

Efficacy and prognosis of surgery combined with ¹²⁵I seed implantation in treatment of recurrent glioma

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Abstract. This study evaluated the efficacy of surgery combined with ¹²⁵I seed implantation in the treatment of recurrent glioma, and analyzed prognosis-influencing factors. A total of 66 patients with recurrent gliomas in Yidu Central Hospital of Weifang were enrolled in the study from April, 2011 to March, 2014. Patients were randomly divided into a control and an observation group, with 33 patients in each group. Patients in the control group were treated with surgery alone, and those in the observation group received surgery combined with ¹²⁵I seed implantation. Short-term curative effects in the two groups were compared using evaluation criteria for solid tumors. The comparison included the postoperative adverse reactions, the life quality (using the Karnofsky Performance Status or KPS), the survival time and prognostic factors (using the Kaplan-Meier survival, log-rank test and Cox regression analyses). Our results showed the objective response and disease control rates in the observation group were significantly higher than those in the control group ($P < 0.05$). While no significant differences in postoperative adverse reactions were found between the two groups ($P > 0.05$). The KPS score in the observation group was significantly higher than that in the control group at different time points after surgery ($P < 0.05$). The survival rate and overall survival time of those in the observation group were significantly higher than those of the patients in the control group ($P < 0.05$). The univariate analysis showed that preoperative KPS score, tumor pathological grade and degree of tumor resection were adverse factors influencing the prognosis of the patients ($P < 0.05$). Also, multivariate Cox regression showed that preoperative KPS score, tumor pathological grade, and degree of tumor resection were

independent risk factors of prognosis. Based on our findings, surgery combined with ¹²⁵I seed implantation can improve the survival rate of patients with recurrent glioma and prolong their survival time. Tumor pathological grade, degree of tumor resection and KPS score are the most important factors influencing the prognosis.

Introduction

Gliomas are the most common malignant tumors of the central nervous system, accounting for ~50% of all intracranial tumors. Gliomas are often located in functional areas exhibiting invasive growth and leading to progressive deterioration; also recurrences are common (1). Treatments for glioma include surgery, radiotherapy, chemotherapy, molecular biology approaches and gene therapy, with surgery being the most common approach. However, complete removal is hard to achieve, resulting in common unsatisfactory outcomes and a high recurrence rate (2). The survival time of patients with recurrent glioma is usually short. Without timely treatment, survival time is usually shorter than 6 months. In addition, the life quality of patients is usually poor. Therefore, recurrent gliomas present an ongoing challenge for the treatment of neurological diseases (3). Although *in vitro* radiotherapy can effectively kill glioma tumor cells, it can also bring damage to surrounding healthy brain tissue, skin and scalp, and the amount of collateral damage increases with higher doses. In all, the development of a novel treatment that can effectively kill tumor cells and improve outcomes, while reducing the side effects of radiation treatment is urgently needed (4,5). ¹²⁵I seed implantation is a kind of *in vivo* radiotherapy. ¹²⁵I seed implantation achieves low dose continuous exposure, high accuracy and killing of tumor cells in short-range (6). In this study, patients with recurrent glioma were treated with surgery combined with ¹²⁵I seed implantation, and their prognosis was analyzed. Our study provides scientific evidence for the effectiveness of this treatment.

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Materials and methods

General information: Sixty-six patients with recurrent gliomas were selected in Yidu Central Hospital of Weifang from April, 2011 to March, 2014. Patients were randomly divided

Table I. Comparison of general information between two groups.

