions [19]. In the present series, tumor location was not significantly associated with survival, perhaps because many deep tumors were resected; subcortical location was associated with poor survival in patients with grade IV glioma who underwent biopsy as the sole surgical procedure.

Surgical Treatment

Objectives of surgery in a patient with a clinically and neuroradiographically probable malignant glioma are to establish a pathologic diagnosis, relieve mass effect on the surrounding brain, thereby improving patient symptoms and signs, and, if possible, surgical excision for maximum cytoreduction to possibly reduce the risk of immediate death by as much as half, especially in patients with midline shifts, except in cases of deep-seated small lesions; in these cases, a stereotactic procedure might be beneficial.

Excision also entails a lesser risk of neurological deterioration, by virtue of decompression, compared with a biopsy or minor resection. Microsurgical excision not only provides space by decompression, but significant cytoreduction also is provided by removal

of the radioresistant hypoxic neoplastic cells in patients with large tumors undergoing necrosis. Postoperative radiotherapy, following extensive surgical excision, has significantly improved survival rates in recent reports [1,19].

Radiation Therapy

Radiotherapy is so strongly correlated with survival in high-grade glial neoplasms that the benefit of surgery on survival in patients who have completed radiation therapy is unclear [20]. In our study models reported here, the benefit of resection on survival in patients who completed a course of radiation therapy (dose levels >50 Gy) was significant in patients with grade IV gliomas.

Prognostic Indicators

The literature is consistent in reporting good prognostic indicators such as younger age (<45 years), prediagnostic duration of less than 6 months, presentation with seizures instead of altered mental status, good performance score and lobar location (frontal lobe) of the tumor, and radical excision of the tumor[1,18,19]. Both survival and quality of life are favorably influenced by gross or near total excision of the tumor.

Outcome

Although many recent series report less than 1% overall mortality[1], morbidity and mortality rates are higher for patients undergoing biopsy alone; the short-term risk of death in these patients is twice as high compared with those undergoing craniotomy and debulking of the tumor.

In our series, there were 4.34% morbidity and 8.69% mortality within 30 days of biopsy, whereas there was no mortality except 20.3% morbidity after gross total or subtotal resection of the tumor within the same time period. This study indicated that patients with malignant glial tumors who completed radiation therapy (doses > 50 Gy) after resection of tumor mass survived longer than those who received biopsy alone, even after adjustment for the effects of clinical prognostic factors.

CONCLUSIONS

According to the available reports in the literature, high-grade glioma seems to be a disease with no cure, even with aggressive surgical and adjuvant treatments. However, long term survival is possible with good quality of life in some of these cases [21,22]. Surgical excision with maximum cytoreduction is shown to yield best results in some groups of patients. In selected malignant gliomas, resection of the tumor mass followed by radiation therapy is associated with longer survival times than radiation therapy after biopsy alone.

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