Free Survival Time of Recurrence and Malignant Transformation and Associated Factors in Patients with Supratentorial Low-Grade Gliomas

Ittichai Sakarunchai MD*, Rassamee Sangthong MD, PhD**,
Nakornchai Phuenpathom MD*, Monlika Phukaoloun MD***

** Division of Neurosurgery, Department of Surgery, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand*
*** Epidemiology Unit, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand*
**** Department of Pathology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand*

Objective: *To determine the recurrence and maliqnancy free survival time and associated factors with recurrence and malignant transformation of patients with low-grade gliomas after primary surgical resection.*
Material and Method: *The present study was retrospective. Patients who underwent surgery and were diagnosed with low-grade gliomas between January 2000 and October 2009 were recruited. Time to recurrence and malignant transformation were analyzed using Kaplan-Meier method and multivariate Cox proportional hazard regression models.*
Results: *Seventy-seven patients underwent surgery for low-grade glioma. The pathological reports were diffuse astrocytoma in 55 patients (71%), oligodendroglioma in 19 patients (25%), and oligoastrocytoma in three patients (4%). The types of tumor resection were biopsy in 39 patients (50%), subtotal resection 34 patients (44%), and total resection in four patients (5%). The overall mean time to follow-up was 40 months, the median recurrence and malignant transformation times were 14 and 24 months. The 5-year recurrence-free and malignant-free survival rate was 50% and 68%. Factors associated with tumor recurrence were age, sex, presenting symptoms, preoperative Karnofsky performance status (KPS) score, tumor volume, and contrast enhancement. None of these factors showed statistically significant association with malignant transformation.*
Conclusion: *One fourth of the patients had tumor recurrence and malignant transformation in a short period of time. Delayed recurrence and malignant transformation after primary resection are associated with several factors. The type of surgery especially total-subtotal resection might favor prognosis.*

Keywords: *Recurrence, Malignant transformation, Low-grade gliomas, Recurrence-free survival rate, Malignancy-free survival rate*

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Approximately half of newly diagnosed primary brain tumors originate from glial cells. Glial cell tumors are commonly classified by virulence into high-grade and low-grade levels. The treatment outcome of high-grade gliomas is still not always successful. Low-grade gliomas (LGG) generally have longer survival time than high-grade but tumor recurrence and malignant transformation are also fatal[1]. Thus, delay of progression or malignant transformation of LGG can prolong survival time and reduce morbidity.

Correspondence to:
Sakarunchai I, Division of Neurosurgery, Department of Surgery, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.
Phone: 074-451-400, Fax: 074-429-384
E-mail: it_swu039@hotmail.com

LGG are classified by WHO into diffuse astrocytomas, oligodendrogliomas, and mixed tumors[2]. Astrocytoma accounts for 30 to 40% of LGG and is more likely to recur and transform to high-grade tumors than the other two[3]. In Thailand, astrocytoma is the most common primary brain tumor accounting for 35% of all brain tumors[4].

The treatment can be varied from close observation to maximal surgical resection combined with postoperative radiation. The 5-year survival of patients after these treatments was 40 to 90%[5]. From recent studies, the recurrence and malignant transformation rate were about 40% and 20% respectively whereas the 5-year recurrence and malignancy free survival rates were 44% and 74% respectively[6].

Most of the previous studies have examined factors associated with prolonged overall survival but only a few of them have investigated the determinants of recurrence and malignant transformation after primary resection[7,8]. Factors associated with tumor recurrence were short duration of symptoms, large tumor size, preoperative neurological deficit, and presentation of contrast enhancement on MRI. Factors associated with malignant transformation were fibrillary astrocytoma, large tumor size, and inability to do gross total removal[9,10].

There is no established guideline or consensus in the treatment of patients with LGG. One of the reasons may be the paucity of studies, especially randomized controlled trials in the literature. The present study may help to increase the knowledge to establish the standard treatment in the future.

The present study aimed to examine the recurrence and malignancy-free survival profile and identify factors associated with recurrence and malignant transformation of LGG.

Material and Method

After the present study was reviewed for the reporting by the ethics committee (Faculty of Medicine, Prince of Songkla University) and given approval, a retrospective review of patients who underwent surgery for LGG between January 2000 and October 2009 from a hospital database and medical records was done. Eligibility criteria were age above 18 years, having tissue-proven diagnosis of supratentorial low-grade gliomas verified by WHO classification grade II (diffuse astrocytoma, oligodendroglioma, and oligoastrocytoma), undergoing surgery, and having a post-operative follow-up for at least two months.

