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Retrospective analysis of re-irradiation in malignant glioma: a single-center experience

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Zweitbestrahlung bei malignen Gliomen: eine retrospektive Auswertung

Zusammenfassung. *Einleitung:* Aktuelle Behandlungskonzepte für maligne Gliome umfassen neurochirurgische Resektion, Chemotherapie und Bestrahlung, ein Rezidiv oder Progress kann jedoch im Allgemeinen nicht verhindert werden. In dieser Situation ist eine palliative Chemotherapie relativ gut etabliert, in ausgewählten Patienten ist jedoch eine zweite lokale Behandlung möglich. Wir berichten unsere Erfahrung mit Zweitbestrahlungen bei Patienten mit progredienten malignen Gliomen.

Patienten und Methode: 22 Patienten wurden behandelt, in Abhängigkeit von der Tumorgröße wurde eine hypofraktionierte stereotaktische oder eine konventionell fraktionierte konformale Bestrahlung durchgeführt. Wenn möglich erfolgte vor der Zweitbestrahlung eine neuerliche neurochirurgische Resektion. Zeit zum Erkrankungsprogress (TTP) und Überleben wurden mittels der Kaplan-Meier-Schätzung ermittelt.

Ergebnisse: Das mediane Alter der Patienten war 31 (8–77) Jahre. Mediane TTP nach Beginn der Zweitbestrahlung war 4 (1–31) Monate, medianes Überleben nach Zweitbestrahlung 7 (1–46) Monate und medianes Gesamtüberleben 49 (7–136) Monate. Eine signifikant längere TTP ($p = 0.008$) und ein signifikant längeres Überleben ($p = 0.005$) nach Zweitbehandlung zeigte sich bei den Patienten, bei denen auch eine zweite neurochirurgische Resektion möglich war.

Diskussion: Eine Zweitbestrahlung bei malignen Gliomen ist eine relativ sichere und effektive Behandlungsmethode. Ein möglicher Vorteil dürfte vor allem für die Patienten bestehen, die für eine neuerliche Resektion in Frage kommen. Um eine endgültige Einschätzung zu ermöglichen, sind aber größere, randomisierte Studien nötig.

Summary. *Introduction:* Malignant gliomas are brain tumors deriving from the brain's glia cells. Primary treatment comprises resection, irradiation and chemotherapy, but these tumors almost always recur. In this situation, palliative chemotherapy is relatively well established, but a second local treatment is sometimes possible. We evaluated the safety and efficacy of re-irradiation in patients with recurrent malignant glioma.

Patients and methods: Twenty-two patients were treated with a second irradiation for recurrent or progressive glioma. Patients either received hypo-fractionated stereotactic treatment or conventionally fractionated conformal therapy, depending on tumor size. Wherever possible, a second resection was performed. Time to progression (TTP) and survival were estimated using the Kaplan-Meier product-limit method.

Results: Median age was 31 (8–77) years. Median TTP after onset of re-treatment was 4 (1–31) months. Median overall survival was 7 (1–46) months, and overall survival from primary diagnosis was 49 (7–136) months. Significantly longer TTP ($P = 0.008$) and overall survival ($P = 0.005$) were observed in re-resected patients than in those without a second surgical intervention.

Conclusion: Re-irradiation in malignant glioma is a feasible and safe treatment option, and the benefit appears to be especially large in re-resected patients. To make a final conclusion possible, larger prospective trials are warranted.

Key words: Recurrent malignant glioma, re-irradiation, stereotactic irradiation, re-treatment, palliative chemotherapy.

Introduction

Gliomas are a heterogeneous group of neoplasms that comprise the majority of tumors originating in the central

nervous system. In adults, the most frequently encountered of these are high-grade or malignant neoplasms of astrocytic and oligodendrocytic lineage, i.e., anaplastic astrocytoma, glioblastoma multiforme (GBM), and anaplastic oligodendroglioma, respectively [1]. GBM is the most commonly diagnosed primary malignant brain tumor in adults, with an incidence of 2.6 per 100,000 person-years [2]. Two subtypes of GBM are differentiated: primary (de novo) GBM develops without a previous history of lower grade astrocytoma and occurs mostly in older patients, whereas secondary GBM evolves from lower grade astrocytoma and is more common in younger patients [3].