Items	Control group (n=33)	Observation group (n=33)	t/ χ^2 -test	P-value
Sex (male/female)	16/17	18/15	0.061	0.806
Age (years)	40-70	40-75		
Average age (years)	54.78±6.49	54.32±6.58	0.286	0.776
Preoperative KPS score	62.78±5.49	62.32±5.58	0.338	0.737
Tumor site (n, %)				
Superficial	19 (57.58)	21 (63.64)	0.064	0.801
Near midline	14 (42.42)	12 (36.36)		
Pathological grade (n, %)				
Grade II	8 (24.24)	7 (21.21)	0.011	0.995
Grade III	15 (45.45)	17 (51.52)		
Grade IV	10 (30.30)	9 (27.27)		

KPS, Karnofsky Performance Status.

into a surgery alone (control) group and a surgery combined with ¹²⁵I seed implantation (observation) group, with 33 patients in each. The presence of a malignant glioma diagnosed by pathological examination, with recurrent tumor diagnosed by head MRI, measurable lesions and an expected survival longer than 8 weeks were all characteristics of the inclusion criteria for the patients. Additionally, all signed informed consent forms. Patients excluded from the study were those with severe uncontrollable hypertension, transient ischemic attack, shock or cerebral hemorrhage; patients with severe coagulation dysfunction; and patients with a preoperative Karnofsky Performance Status (KPS) score lower than 50 points. There were no significant differences in the general information of patients between the two groups ($P>0.05$) (Table I).

Methods

Surgical treatment. Patients in both groups were treated with surgery under general anesthesia. A site on the original surgical incision showed the shortest distance to the tumor surface. The bone flap was lifted up and meninges were opened. Adhesions between the tumor and brain tissues were dissected. Tumor and peripheral edema tissue resection was maximized regardless of proximity to important brain function area and its blood vessels. If the tumor capsule showed serious hemorrhage necrosis, some of the necrotic tissue was removed. If the tumor capsule showed cystic changes, fluid was first removed by aspiration, and then the tumor was resected piecemeal along the edges.

Seed implantation. The National Research Centre of Isotope Technology produced the ¹²⁵I seed, in the China Institute of Atomic Energy. The seed activity was reportedly 0.5-0.7 mCi. According to the results of preoperative enhanced MRI results, the ¹²⁵I seed was implanted within a 1 cm radius to the center of the original tumor. Interval was 1.0 cm, depth was 0.5-1.0 cm and functional area was 80 Gy. After implantation, gelatin sponge and hemostatic gauze were used to cover the manipulation position to prevent shedding of seed and local bleeding.

Postoperative treatment. After treatment, patients were subjected to conventional anti-infection and antiepileptic

prophylactic treatments. Enhanced MRI examination was performed every 2 months after surgery to observe any developing changes in the patients' physical signs, and tumor volumes. Changes in KPS scores, ensuing complications and survival time were recorded.

Evaluation criteria. The efficacy of treatment was evaluated 3 months after surgery, according to the evaluation criteria for solid tumors. Complete remission (CR) meant all visible lesions had disappeared for >4 weeks after the surgical procedure. Partial remission (PR) meant the tumor diameter was reduced >50% and remained so for >4 weeks after surgery. A stable disease (SD) meant the tumor was still present and had not improved to at least to the level of the PR. Progression of disease (PD) was obvious if the target lesion had increased in diameter by >20% or if a new lesion appeared. The overall objective response rate (ORR) was calculated by the equation $ORR = (CR + PR)/total\ number$, and the disease control rate (DCR) by the equation $DCR = (CR + PR + SD)/total\ number$.

The occurrence of any adverse reactions within 1 month after surgery was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) (7). Grade I patients had mild or no symptoms, and no treatment was needed. Grade II patients had instrumental activities of daily living limited by adverse reactions but only local or non-invasive treatment was needed to improve their well being. Grade III patients had their daily life activities limited, they had severe responses or disability but no immediate threat to life, they needed to be hospitalized or their hospital stay needed to be extended. Grade IV patients experienced life-threatening complications, needing emergency treatment. Finally, patients were classified in grade V if death ensued due to complications.

The life qualities of patients at 6, 12 and 18 months after surgery were evaluated according to KPS scoring criteria (8). The scores were positively correlated with the life quality of the patients (Table II).

Statistical analysis. Data were processed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA) software. Measurement data were expressed as mean \pm standard deviation (mean \pm SD),

Table II. KPS scoring criteria.