Main variables obtained were baseline demographic characteristics and clinical data including age, sex, presenting symptoms, duration of symptoms, preoperative Karnofsky performance status score, pre- and post-operative imaging data, details of operation, pathological findings, adjuvant therapy, and treatment outcome.

Information on preoperative and post-operative MR imaging of the brain (T1-weight with and without contrast enhancement, T2-weight and FLAIR) included location, adjacent eloquent area, and presence of contrast enhancement of the tumor. Maximum preoperative tumor volume (cm^3) based on axial T1-weight with gadolinium by ellipsoid model (¶/6xAxBxC; A, B, C representing three largest perpendicular diameters in cms) was calculated. Postoperative MR imaging was performed to reexamine the amount of residual tumor at approximately six months or before that if patients had clinical deterioration. Resection was categorized into total resection, subtotal resection, and biopsy. Total and subtotal resections refer to gross tumor resection of more than 90% and more than 60% to 90% of total volume respectively. Biopsy refers to minimal tissue resection or gross tumor resection of less than 20% of total tumor volume.

Tumor recurrence or malignant transformation were defined as progressive growth of tumor after primary resection indicated by follow-up MR imaging compared to preoperative MRI results or undergoing secondary resection due to tumor progression. Histopathology remained unchanged in tumor recurrence but progressed to higher grade in tumor transformation. Recurrence and malignant transformation free periods were measured from the first surgery date to the date of diagnosis either by imaging or secondary surgery. Patients were given an appointment to visit every two months to follow-up their neurological functions measured by Glasgow outcome scales, otherwise patients or their close relatives were interviewed by telephone.

Statistical analysis

Descriptive analysis was used to examine baseline characteristics and relevant baseline clinical information. Recurrence-free and malignancy-free survival rates were estimated by Kaplan-Meier curves. Cox-proportional hazard models were used to identify variables associated with tumor recurrence and transformation using a significance level of $p<0.05$. Hazard ratios (HRs), 95% confidence interval (95% CI) and p-value were obtained from the best fitting model.

Results

Eighty-two patients were diagnosed with LGG. Five patients were excluded due to missing data and ambiguous pathological reports. Patient information is summarized in Table 1. All 77 patients underwent surgery.

The overall mean follow-up duration was 40 months for all patients (range 3-300 months). Five patients died (all due to severe infection after primary operation at 3, 4, 5, 5, and 6 months respectively), 23 patients (30%) were lost to follow-up (all-time for follow-up) due to stable disease and

Table 1. Demographic, clinical, and procedural characteristics of the patients (n = 77)

Characteristics	n (%)
Age (years)[a]	43 (18, 74)
18-40	34 (44.2)
>40	43 (55.8)
Sex	
Male	48 (62.3)
Female	29 (37.7)
Presenting symptoms	
Motor deficit	20 (26.0)
Headache	22 (28.6)
Seizure	37 (48.1)
Other	6 (7.8)
KPS score[a]	80 (40, 100)
<80	20 (26.0)
≥80	57 (74.0)
Duration of symptoms (days)[a]	
<30	34 (44.0)
≥30	43 (56.0)
Median (min, max)	40 (0, 980)
Characteristic on imaging	
Location	
Lobar	66 (85.7)
Deep	11 (14.3)
Contrast	
Enhancement on MRI	20 (26.0)
Non-enhancement on MRI	57 (74.0)
Mean tumor volume (cm^3)[b]	29 (2, 92)
Eloquent area	23 (30.0)
Pathology	
Diffuse astrocytoma	55 (71.4)
Oligodendroglioma	19 (24.7)
Oligoastrocytoma	3 (3.9)
Type of primary resection	
Biopsy	39 (50.7)
Subtotal removal	34 (44.0)
Total removal	4 (5.3)
Secondary resection	27 (35.0)
Mean tumor volume after primary resection (cm^3)[b]	25 (0, 98)
Adjuvant therapy	
Radiation	63 (81.8)
Chemotherapy	3 (3.9)
GOS	
Dead	5 (6.5)
Vegetative	2 (2.6)
Severe disability	8 (10.4)
Moderate disability	17 (22.1)
Good recovery	45 (58.4)
Duration of outcome (months)	
Time to follow-up[b]	39.50 (3.2-100.2)
Recurrence time[a]	14.11 (2.5-56.6)
Malignant transformation time[a]	23.68 (3.1-71.7)
Recurrence	20 (26.0)
Malignant transformation	15 (19.5)

[a] Median (min, max)
[b] Mean (min, max)
KPS = Karnofsky performance status score; GOS = Glasgow outcome scale

being uncontactable. The median recurrence time was 14 months, the median malignant transformation time was 24 months, twenty patients (26%) had recurrence (12 patients proved by surgery, eight patients proved by imaging), and 15 patients (20%) had malignant transformation. The 5-year recurrence-free survival rate was 50% and the 5-year malignancy-free survival rate was 68% (Fig. 1, 2). The median recurrence-free survival time was 56 months and the median malignancy-free survival time was 68 months.