Current treatment options for anaplastic astrocytoma and GBM comprise neurosurgical intervention, radiation therapy and concomitant or adjuvant chemotherapy. Temozolomide plus irradiation is usually regarded the most effective regimen [1, 4, 5]. In irradiation, a 3-D planned conventionally fractionated conformal therapy is standard today. Over the last two decades this approach has lengthened time to progression (TTP) and increased overall survival [6], but tumor progression or recurrence is almost always inevitable. However, a very small proportion of patients appear to remain without recurrence over a long period, which might be due to biological differences in a subset of tumors. Significant prognostic factors identified for overall survival are: age (younger patients fare better than older ones), Karnofsky performance score (KPS), mental status, tumor grade, histology and extent of surgical resection [7].

In cases of tumor progression after primary treatment, palliative second-line chemotherapy is relatively well established, with dacarbacine and fotemustine a well tolerated option [8]; other authors prefer single–agent cytotoxic therapy in this situation, because of the smaller number of side effects [9]. The classic PCV regimen also remains a valuable option [10]. Re-operation, if possible, is indicated when local mass effect limits the quality of life. Re-irradiation (using hypo-fractionated stereotactic or conventionally fractionated techniques) with or without concomitant cytotoxic chemotherapy as radiation sensitizer can prolong high quality survival in selected patients [9, 11].

Indications for re-irradiation at our center are a minimum elapse of six months since primary irradiation, KPS 70% or higher, and a lesion not located in the brain-stem area.

In this analysis we report our experiences with re-irradiation (conventionally fractionated conformal and hypo-fractionated) after recurrence or progression of malignant gliomas. We analyzed safety and toxicity of re-irradiation and the outcome in terms of TTP and overall survival.

Patients and methods

All data were collected from the Department of Radiotherapy and Radiobiology at the Medical University of Vienna, Vienna, Austria.

Patients

Twenty-two patients with histologically confirmed anaplastic astrocytoma or glioblastoma were investigated.

Patients were re-treated if more than six months had elapsed since primary irradiation and the KPS was 70% or higher. Localization of the tumor in the brain-stem area was deemed a contraindication to secondary therapy, and patients with disseminated intracerebral disease were also excluded from the analysis because it was not believed that these patients profit from secondary local treatment.

For staging evaluations, magnetic resonance imaging (MRI) of the brain with further workup if indicated (both methionine and FDG PET scan) was mandatory and, if a second operation was performed, postoperative cranial computed tomography (CT) also. For re-irradiation planning, a contrast-media enhanced CT scan and an MRI scan were both performed.

Treatment and patient evaluation

Patients were treated in two different groups according to tumor size. One group with tumors larger than 4 cm in maximum diameter (preoperative tumor size) received a second conventionally fractionated conformal radiation therapy, with doses of 45–54 Gy in fractions of 2 Gy or 3 Gy depending on earlier dosage in the region (15 x 3 Gy to 27 x 2 Gy). The other group was treated hypo-fractionated in stereotactic masks (6 x 5 Gy on the 80% isodose) over a period of 2 weeks.

Table 1. Irradiation data

Characteristics		Patients
Primary irradiation		**22**
2/3 Fields conformal technique		21
Lateral opposed fields		1
PTV	Median	382 cm^3
	Range	200 – 700 cm^3
	Not available	4
Re-irradiation (conventional)		**14**
PTV	Median	154.4 cm^3
	Range	14–474 cm^3
Fields	n = 2	3
	3	8
	8	2
	9	1
Multileaf		3
Re-irradiation (hypo-fractionated)		**8**[1]
PTV1	Median	41.7 cm^3
	Range	4–69 cm^3
Fields	n = 3	1
	8	1
	9	4
	10	1
	11	2
Multileaf		7
Rotation		1

[1] One patient with two PTVs (PTV1 9 fields, PTV2 11 fields).

