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# Photodynamic therapy during second surgery for recurrent gliomas improves survival

Yongning Li [a], Fang Wang [b], Bo Li [c,*]

[a] Department of Emergency, the First Affiliated Hospital of Da Lian Medical University, Dalian, Liaoning 116011, China
[b] Department of Neurosurgery, the Second Affiliated Hospital of Harbin Medical University, Harbin 150086, China
[c] Department of Neurosurgery, Huangyan Hospital, Wenzhou Medical University, Taizhou, Zhejiang 318000, China

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ABSTRACT

*Background:* Glioma accounts for most central nervous system tumors, and the degree of invasion and malignancy are higher in the recurrent glioma. Photodynamic therapy (PDT) is an effective strategy in glioma. This study aimed to explore the risk factors for re-recurrence after a second glioma surgery and the effects of PDT on re-recurrence.

*Methods:* This was a retrospective study in the Second Affiliated Hospital of Harbin Medical University in China, and 43 patients that received the secondary surgery for recurrent glioma were included. The Kaplan-Meier test and Cox proportional hazard method were used to analyze.

*Results:* The total re-recurrence rate after the second surgery for recurrent glioma was 48.84%. When the age increased by 1, the risk of re-recurrence increased 1.065 times (95% CI 1.000–1.134, $P = 0.049$). High matrix metalloproteinase (MMP) 2 expression was associated with a significantly higher risk of re-recurrence than low MMP2 expression (HR = 25.550, 95% CI 3.190–204.650, $P = 0.002$). Pathological grades IV and III were associated with a significantly higher risk of re-recurrence than pathological grade II (HR = 17.121, 95% CI 2.345–124.986, $P = 0.005$; HR = 2863.470, 95% CI 100.697–81,427.197, $P < 0.001$). PDT decreased the risk of re-recurrence (HR = 25.550, 95% CI 3.190–204.650, $P = 0.002$) and increased survival time (HR = 3.611, 95% CI 1.012–12.888, $P = 0.048$).

*Conclusion:* The age, MMP2 expression, and pathological grade are independent risk factors for re-recurrence after a second surgery for recurrent glioma. PDT during the second surgery decreased the risk of re-recurrence and increased survival time.

## 1. Introduction

Presently, there are more than 120 kinds of malignant brain tumors, and glioma accounts for approximately 80% of them [1,2]. It is characterized by its infiltrative nature, extreme aggression, and rapid proliferation. In China, glioma is the most common tumor in the central nervous system [3]. Therefore, early diagnosis and effective treatment are crucial, particularly for glioblastoma, a type of high-grade glioma [4]. Although treatments such as drugs, surgical intervention, radiotherapy, chemotherapy, and immunotherapy have been developed, only 3–5% of patients with glioblastoma live over 3 years [5,6].

Clinically, the recurrence rate of glioma is quite high and approaches 100% for glioblastoma [7]. Ninety percent of recurrent gliomas occur at the edge of the tumor after resection due to the tumor's characteristics [8]. The degrees of invasion and malignancy are higher upon recurrence after the surgery in patients with glioma [9]. Thus, treatment for recurrent glioma is more important. Currently, there are many treatment alternatives for recurrent glioma, including reirradiation and temozolomide [10]. Photodynamic therapy (PDT) is a treatment that involves the administration of a photosensitive drug followed by irradiation with a laser at a specific light wavelength, and the PDT is an effective method for glioma [1,9]. It is an oxidative therapy and the presence of oxygen is essential. However, few studies have concentrated on the disease development and re-recurrence after a second surgery for recurrent glioma in human patients, and the effect of PDT on re-recurrence after a second surgery for recurrent glioma was also not

*Abbreviations:* PDT, Photodynamic therapy; KPS, Karnofsky Performance Score; MMP, matrix metalloproteinase.

* Corresponding author.
*E-mail address:* libo8632344@163.com (B. Li).

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explored. Therefore, the aims of this study were to observe the effects of clinical data and PDT on the re-recurrence of patients with recurrent glioma after a second surgery, and to explore the independent risk factors for re-recurrence by a retrospective cohort study.

## 2. Methods

Data were retrieved from the Medical Record System of the Second Affiliated Hospital of Harbin Medical University. Ethical approval was waived by the Ethics Committee of the Second Affiliated Hospital of Harbin Medical University in view of the retrospective nature of the study and all the procedures being performed were part of the routine care. Patients aged 18 years old or older who underwent a second surgery for recurrent glioma from December 2017 to January 2019 were included in this study. All the patients were treated with radiotherapy and chemotherapy before and after the surgery. However, the patients with primary cancers in other organs and secondary glioma were excluded.