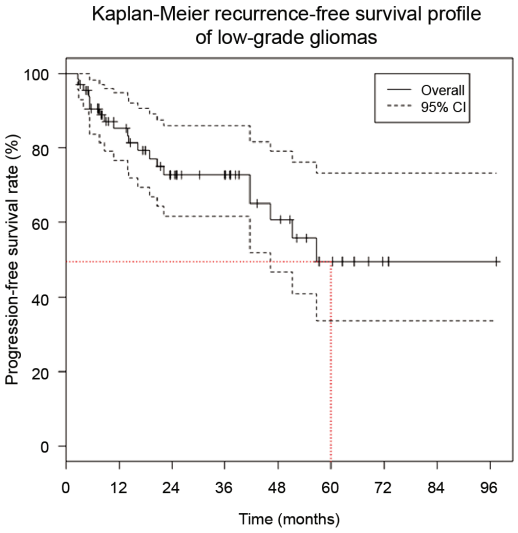

Fig. 1 Kaplan-Meier graph showing recurrence-free survival.

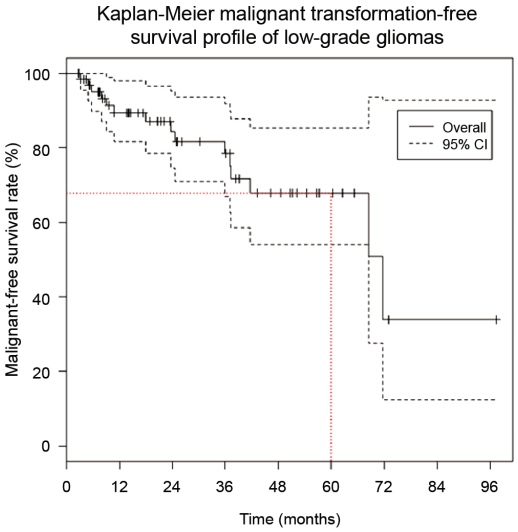

Fig. 2 Kaplan-Meier graph showing malignancy-free survival.

Table 2. Prognostic factors for tumor recurrence from multivariate Cox proportional hazards regression

Variables	5-year recurrence-free survival (%)	Adjusted HR (95% CI)	p-value*
Age (years)			0.005
18-40	83	1	
>40	69	10.8 (1.5, 78.5)	
Sex			<0.001
Male	88	1	
Female	53	12.5 (2.6, 58.8)	
Presenting symptom			0.01
Headache	73	1	
Motor deficit	82	0.03 (0, 0.35)	
Seizure	79	0.9 (0.2, 5.7)	
Behavior change	100	0.4 (0.05, 3.0)	
KPS score			<0.001
<80	62	1	
≥80	80	0.01 (0, 0.2)	
Duration of symptoms (days)			0.101
<30	70	1	
≥30	79	3.9 (0.7, 20.6)	
Contrast			0.002
No enhancement	79	1	
Enhancement	62	18.2 (2.5, 131.6)	
Tumor volume (cm^3)			0.031
<20	76	1	
20-40	78	0.04 (0, 0.63)	
>40	72	1.2 (0.2, 7.7)	
Eloquent area			0.104
Yes	76	1	
No	76	4.6 (0.7, 31.6)	
Type of surgery			0.135
Subtotal-total	89	1	
Biopsy	59	2.9 (0.7, 11.7)	
Pathology			0.832
Oligodendroglioma	78	1	
Diffuse astrocytoma	73	3.7 (0.7, 20.9)	
Oligoastrocytoma	100	0 (0, Inf)	
Radiation			0.065
Yes	76	1	
No	76	3.6 (0.9, 13.9)	

* Likelihood ratio test
HR = hazard ratio; Inf = infinity

Table 2 shows prognostic factors of tumor recurrence identified by the Cox proportional hazards model that included older age, female, presenting with headache, poor preoperative Karnofsky performance status (KPS) score, large tumor volume, and contrast enhancement.

Table 3 demonstrates factors associated with malignant transformation and no variables were identified as being significant but patients who were undergoing a biopsy only showed increased risk.