Status of patients	Score	Status of patients	Score
Normal, no symptoms or abnormal physical signs	100	Dependant on others for daily life and special care is needed	40
Normal activities with minor illness	90	Seriously dependant in daily life	30
Normal activities with slight difficulties	80	Bed-ridden, hospitalization is needed but no threat to life	20
Independent in daily life but cannot work normally	70	Life-threatening situation	10
Mostly independent in daily life and help is needed occasionally	60	Death	0
Help is needed frequently	50		

KPS, Karnofsky Performance Status.

Table III. Comparison of short-term efficacy in the two groups (n, %).

Groups	CR	PR	SD	PD	ORR	DCR
Observation group	12 (36.36)	11 (33.33)	8 (24.24)	2 (6.06)	23 (69.69)	31 (93.94)
Control group	6 (18.18)	8 (24.24)	9 (27.27)	10 (30.30)	14 (42.42)	23 (69.69)
χ^2 test					3.937	4.991
P-value					0.047	0.026

CR, complete remission; PR, partial remission; SD, stable disease; PD, Progression of disease; ORR, objective response rate; DCR, disease control rate.

Table IV. Comparison of adverse reactions between the groups (n, %).

Groups	Cases	Grade I	Grade II	Grade III	Grade IV	Grade V
Observation group	33	24 (72.73)	7 (21.21)	2 (6.06)	0 (0.00)	0 (0.00)
Control group	33	26 (78.79)	6 (18.18)	1 (3.03)	0 (0.00)	0 (0.00)
χ^2 test		0.490				
P-value		0.783				

and t-tests were performed for comparisons between groups. Count data were expressed as rate, and comparisons between groups were performed using χ^2 tests. Survival analysis was performed by Kaplan-Meier survival analysis. Single factor analysis for survival was performed using log-rank test. Factors with statistical significance in single factor analysis were further subjected to multi-factor Cox regression analysis. A $P < 0.05$ was considered to be statistically significant.

Results

The treatment efficacies in the two groups were compared at 3 months after surgery. The results showed that ORR and DCR in the observation group (69.69 and 93.94%, respectively) were higher than those in the control group (42.42 and 69.69%, respectively), and the differences were statistically significant ($P < 0.05$) (Table III).

The occurrence of adverse reactions within 1 month after surgery was compared between the two groups, no significant

differences in adverse reactions were found between the groups (Table IV).

The postoperative KPS score was compared between the two groups. The results showed that the KPS scores in the observation group were significantly higher than those in the control group at 6, 12 and 18 months after operation ($P < 0.05$) (Table V).

The survival of patients in the two groups was also compared. Results showed that the mean survival time was longer and the postoperative survival rate was higher in the observation group when compared to the same parameters in the control group ($P < 0.05$) (Table VI and Fig. 1).

The Kaplan-Meier analysis showed that the survival time was significantly longer in the observation group compared to that in the control group ($P < 0.05$).

The univariate analysis performed by a log-rank test showed that preoperative KPS score, tumor site, tumor pathological grade and degree of tumor resection were all adverse factors influencing the prognosis of the patients ($P < 0.05$) (Table VII).

Table V. Comparison of KPS scores between the two groups.

Groups	6 months after operation	12 months after operation	18 months after operation
Observation group	84.67±3.23	71.35±3.28	60.68±3.24
Control group	76.27±3.64	62.47±3.36	45.83±3.78
t-test	9.215	8.812	11.084
P-value	<0.001	<0.001	<0.001

KPS, Karnofsky Performance Status.

Table VI. Comparison of survival between two groups.

Group	Cases	6-month survival rate (n, %)	12-month survival rate (n, %)	18-month survival rate (n, %)	Mean survival time (week)
Observation group	33	32 (96.97)	27 (81.82)	19 (57.58)	67.56±7.48
Control group	33	25 (75.76)	18 (54.55)	10 (30.30)	52.64±7.53
χ ² /t-test		4.632	4.470	3.937	8.075
P-value		0.031	0.035	0.047	<0.001

Table VII. Univariate analysis for prognosis.