Surgical indications for recurrent glioma included the following: 1. clinical symptoms (increased intracranial pressure and neurological signs) were obvious or severe; 2. imaging presentation such as an operative area with high density or partly or all low density, cystic spaces, severe cerebral edema, and brain tissue or tumor tissue expansion were observed; 3. the patients was relatively young and had a good general state without changes in the function of important organs. Additionally, the patients in whom the residual depth of tumor resection during the second surgery was less than 1 cm were recommended to undergo PDT.

For PDT, it was used as additional intraoperative treatment. The photosensitizer Hematoporphyrin (5ml: 25 mg; Milelonge Pharma; Chongqing; China) was infused intravenously 48 h before craniotomy, and 5 mg/kg was added to 250 ml normal saline for intravenous drip. The patient should be protected from light during and after the infusion. After the tumor bulk had been resected as extensively as possible either 1 or 2 sites of probable tumor invasion in the bottom of resection cavity were irradiated superficially with a 630 nm red laser for 20 min (120 J/$cm^2$) at a power density of 100 mW/$cm^2$.

The clinical data of the patients, including age, gender, type of second surgery, WHO pathological grade, primary histology, Karnofsky Performance Score (KPS), re-recurrence time, distant metastasis, survival time, and matrix metalloproteinase (MMP) 2 expression, as well as and IDH1 mutation, were collected in this study. The death date was according to the Medical Record System and confirmed via telephone. The survival time was calculated from the second surgery date to the death date. The re-recurrence time was calculated from the second surgery date to the re-recurrence ascertained via MRI. All the patients were regularly reexamined, and when the glioma in the brain was found via MRI was defined as re-recurrence. All the patients were followed up for 24 months.

### 2.1. Statistical analysis

All statistical analyses were performed in SPSS 20.0. The quantitative data were expressed as the mean ± standard deviation (SD), and the differences were detected by *t*-test. The ordinal data were expressed as frequencies, and the differences between the two groups were observed by the Chi-squared test. The survival time was analyzed by the Kaplan-Meier test, and the Cox proportional hazard method was used to explore the independent predictors of re-recurrence. $P < 0.05$ represented significant differences.

## 3. Results

### 3.1. Patients' characteristics

The medical records of 51 patients were examined. However, 5 patients with primary cancer of another organ and 3 patients lost to follow-up were excluded. Ultimately, 43 patients were included in this study. Of these 43 patients, aged 55 ± 13 years old, 20 were male and 23 were female. Twenty-one (48.84%) were re-recurrent after the second surgery for glioma, and 22 (51.16%) were not. Other characteristics of these patients are listed in Table 1.

### 3.2. The differences in patients' characteristics in the re-recurrence group and non-re-recurrence group

The patients were grouped into the re-recurrence group and the non-re-recurrence group, and the differences were assessed by independent samples *t*-test and Chi-squared analysis. The age in the re-recurrence group (63.8 ± 8.5 years old) was higher than that in the non-re-recurrence group (47.0 ± 10.4 years old) ($P< 0.05$). The KPS in the re-recurrence group (71.4 ± 13.9) was significantly lower than that in the non-re-recurrence group (85.0 ± 11.0) ($P< 0.05$). Additionally, IDH1 mutation, primary histology, distant metastasis, MMP2 expression, pathological grade, and PDT in the two groups also showed significant differences ($P< 0.05$). However, the gender and type of surgery in the two groups showed no significant differences (Table 2).

### 3.3. The differences in the patients' characteristics in the PDT group and non-PDT group

According to the PDT during the second surgery for glioma, the patients were grouped into the PDT group and non-PDT group, and the differences were assessed by independent samples *t*-test and Chi-squared analysis. After the surgery, the KPS in the PDT group (83.2 ± 12.9) was significantly higher than that in the non-PDT group (74.6 ± 14.1) ($P< 0.05$), and the re-recurrence rate showed a similar trend ($P< 0.05$). However, the age, gender, IDH1 mutation, primary histology, distant