Discussion

In the present study, the median times for tumor recurrence and malignant transformation were shorter than previous studies[6,11]. This might result from inadequate resection or sub-optimal adjuvant therapy. The result was disappointing with high rates

Table 3. Prognostic factors for malignant transformation from multivariate Cox proportional hazards regression

Variables	5-year malignant transformation-free survival (%)	Adjusted HR (95% CI)	p-value*
Age (years)			0.114
18-40	84	1	
>40	79	3.1 (0.7, 13.2)	
Sex			0.114
Male	79	1	
Female	89	0.2 (0.03, 1.7)	
Presenting symptom			0.906
Headache	78	1	
Motor deficit	71	1.13 (0.1, 16.1)	
Seizure	84	0.7 (0.1, 3.9)	
Behavior change	100	0 (0, Inf)	
KPS score			0.759
<80	73	1	
≥80	84	1.4 (0.2, 10.8)	
Duration of symptoms (days)			0.728
<30	69	1	
≥30	89	0.7 (0.1, 3.9)	
Contrast			0.776
No enhancement	77	1	
Enhancement	80	0.7 (0.04, 10.7)	
Tumor volume (cm^3)			0.262
<20	79	1	
20-40	78	1.4 (0.2, 8.9)	
>40	92	0.1 (0.01, 2.5)	
Eloquent area			0.953
Yes	70	1	
No	85	1.0 (0.1, 15.4)	
Type of surgery			0.06
Subtotal-total	88	1	
Biopsy	74	4.4 (0.9, 22.0)	
Pathology			0.495
Oligodendroglioma	93	1	
Diffuse astrocytoma	76	2.3 (0.2, 29.0)	
Oligoastrocytoma	100	0 (0, Inf)	
Radiation			0.023
Yes	76	1	
No	50	0.1 (0, 1.5)	

* Likelihood ratio test

of recurrence and malignant transformation and short durations of recurrence-free and malignancy-free survival. The pathology of gliomas may not be identical throughout the tumor, some part maybe low grade with other parts being malignant in situ. Inadequate resection may yield a wrong diagnosis because minimal tissue may not represent the pathology of the tumor mass.

An interesting point revealed by the Cox models for each outcome (recurrence and malignant transformation) is that a tumor biopsy, although not statistically significant, appear to increase the risk for recurrence and 4-fold to malignant transformation 3-fold (Table 2, 3). These findings correspond with prior studies[5,6,11,12] showing an association of decreased tumor recurrence and malignant transformation rates after maximal resection.

The present study also showed that contrast enhancement of the tumor was associated with increased risk tumor recurrence, corresponding with

a previous study[13] that reported 96% recurrence in glioblastomamultiforme and 20% in LGG. Most of the LGG demonstrated no contrast enhancement. In another study enhancement increased malignant transformation and recurrence rate, decreasing recurrence-free survival and malignancy-free survival[14].

Although not statistically significant, diffuse astrocytomas may increase the risk for malignant transformation compared to other types (oligodendrogliomas, oligoastrocytomas) but the numbers of other types, especially oligoastrocytomas, was small. The present study did not exclude gemistocyte type of astrocytoma because of the small number, but its inclusion may have affected the rate of malignant transformation.

The extent of surgical removal in our institution may be limited by lack of high cost technology assisting equipment such as neuro-navigators, PET scan or somatosensory evoked potential. The authors have only intraoperative ultrasound, which has a limited use in LGG. The functional MR imaging in our institution not routinely used to identify the extent of tumor mass, is frequently used to separate radiation injury or necrosis from tumor recurrence or malignant transformation.

Radiation and chemotherapy have shown benefits in improving progression-free survival but with no significant increase in overall survival[15,16]. Chemotherapy play a role in LGG in patients with deletion of 1p/19q in anaplastic oligodendroglioma, leading to a better response to treatment[17] Chemotherapy cannot be evaluated in our institution because it was not routinely used. The authors tried some chemotherapy regimens only in the patients with recurrence or malignant transformation.

The limitation of the present study was the small number of patients with many receiving only a biopsy (50%) and this may have led to a high recurrence and malignant transformation rate. As stated above, the biopsy procedure received only a small tissue volume from a non-specific area of the tumor with heterogenous nature. In addition, the high rate of loss to follow-up of the patients after treatment may have led to an inaccurate determination of the time of true recurrence and malignant transformation.

Conclusion

To date, the LGG is not easy to treat. There is no consensus for the treatment.