Items	Proportion (n, %)	Median survival time (weeks)	95% confidence interval (95% CI)	cLog-rank test	
				χ ² test	P-value
Age					
<60 years	30 (45.45)	54.93	23.62-62.75	0.122	0.531
≥60 years	36 (54.55)	52.43	20.74-61.62		
Sex					
Male	34 (51.52)	55.82	21.53-63.84	0.006	0.943
Female	32 (48.48)	56.63	22.72-68.47		
Tumor pathological grade					
Grade II	15 (22.73)	74.86	29.82-81.39	23.759	<0.001
Grade III	32 (48.48)	56.75	28.71-66.32		
Grade IV	19 (28.79)	41.32	14.36-56.73		
Tumor site					
Superficial	39 (59.09)	63.48	25.76-78.32	7.994	0.019
Near midline	27 (40.91)	51.56	23.48-59.65		
Tumor resection degree					
Total resection	45 (68.18)	66.57	28.31-79.46	9.264	0.017
Subtotal resection	21 (32.82)	50.72	24.46-58.23		
Preoperative KPS score					
≥70	44 (66.67)	63.62	28.33-70.36	11.543	0.001
<70	22 (33.33)	54.58	23.48-59.53		
Tumor diameter (cm)					
>3	30 (45.45)	56.39	27.73-74.92	0.469	0.541
≤3	36 (54.55)	58.47	24.86-76.53		

The multivariate Cox regression analysis for prognosis showed that preoperative KPS score, tumor pathological grade

and degree of tumor resection were all independent risk factors of prognosis (P<0.05) (Table VIII).

Table VIII. Multivariate Cox regression analysis for prognosis.

Factors	B	SE	Wald	HR	95% CI	P-value
Preoperative KPS score	0.789	0.030	9.021	3.215	1.731-6.158	0.008
Degree of tumor resection	0.331	0.512	3.783	1.231	0.975-2.957	0.014
Tumor pathological grade	0.467	0.673	5.327	9.013	3.456-14.854	0.026

KPS, Karnofsky Performance Status.

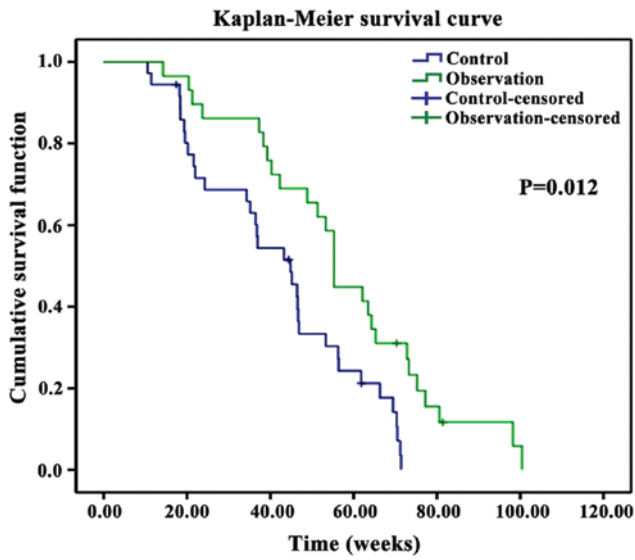


Figure 1. Survival curve for two groups of patients.

Discussion

Gliomas usually develop deep within the brain. These tumors usually cause poor life quality and show invasive growth and characteristics leading to high mortality rates like rapid progression and a low curing rate (9). Clinical manifestations of glioma include malignant vomiting, headaches, optic disc edema, neurological deficits, psychological changes, hemiplegia and ataxia, and invasion and distant metastasis can easily occur (10). Surgery is the preferred treatment for gliomas. However, gliomas can frequently recur within 6-10 months after surgery. Once recurrence has happened, neurological damage in patients increases, the area of the nerve structures damaged is enlarged, and short-term decline in the level of awareness ensues, eventually leading to brain failure and death (11). The main reason for recurrence is the existence of glioma cell infiltration around the primary tumor, and most of the recurrent lesions are found in an area within 2 cm around the tumor, so control of local recurrence is essential for treatment of malignant gliomas (12).