**Table 1**
Patients' characteristics.

| Index | Patients, n (%) |
|---|---|
| Gender | |
| male | 20 (46.51%) |
| female | 23 (53.49%) |
| Age (years old) | |
| < 40 | 6 (13.95%) |
| 40–60 | 20 (46.51%) |
| > 60 | 17 (39.54%) |
| Type of surgery | |
| Total resection | 24 (55.81%) |
| Debulking Resection | 19 (44.19%) |
| Primary histology | |
| Glioblastoma | 11 (25.58%) |
| Anaplastic astrocytoma | 5 (11.63%) |
| Oligoastrocytoma | 9 (20.93%) |
| Astrocytoma | 9 (20.93%) |
| Anaplastic oligoastrocytoma | 9 (20.93%) |
| Pathological grade | |
| II | 18 (41.86%) |
| III | 14 (32.56%) |
| IV | 11 (25.58%) |
| Karnofsky Performance Score (KPS) | |
| ≥ 80 | 25(58.14%) |
| < 80 | 18 (41.86%) |
| Re-recurrence | |
| Yes | 21 (48.84%) |
| No | 22 (51.16%) |
| Distant metastasis | |
| Yes | 4 (9.30%) |
| No | 39 (90.70%) |
| MMP2 expression | |
| High | 20 (46.51%) |
| Low | 23 (53.49%) |
| IDH1 mutation | |
| Yes | 23 (53.49%) |
| No | 20 (46.51%) |

**Table 2**
Results of patients' characteristics in re-recurrence group and non-re-recurrence group.

| Index | Re-recurrence | | $t/\chi^2$ | $P$ |
|---|---|---|---|---|
| | No | Yes | | |
| Age (years old) | 47.0 ± 10.4 | 63.8 ± 8.5 | 5.767 | < 0.001 |
| Gender, n (%) | | | 0.220 | 0.639 |
| Male | 9 (40.91%) | 11 (52.38%) | | |
| Femal | 13 (59.09%) | 10 (47.62%) | | |
| IDH1 mutation, n (%) | | | 8.656 | 0.003 |
| No | 5 (22.73%) | 15 (71.43%) | | |
| Yes | 17 (77.27%) | 6 (28.57%) | | |
| Karnofsky Performance Score (KPS) | 85.0 ± 11.0 | 71.4 ± 13.9 | 3.559 | 0.001 |
| Primary histology, n (%) | | | 59.872 | < 0.001 |
| Glioblastoma | 1 (4.55%) | 10 (47.62%) | | |
| Anaplastic astrocytoma | 4 (18.18%) | 1 (4.76%) | | |
| Oligoastrocytoma | 7 (31.82%) | 2 (9.52%) | | |
| Astrocytoma | 6 (27.27%) | 3 (14.29%) | | |
| Anaplastic oligoastrocytoma | 4 (18.18%) | 5 (23.81%) | | |
| Distant metastasis, n (%) | | | 2.638 | 0.048 |
| Yes | 0 (0%) | 4 (19.05%) | | |
| No | 22 (100.00%) | 17 (80.95%) | | |
| MMP2 expression, n (%) | | | 4.701 | 0.030 |
| Low | 16 (72.73%) | 7 (33.33%) | | |
| High | 6 (27.27%) | 14 (66.67%) | | |
| Pathological grade, n (%) | | | 59.093 | < 0.001 |
| II | 13 (59.09%) | 5 (23.81%) | | |
| III | 8 (36.36%) | 6 (28.57%) | | |
| IV | 1 (4.55%) | 10 (47.62%) | | |
| Photodynamic therapy, n (%) | | | 3.917 | 0.048 |
| Yes | 13 (59.09%) | 6 (28.57%) | | |
| No | 9 (40.91%) | 15 (71.43%) | | |
| Type of surgery, n (%) | | | 1.369 | 0.242 |
| Total resection | 13 (59.09%) | 11 (52.38%) | | |
| Debulking Resection | 9 (40.91%) | 10 (47.62%) | | |