Recurrence and malignant transformation after primary resection are associated with several factors. In addition, truly, its natural course is not benign. Understanding the factors influencing tumor recurrence and malignant transformation may help to improve the outcome. However, the only way to potentially increase survival time and delay recurrence and malignant transformation is maximal tumor resection. We recommend that treatments can be performed by a team that includes neuro-surgeons, neuropathologists, neurooncologists, and neuroradiologists for more accuracy outcome of this tumor.

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What is already known on this topic?

In low-grade gliomas, most patients die from tumor recurrence and malignant transformation. Few studies have determined the factors associated with recurrence and malignant transformation after primary resection. There are no established guidelines or consensus in the treatment of patients with low-grade gliomas.

What this study add?

This report describes factors associated with recurrence and malignant transformation. In addition, it examines the recurrence and malignancy-free survival profile. Understanding these factors may help to predict or improve the outcome of the management.

Potential conflicts of interest

None.

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การศึกษาถึงระยะเวลาและปัจจัยที่มีผลต่อการกลับเป็นซ้ำและการกลายตัวเป็นมะเร็งตลอดจนระยะเวลาของการมีชีวิตรอดของเนื้องอกสมองชนิด low-grade gliomas

อิทธิชัย ศักดิ์อรุณชัย, รัศมี สังข์ทอง, นครชัย เผื่อนปฐม, มัลลิกา ภูเก้าล้วน

วัตถุประสงค์: เพื่อหาระยะเวลาและปัจจัยที่มีผลต่อการกลับเป็นซ้ำและการกลายตัวเป็นมะเร็ง ตลอดจนระยะเวลาของการมีชีวิตรอดของเนื้องอกสมองชนิด low-grade gliomas หลังจากการผ่าตัด

วัสดุและวิธีการ: วิเคราะห์ย้อนหลังจากเวชระเบียนของผู้ป่วยที่เข้ารับการรักษาโดยการผ่าตัดและวินิจฉัยว่าเป็น low-grade gliomas ตั้งแต่เดือนมกราคม พ.ศ. 2543 ถึง เดือนตุลาคม พ.ศ. 2552 โดยใช้วิธีวิเคราะห์หลายตัวแปรเพื่อเปรียบเทียบและหาปัจจัยที่มีผลดังกล่าวตลอดจนหาอัตราการรอดชีวิตโดยวิธี Kaplan-Meier และ multivariate Cox proportional hazard regression models

ผลการศึกษา: จำนวนผู้ป่วยทั้งหมด 77 ราย พบว่ามีจำนวนผู้ป่วยที่เป็นเนื้องอกชนิด diffuse astrocytoma 55 ราย (71%), oligodendroglioma 19 ราย (25%) และ oligoastrocytoma 3 ราย (4%) แยกเป็นการผ่าตัดแบบสุ่มตรวจชิ้นเนื้อ 39 ราย (50%) ผ่าตัดออกแบบบางส่วน 34 ราย (44%) และผ่าตัดออกทั้งหมด 4 ราย (5%) ระยะเวลาที่ติดตามไปทั้งหมด 40 เดือน ค่าเฉลี่ยของระยะเวลาการกลับเป็นซ้ำและการกลายตัวเป็นมะเร็งอยู่ที่ 14 และ 24 เดือน ตามลำดับ อัตราของการปลอดโรคที่ 5 ปี ของการกลับเป็นซ้ำและการกลายตัวเป็นมะเร็งอยู่ที่ร้อยละ 50 และ 68 ตามลำดับ ส่วนปัจจัยที่มีผลต่อการกลับเป็นซ้ำได้แก่ อายุ เพศ อาการนำ สภาพของผู้ป่วยก่อนผ่าตัด ปริมาตรของเนื้องอก และการขึ้นสีของเนื้องอกจากภาพทางรังสีวิทยา แต่ไม่พบปัจจัยที่มีผลต่อการกลายตัวเป็นมะเร็งของเนื้องอกสมอง low-grade gliomas

สรุป: ผู้ป่วยประมาณร้อยละ 25 จะมีระยะเวลาของการกลับเป็นซ้ำและการกลายตัวเป็นมะเร็งในช่วงสั้น ๆ ซึ่งมีหลายปัจจัยที่มีผลดังกล่าว แต่การผ่าตัดเอาเนื้องอกออกให้ได้มากที่สุด จะเพิ่มระยะเวลาของการกลับเป็นซ้ำ และการกลายตัวเป็นมะเร็งของเนื้องอกสมองชนิด low-grade gliomas ได้นานมากขึ้น