Technical data

An ELEKTA Precise linear accelerator was used for treatment. Conventional therapy was planned using the HELAX system (HELAX-TMS, 6.1B 2003); hypo-fractionated treatment was planned using the BrainSCAN 5.21 2003 system by BrainLAB AG (Image 1).

Primary irradiation was applied with a two- or three-field irradiation plan in conformal technique with wedges; in one patient lateral opposed fields without wedges were used. The median planning target volume (PTV) in primary treatment was 282 (200–700) cm^3. Doses applied were 54–66 Gy, in fractions of 2 Gy per day. In the conventionally fractionated re-irradiation group, median PTV was 154.4 (14–474) cm^3; in the stereotactic re-irradiation group, median PTV was 41.7 (4–69) cm^3. Table 1 lists the technical irradiation data. PTV was identified as the contrast-media enhancing tumor (gross tumor volume, GTV) plus a margin of 5 mm in conventionally treated patients. In stereotactic planning, clinical target volume (CTV) was defined as GTV plus a margin of 3 mm. We regard such a margin to be necessary in stereotactic re-irradiation of glioblastoma because these tumors tend to infiltrate the surrounding brain tissue in a diffuse manner. PTV was defined as CTV plus a margin of 2 mm, as is usual in stereotactic treatment. In patients with re-resection, the pretreatment enhancing tumor mass was used for treatment planning. The median time elapsing between primary irradiation and re-irradiation was 19 (6–126) months.

Patients and their relatives were advised to report any adverse events, especially worsening of the neurological situation. Any neurological dysfunction and its development over time was observed and reported.

Statistical analysis

TTP was defined as the interval from the first day of re-irradiation until radiologically proven tumor progression. Progression was defined as increase in tumor size after re-treatment or development of a new lesion. Survival time was measured from the first day of re-treatment until death. Overall survival was measured from primary tumor diagnosis until death. Data were analyzed as of September 2004. The distributions of TTP and time to death were estimated using the Kaplan-Meier product-limit method [12]. The log-rank test was used to test the difference between survival curves. *P* values less than 0.05 were considered to indicate statistical significance. Tumor progression was analyzed with an MRI scan every 3 months, followed by PET scan if indicated (both methionine and FDG). Toxicity was evaluated at every follow-up visit by asking the patient and their relatives if any increase in neurological dysfunctions had occurred. If differentiation between tumor progress and radiotherapy necrosis was not possible from MRI scan alone, a methionine and FDG PET scan was performed.

Table 2. Patient characteristics

Characteristics		Patients
Entered		**22**
Sex	Male	14
	Female	8
Karnofsky performance score		80 – 100%
Age	Median age (range)	31 (8–77) years
Primary treatment		
Resection		22
	Complete (macroscopic)	13
	Incomplete	9
Histology		
	Glioblastoma	13
	Astrocytoma III	3
	Astrocytoma II/III	3
	Astrocytoma II	3
1st line chemotherapy		15
	CCNU	3
	Fotemustine/dacarbacine	4
	Temozolomide	1
	Others	7
2nd line chemotherapy		5
	CCNU	2
	Temozolomide	2
	Imatinib	1
Secondary treatment		
Secondary Resection		11
	Complete	4
	Incomplete	7
Histology		
	Glioblastoma	20
	Astrocytoma III	2
Re-irradiation		
	Hypo-fractionated	8
	Conventionally fractionated	14
1st line chemotherapy		17
	CCNU	1
	Fotemustine/Dacarbacine	6
	Temozolomide	7
	Thalidomide	2
	Others	1
2nd line chemotherapy		7
	Fotemustine/Dacarbacine	2
	Temozolomide	1
	Thalidomide	3
	Gefitinib	1

Results

Patient characteristics

Twenty-two patients (female/male: 8/14) suffering from progressive or recurrent malignant glioma were included in this evaluation. Median age was 31 (8–77) years. Two patients younger than 20 years were included (8 and 18 years old). Fourteen patients had conventionally fractionated and eight hypo-fractionated re-treatment.