**Table 3**
Results of patients' characteristics in photodynamic therapy group and non-photodynamic therapy group.

| Index | Photodynamic therapy | | $t/\chi^2$ | $P$ |
|---|---|---|---|---|
| | No | Yes | | |
| Age (years old) | 55.0 ± 12.4 | 55.5 ± 13.4 | 0.131 | 0.896 |
| Gender, n (%) | | | 0.678 | 0.654 |
| Male | 13 (54.17%) | 7 (36.84%) | | |
| Female | 11 (45.83%) | 12 (63.16%) | | |
| IDH1 mutation, n (%) | | | 0.043 | 0.836 |
| No | 12 (50.00%) | 8 (42.11%) | | |
| Yes | 12 (50.00%) | 11 (57.89%) | | |
| Karnofsky Performance Score (KPS) | 74.6 ± 14.1 | 83.2 ± 12.9 | 2.050 | 0.047 |
| Primary histology, n (%) | | | 1.144 | 0.955 |
| Glioblastoma | 6 (25.00%) | 5 (26.32%) | | |
| Anaplastic astrocytoma | 3 (12.50%) | 2 (10.53%) | | |
| Oligoastrocytoma | 6 (25.00%) | 3 (15.79%) | | |
| Astrocytoma | 4 (16.67%) | 5 (26.32%) | | |
| Anaplastic oligoastrocytoma | 5 (20.83%) | 4 (21.04%) | | |
| Distant metastasis, n (%) | | | 0.080 | 0.777 |
| Yes | 3 (12.50%) | 1 (5.26%) | | |
| No | 21 (87.50%) | 18 (94.74%) | | |
| MMP2 expression, n (%) | | | 0.678 | 0.410 |
| Low | 11 (45.83%) | 12 (63.16%) | | |
| High | 13 (54.17%) | 7 (36.84%) | | |
| Pathological grade, n (%) | | | 0.018 | 0.991 |
| II | 10 (41.67%) | 8 (42.11%) | | |
| III | 8 (33.33%) | 6 (31.58%) | | |
| IV | 6 (25.00%) | 5 (26.31%) | | |
| *Re*-recurrence, n (%) | | | 3.917 | 0.048 |
| Yes | 15 (62.50%) | 6 (31.58%) | | |
| No | 9 (37.50%) | 13(68.42%) | | |
| Type of surgery, n (%) | | | 0.307 | 0.580 |
| Total resection | 12 (50.00%) | 12 (63.16%) | | |
| Debulking Resection | 12 (50.00%) | 7 (36.84%) | | |

metastasis, MMP2 expression, pathological grade, and type of surgery in the two groups showed no significant differences (Table 3).

### 3.4. The difference of re-recurrence of PDT and non-PDT in total resection and debulking resection

The patients were grouped according to total resection and debulking resection. In the total resection group, the re-recurrence of PDT was significant lower than that of non-PDT ($P< 0.05$). While, in the debulking resection group, the re-recurrence of PDT had no differences compared with that of non-PDT (Table 4).

### 3.5. The factors of re-recurrence after multivariate Cox regression analysis

To explore the independent risk factors of re-recurrence, the significant factors in univariate analysis (age, IDH1 mutation, KPS, primary histology, distant metastasis, MMP2 expression, pathological grade and PDT were considered as independent variables and the re-recurrence was considered a dependent variable, multivariate stepwise Cox regression analysis was performed using the forward method. The results showed that the factors of age, MMP2 expression, pathologic grade and PDT were independent risk factors for re-recurrence. When the age increased by 1, the risk of re-recurrence increased 1.065 times (95% CI 1.000–1.134, $P= 0.049$). High MMP2 expression (the percentage of positive cells > 50% via immunohistochemical staining) was associated with a significantly higher risk of re-recurrence than low MMP2 expression (HR = 25.550, 95% CI 3.190–204.650, $P= 0.002$), and PDT was associated with a significantly lower rate of re-recurrence than no PDT (HR = 3.141, 95% CI 1.055–9.351, $P= 0.040$). Additionally, pathological grade III was associated with a significantly higher risk of re-recurrence than pathological grade II (HR = 17.121, 95% CI 2.345–124.986, $P= 0.005$), and pathological grade IV was associated with a significantly higher risk of re-recurrence than pathological grade II (HR = 2863.470, 95% CI 100.697–81,427.197, $P< 0.001$) (Table 5).

### 3.6. The survival time after PDT during the second surgery for recurrent glioma

All the patients in this study in both groups received radiochemotherapy after the second surgery for glioma. However, the patients who had not received PDT for economic reasons were divided into the non-PDT group. The survival time in the PDT group ($12.9 \pm 4.5^{+}$ m) was significantly higher than that in the non-PDT group ($10.7 \pm 4.4^{+}$ m) ($P< 0.05$) (Fig. 1).