Treatment of recurrent gliomas requires secondary surgery or chemotherapy and radiotherapy. However, the blood-brain barrier increases difficulties in delivering drugs to brain, so chemotherapy drugs cannot be used to effectively treat gliomas. In addition, chemotherapy is usually accompanied by severe adverse side effects, seriously affecting life quality of the patients (13). Radiation therapy can be used to reduce the

size of the tumor through ionization, which in turn alleviates the symptoms and extends the survival time of patient (14). However, before reaching tumor tissues, radiation will first bring damage to surrounding brain tissue and subcutaneous structures, and this damage can be increased with the increase in radiation dose (15).

Seed implantation therapy is a new type of brachytherapy, and is also called interstitial brachytherapy. Based on the inverse square law, the radiation dose is reduced substantially with distance from the source. Energy release can usually reach 80% of its total within the area 1 cm round the seed implant, and tumor cells within this range can be effectively killed, while the damage to normal cells within this area is reduced due to the rapid decline in dose (16,17). The results of this study showed the effective rate of treatment in the observation group was significantly higher than that in the control group at 6 months after operation ($P < 0.05$), but no significant differences in adverse reactions were found between the groups ($P > 0.05$). The KPS scores in the observation group were significantly higher than those in the control group at 6, 12 and 18 months after operation ($P < 0.05$), the reason probably being that the half-life of the ^{125}I seed is 59.4 day, providing effective radiation for four half-lives, and releasing low-energy radiation to kill tumor cells, which improves outcomes (17). Moreover, the dose distribution is more uniform in seed implantation treatment compared with other treatments, so infections caused by surgery can be reduced without inducing significant increase in normal brain tissue damage (17). The ^{125}I seed can provide 240 days of continuous irradiation, so that the treatment effect can last longer. Therefore, symptoms of patients can be effectively alleviated and life quality can be significantly improved (16).

Surgical treatment of recurrent gliomas requires maximum resection of tumoral tissues sparing important cortical functional areas (18). Seed implantation should be combined with MRI, to ensure optimal placement, the implanted particles should show triangle or square shape (19). In order to avoid the shedding of ^{125}I seed and hemorrhages, the seed should be fixed in position with a gelatin sponge. The puncture point should be treated with hemostatic treatment, and there should be constant monitoring to detect internal bleeding.

This study included analyses of prognostic factors. Multivariate Cox regression showed that preoperative KPS scores, tumor pathological grade and degree of tumor resection were independent risk factors of prognosis ($P < 0.05$). All those three factors can affect the patient's neurological status. Life quality of patients with recurrent glioma is clinically reflected in their KPS score, and KPS scoring is an important

part of prognosis prediction providing importance guidance. The median survival time of patients with KPS scores ≥ 70 was significantly higher than that of patients with KPS scores < 70 . This is because tumor metastasis and invasion can be indirectly evaluated by the KPS score. The degree of tumor resection can affect the depth and location of ¹²⁵I seed implantation, resulting in better efficacies when resection is highly successful so that the inhibitory effect of ¹²⁵I seed implantation is optimal. Also, the survival rate of recurrent gliomas is decreased with the increase of pathological grade, which is consistent with the results of case studies world-wide, meaning that pathological grade is a risk factor of prognosis (20).

We are aware of the limitations of our study due to the small sample size, so larger studies are needed. Nevertheless, based on our findings, surgery combined with ¹²⁵I seed implantation can effectively inhibit the growth of recurrent gliomas, improve the patient's condition, delay the recurrence of the tumors, and extend the survival time.

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