At the time of primary treatment, only 13 of the 22 patients were suffering from glioblastoma; among the other nine patients three were diagnosed with anaplastic astrocytoma, three with astrocytoma II/III and three with astrocytoma II. At the time of re-irradiation, 20 patients had histologically confirmed glioblastoma and two patients anaplastic astrocytoma. At the time of primary diagnosis, all 22 patients underwent neurosurgical intervention: in 13 of these a macroscopic complete resection was achieved and in nine patients only parts of the tumor were resected. Before re-irradiation, a second surgery was performed in 11 patients: four second complete resections

and seven partial resections. After primary treatment, 15 patients received first-line chemotherapy and five of the fifteen a second-line treatment also. After re-irradiation, 17 patients received chemotherapy, and seven of the 17 also had a second treatment line. Information about chemotherapy was not available for one patient. Table 2 lists the characteristics of the 22 patients. Primary treatment and re-irradiation fields were overlapping in all patients.

Response and survival data

After re-irradiation of the 22 patients, ten (45.5%, 8/10 without secondary resection) showed tumor progression or recurrence after 1–3 months, two (9.1%, 1 without secondary resection) relapsed at 3–6 months, one (4.5%, no resection) at 6–9 months, one (4.5%, resection) at 9–12 months, and two (9.1%, both after secondary resection) at 12–18 months. Three others (13.6%) showed no sign of progression to date. At the time of evaluation, fifteen patients (68.2%) had died, four (18.2%) were alive, and three (13.6%) were lost to follow-up without sign of tumor progression at last visit.

Time of observation was 5 (1–46) months. Median TTP was 4 (1–13) months, 95% CI 2.83–5.17. Median overall survival time from onset of re-treatment was 7 (1–46) months, 95% CI 3.19–10.81. Overall survival from primary diagnosis was 49 (7–136) months, 95% CI 17.78–80.22.

In the group analysis, TTP in the group without re-resection was 3 (1–7) months, 95% CI 2.30–3.70, and in those with a second surgical treatment TTP was 13 (1–31) months, 95% CI 3.14–22.86. The difference in TTP between the two groups was statistically significant ($P = 0.008$).

Overall survival from onset of re-treatment was 5 (1–17) months, 95% CI 2.24–7.76, in patients not re-resected, and 13 (1–46+) months, 95% CI 10.50–15.50, in the second group. The difference in overall survival between the two groups was statistically significant ($P = 0.005$) (Fig. 1).

Overall survival times from primary diagnosis were 22 (7–136) months, 95% CI 10.31–33.69, and 50 (8–160) months, 95% CI 47.43–52.57, respectively ($P = 0.086$).

No significant difference was observed in time from primary to secondary treatment between the two groups ($P = 0.490$).

We also compared TTP and overall survival from onset of re-treatment and overall survival from primary diagnosis in patients on hypo-fractionated stereotactic re-irradiation versus those with a second conventionally fractionated conformal radiotherapy. No significant difference was found between the two data sets.

Toxicities

Re-irradiation was relatively well tolerated, and all patients completed therapy. No acute WHO grade III or IV toxicities were observed. We did not observe any case of radiotherapy necrosis. At time of presentation for re-irradiation, nine of the 22 patients (40.9%) showed neurological symptoms, consisting of paresis (4 cases), concentration defects (2 cases), memory defects (3 cases), ataxia (1 case), aphasia (1 case), and apraxia (1 case). In two patients, additional symptoms possibly deriving from re-irradiation developed during follow-up, although tumor progress might have been responsible (1 patient in the hypo-fractionated treatment group and 1 in the conventionally fractionated treatment group). One of these two patients presented with impaired short-term memory, the other with aphasia. In both patients, we were able to rule out radiotherapy necrosis by both FDG and methionine PET. Symptoms clearly deriving from tumor progression, e.g. symptoms of intracerebral pressure such as nausea and vomiting, were observed but not included in the evaluation.