**Table 4**
The re-recurrence of PDT and non-PDT in total resection and debulking resection.

| | | Total resection | | Debulking resection | |
|---|---|---|---|---|---|
| | | PDT | Non-PDT | PDT | Non-PDT |
| ***Re*-recurrence** | Yes | 3 | 8 | 3 | 7 |
| | No | 9 | 4 | 4 | 5 |
| | | $X^2 = 4.196$; $P = 0.041$[a] | $X^2 = 0.178$; $P = 0.673$[c] | $X^2 = 0.425$; $P = 0.515$[d] | |
| | | $X^2 = 0.652$; $P = 0.419$[b] | | | |

a: compared with the non-PDT in total resection; b: compared with the PDT in debulking resection; c: compared with the non-PDT in debulking resection; d: compared with the non-PDT in debulking resection.

**Table 5**
P values for multivariate Cox regression analysis on re-recurrence.

| Index | B | SE | WALD | P | HR | 95% CI |
|---|---|---|---|---|---|---|
| Age | 0.063 | 0.032 | 3.867 | 0.049 | 1.065 | 1.000–1.134 |
| MMP2 expression | | | | | | |
| Low | – | – | – | – | 1 | – |
| High | 1.145 | 0.557 | 4.230 | 0.040 | 3.141 | 1.055–9.351 |
| Pathological grade | | | | | | |
| II | – | – | – | – | 1 | – |
| III | 2.840 | 1.014 | 7.842 | 0.005 | 17.121 | 2.345–124.986 |
| IV | 7.960 | 1.708 | 21.718 | 0.000 | 2863.470 | 100.697–81,427.197 |
| Photodynamic therapy | | | | | | |
| No | – | – | – | – | 1 | – |
| Yes | 3.241 | 1.062 | 9.318 | 0.002 | 25.550 | 3.190–204.650 |

## 4. Discussion

In this study, the total re-recurrence rate after the second surgery for recurrent glioma in patients was 48.84%. With increased age, MMP2 expression, or WHO pathological grade, the risk of re-recurrence after the second surgery for recurrent glioma in patients was increased.

However, the gender, IDH1 mutation, primary histology, distant metastasis, KPS, and type of surgery of the patients were not independent risk factors of re-recurrence. Additionally, PDT during the second surgery for recurrent glioma could decrease the rate of re-recurrence to 31.58%, and PDT increased the survival time from MD 11.1 months to MD 12.8 months.

Age is an important research indicator for postoperative recovery in patients with tumors [11]. After reaching a certain age, the body's defense and resistance decrease gradually with the increase in age, and the ability to recover after tumor resection is also significantly reduced [11]. In this study, the age of the non-re-recurrent patients was approximately 40 years old, while it was 60 years old for the re-recurrent patients. Many studies showed the similar results. Tan et al. found that younger age at surgery was an independent predictor of favorable epileptic seizure control after glioma resection in adults [12]. Little et al. reported that older age was associated with an increased risk of glioma [13]. So the age was closely related to the risk of glioma. Oberheim Bush and Chang reported that patients with an age younger than 40 years old were stratified into low risk for glioma in adults [14]. We also found that when the age was over 40 years old, the risk of re-recurrence increased 1.065 times as age increased by 1. Therefore, the age was an important independent risk factor for re-recurrence after the second surgery for recurrent glioma, and we recommended that the patients with the age more than 40 years old should received the PDT in the second surgery for recurrent glioma.

The expression of MMPs was minimal in normal tissues, and malignant tumors could induce invasion and recurrence rapidly by degrading proteins in the extracellular matrix by MMPs [15]. Previous studies showed that glioma tissues could secrete large amounts of MMP2, and the risk of invasiveness and recurrence of glioma increased with the increase in MMP2 expression [16]. Similar to other malignant tumors, glioma showed destructive invasive growth, and even though the operation was considered a total resection, there was still a high recurrence rate. In this study, with the increase in MMP2 expression, the risk of re-recurrence and re-recurrence increased. The reasons are as follows. First, MMP2 was closely related to tumor angiogenesis, and angiogenesis was an important pathological basis for malignant tumor recurrence and invasion [17]. Second, an inflammatory response was induced through the destruction of normal tissue by MMP2, which ultimately affected the recurrence of the tumor [18]. Zhou et al. concluded that higher expressions of MMP2 indicate poor prognosis in glioma recurrence [19]. Zhang et al. reported that the MMP-2 were independent prognostic factors for glioma [20]. We also found that higher the expression of MMP2, the higher the risk of re-recurrence for glioma was. Therefore, MMP2 expression was also an important independent risk factor for re-recurrence after the second surgery for recurrent glioma patients, and the patients with higher the expression of MMP2 should received the PDT in the second surgery for recurrent glioma.

Low-grade gliomas (WHO grade I-II) were well differentiated, and the prognosis was good, although these tumors were not benign tumors. High-grade gliomas (WHO grade III-IV) were poorly differentiated, and these tumors were malignant for patients with poor prognosis [21]. In this study, the patients with high pathological grade recurrent glioma showed a high risk of re-recurrence. Many studies displayed a similar trend. Li found that high pathological grade glioma was significantly associated with miR-372 expression, which was an independent prognostic factor for recurrence [22]. Lu reported that high pathological grade was an independent factors predicting poor prognosis for gliomas and poor overall survival [23]. In this report, pathological grade was one of the important indexes to evaluate re-recurrence after the second surgery for recurrent glioma patients, and the patients with higher pathological grade should receive the PDT.

PDT was based on the reactive oxygen species produced by exciting the laser photosensitizer with a specific wavelength light to induce cell death [24]. At the beginning of the 1990s, PDT was applied for cancer therapy [25], and PDT can kill tumor cells in normal tissues and has been used in oncology for more than 20 years in Europe and America [26,27]. PDT has also become a therapy for brain tumors, including gliomas [28], and patients who needed reoperation for postoperative recurrence or incomplete resection during the surgery were recommended to undergo PDT combined with other comprehensive treatments, except for those who had known allergies to photosensitizers [29]. Stylli et al. found that PDT could reduce the recurrence time and increase the survival time of patients with glioma [30,31]. This study

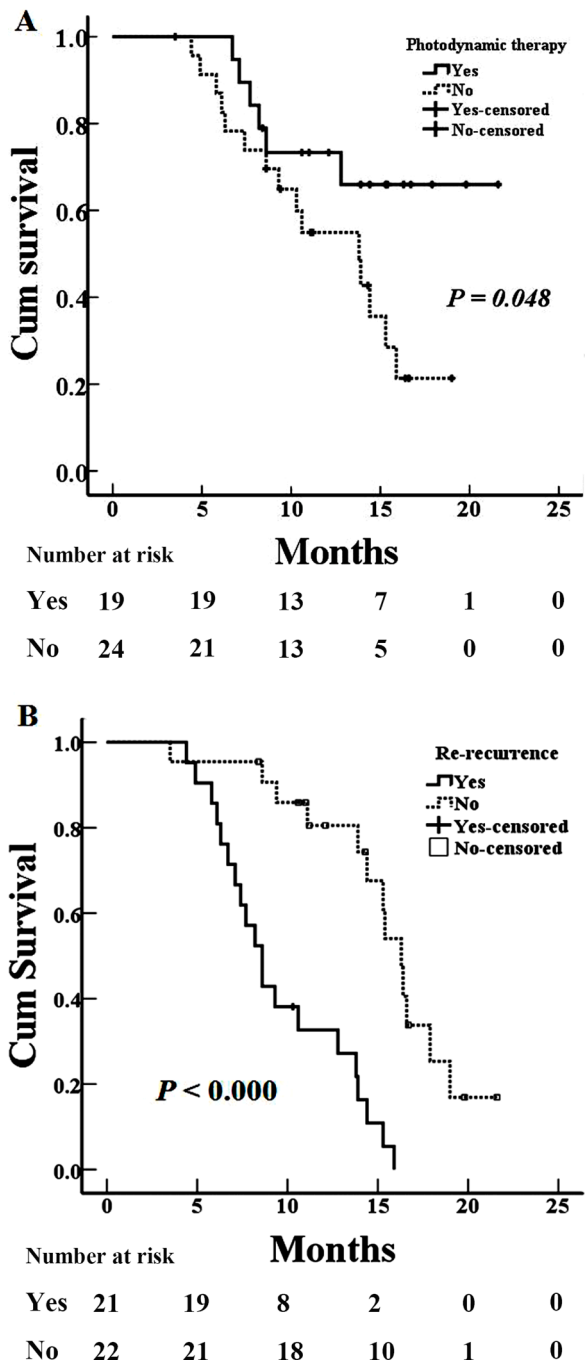


**Fig. 1.** Kaplan-Meier curves for cumulative survival time of patients after the second surgery. A. The cumulative survival time with or without photodynamic therapy. B. The cumulative survival time with or without re-recurrence.