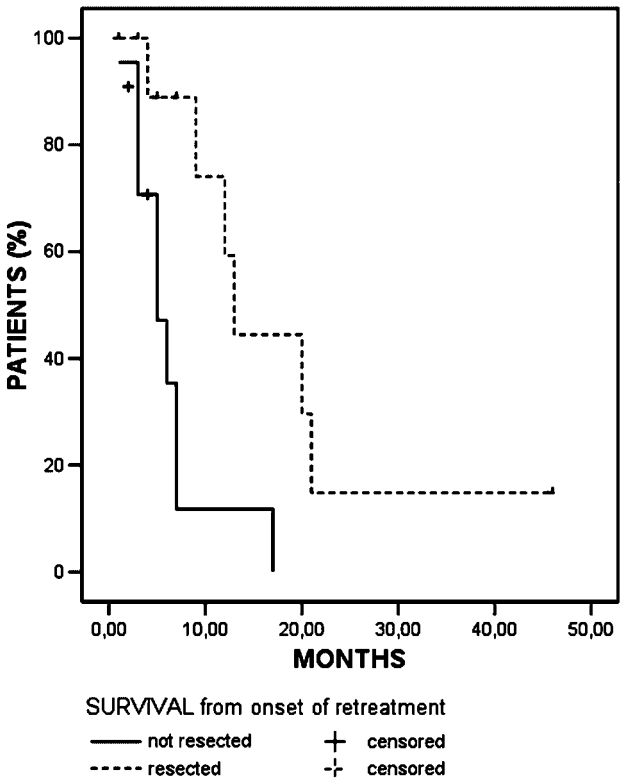

Fig. 1. Survival (from onset of re-treatment); P = 0.005 significant

Discussion

Radiation therapy remains, together with surgical resection and, in the last decade, also chemotherapy, an important part of primary treatment in malignant glioma. But despite these combined treatment options, this disease almost always recurs and eventually leads to the patient's death.

In recurrent malignant glioma, palliative chemotherapy is relatively well established; nevertheless patients should be evaluated for the possibility of re-irradiation and/or secondary neurosurgical resection because at least some of them seem to benefit from secondary local treatment.

Our data show that re-irradiation is a feasible and relatively safe option in the treatment of recurrent malignant glioma. Our entry criteria were as liberal as possible, to provide the maximum number of patients with the opportunity of undergoing re-irradiation. Median time to progression was four months and overall survival from

onset of re-treatment seven months, translating into an overall median survival time from primary diagnosis of 49 months. The survival data reported here compare well with the six to nine months reported by various other groups in patients receiving chemotherapy and/or re-irradiation [13–16]. A significant difference between the two different treatment groups (hypo-fractionated and conventionally fractionated) was not found. With hypo-fractionated stereotactic radiotherapy, a short-duration treatment option is available, which we believe to be as effective as conventionally fractioned treatment. Patients' time in hospital is reduced and this, in addition to symptom control, might further increase their quality of life, as found in a trial on microsurgery for glioblastoma [17]. Quality of life in general is of great importance in this situation, as no curative treatment can be provided. In addition, no difference in treatment side effects was found between the two groups. However, our patient numbers are rather small and the significance of the results is therefore limited.

There is one result of special interest: whereas most other groups have found a median overall survival of 25 to 39 weeks from onset of re-treatment with either palliative chemotherapy, re-irradiation or re-resection alone [18, 19], those patients in our series who were able to undergo all three treatment options had a significant advantage in terms of both TTP and overall survival. Patients receiving re-irradiation and chemotherapy had a median survival of five months; those undergoing re-resection, chemotherapy and re-irradiation had a median survival of 13 months. This difference was statistically significant, emphasizing the point that re-irradiation can be only a part of treatment, and combination with chemotherapy and surgical procedures is advantageous. Lack of difference between the two groups in overall survival from primary diagnosis may be explained by the different distribution of low-grade tumors and is therefore not to be seen as significant in the evaluation of therapeutic efficacy. To assess the exact impact of re-irradiation on TTP and overall survival, prospective trials with larger patient numbers are warranted. Interestingly, another study comparing the effect of re-resection, re-irradiation and chemotherapy with CCNU reported different results [20]: whereas overall survival from onset of re-treatment was 13.7 months and therefore similar to our results, there was no difference in survival between patients who underwent surgery and those who did not. We cannot be sure what the reason for this might be, although the authors of the study were surprised by the relatively long median survival of all patients. It is possible that the unexpectedly long survival of patients who were not re-resected has blurred the results. A possible bias also exists in our study: usually only patients with a high performance score (who are known to have better survival) and without disseminated disease are re-resected, thus possibly confounding our data [7]. Again, there is a need for larger trials.