also showed similar results that PDT reduced the rate of re-recurrence in patients with recurrent gliomas and improved the survival time significantly. Compared with other treatment options, such as radiotherapy and chemotherapy, PDT has its own unique advantages: no serious toxicity, precise effects, no drug resistance, and the selective destruction of diseased tissue [32]. Therefore, PDT was a crucial treatment to decrease the risk of re-recurrence after the second surgery for recurrent glioma patients and increase the survival time. Additionally, we found that in the patients of total resection, the PDT decreased re-recurrence significantly compared with non-PDT, but we did not found similar effect in the patients of debulking resection. We think the mode of operation may be the main factor in the re-recurrence. Under PDT, the patients of total resection had a better chance of avoiding re-recurrence.

PDT was a therapy for the treatment of tumors in the 1970s [33]. The photosensitizer accumulated in tumor cells is usually excited by laser, and photochemical reaction occurs under aerobic conditions to release reactive oxygen species to induce apoptosis and necrosis of tumor cells, so as to kill tumor [34]. At first, there were many deficiencies in the research and understanding of PDT, which did not get people's attention. With the deepening of research and technical improvement, PDT has been widely used in the treatment of various tumors, such as digestive tumor [35], respiratory tumor [36], urinary tumor [37] and glioma [38], and achieved good effects. It has been found that PDT can activate tumor immune response [39], and the combination of radiotherapy and chemotherapy showed enhanced effect [40,41]. Of course, limited by hypoxia in the tumor microenvironment, the efficacy of PDT is bound to be reduced to a certain extent [42], which is also the deficiency of PDT. However, PDT is still an anti-tumor treatment method with broad application prospects, and it should be considered for clinical applications.

In this study, we also found 4 cases of distant metastasis, including 3 cases of pulmonary metastasis and 1 case of hepatic metastasis. The conventional perception was that primary glioma did not induce distant metastasis [43]. However, the distant metastasis of glioma has attracted the attention of researchers in recent years. The distant metastasis of glioma had been detected from the initial discovery with an interval from a few days to 17 years [44]. However, the mechanism of primary glioma to extracranial distant metastasis was unclear. Rickert reported that the more times patients underwent surgery, the greater the likelihood of distant metastasis, which was associated with the destruction of the natural protective system of the brain [44]. Meyer PT found that the high degree of malignancy, surgery, radiotherapy, and chemotherapy were risk factors for the distant metastasis of glioma, which increased the rate of distant metastasis from 7 to 53% [45].

This study also had limitations. First, this study was conducted in a single center with a small sample size, thus, it was difficult to analyze the types of histology or one pathological grade of glioma. Multicenter, large samples of clinical research are needed in the future. Second, although the IDH1 mutation, KPS, primary histology, and distant metastasis showed significant differences in the re-recurrent group and non-re-recurrent group, they were not independent risk factors for postoperative re-recurrence in patients with recurrent gliomas following the multivariate Cox regression analysis. This needs to be confirmed in a multicenter, large sample study. Then, it was patient's choice whether to select PDT treatment, the decision can be affected by the cost of PDT. This may make many suitable patients unable to receive PDT, which reduced the effect of PDT to some extent. Finally, due to the limited storage information of our hospital system, information about the first surgery was not available in all patients, and the patients could also not clearly describe it, so it was difficult to exclude the influence of the first operation on the results of this study.

## 5. Conclusion

The older age, high MMP2 expression, and high WHO pathological grade increased the risk of re-recurrence after the second surgery for patients with recurrent glioma. Surgery combined with PDT during the second surgery decreased the risk of re-recurrence and increased survival time. It should thus be considered as a new direction of treatment in the future.

## Availability of data and material

The data that support the findings of this study are available from the corresponding author on reasonable request.

## CRediT authorship contribution statement

**Yongning Li:** Visualization, Conceptualization, Resources, Writing – original draft, Writing – review & editing. **Fang Wang:** Visualization, Conceptualization, Data curation, Formal analysis, Writing – review & editing. **Bo Li:** Visualization, Conceptualization, Resources, Writing – original draft, Writing – review & editing.

## Declaration of Competing Interest

All authors declare no conflicts-of-interest related to this article.

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