A very important point about re-irradiation is its apparently low short-term toxicity. Chemotherapy produces mostly short-term toxicity depending on the substances used, and re-irradiation is believed to increase neurological symptoms in the medium and long range. However, we did not find a significant increase in neurological dysfunction. We believe this is due to the relatively small PTVs used in the patients presented here; this theory is supported by another report where a clear correlation between neurological decline (any cause) and treatment volume was found [21]. Many of the patients in our analysis already showed neurological symptoms deriving from the disease or from primary treatment at the time of presentation for re-irradiation, and therefore we compared the symptoms before re-treatment and during follow-up. We tried to clearly differentiate between symptoms deriving from tumor progression and all other neurological changes in an effort to assess the real danger of re-irradiation as exactly as possible. As expected, some patients showed reduction of neurological symptoms after combined treatment, although an increase of symptoms, which we believe to be caused by re-irradiation, was reported in two patients. Despite this, our toxicity data are among the best reported with re-irradiation [13, 18, 22]. Only one group has found even better results in terms of toxicity, but in that trial the interval between the two treatments was at least a year and so the results might be due to tissue repair mechanisms [23]. Most importantly, no case of radiotherapy necrosis was observed in our patients. This finding differs greatly from a study by Bauman et al. reporting an actuarial risk of necrosis of 22% at 1 year following re-treatment [24]; however, this is the highest risk ratio found in the literature. A possible explanation for our better outcomes might be that half our patients underwent re-resection, thereby reducing the amount of tissue at risk of necrosis. Further, in the study by Bauman et al. repeat irradiation of 15 from a total of 34 patients included the whole brain, so it must be assumed that larger treatment volumes were the cause of the increased side effects. Two further explanations are possible: first, survival time in our study is relatively short. It is therefore not possible to rule out that necrosis would have developed in the following months; second, according to the alpha/beta model, there is no significant difference between total doses in whole-brain radiotherapy (WBRT) plus stereotactic radiosurgery (30 Gy WBRT in fractions of 3 Gy plus 20 Gy/fraction radiosurgery) and the conventionally fractioned dose of 54–66 Gy in primary brain tumors plus a 6×5 Gy boost after an interval of minimum 6 months. In the treatment of brain metastases, radiotherapy necrosis develops in only a few cases [25]. One might therefore assume that the rate of necrosis after re-irradiation is lower than previously thought.

Because of the relatively small number of patients in our analysis and the wide array of salvage chemotherapy regimens received, no statement can be made on the optimal concomitant substance. It is possible that with newer drugs and additional lines of therapy, especially with the advance of biologicals (imatinib, gefitinib), even longer survival times can be achieved [26, 27].

In conclusion, the data presented here show that re-irradiation is a safe and feasible treatment option in patients with recurrent malignant glioma. Low short-term toxicity and the possibility of lengthening patients' lives make it a treatment option that should be further evaluated in larger trials. However, it is possible that only those patients who are eligible for a combination of re-resection, re-irradiation and chemotherapy benefit from this treatment.

References

1. Burton EC, Prados MD (2000) Malignant gliomas. Curr Treat Options Oncol 1: 459–468
2. Simpson JR, Horton J, Scott C, et al (1993) Influence of location and extent of surgical resection on survival of patients with glioblastoma multiforme: Results of three consecutive radiation therapy oncology group (RTOC) clinical trials. Int J Radiat Oncol Biol Phys 26: 239–244
3. Pan E, Prados MD (2004) Translational research in neuro-oncology. ASCO Educational book 120–131
4. Lanzetta G, Campanello C, Rozzi A, et al (2003) Temozolamide in radio-chemotherapy combined treatment for newly-diagnosed glioblastoma multiforme: phase II clinical trial. Anticancer Res 23: 5159–5164
5. Stupp R, Mason WP, van den Bent MJ, et al (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352: 987–996
6. Fazeny-Dorner B, Gyries A, Rossler K, et al (2003) Survival improvement in patients with glioblastoma multiforme during the last 20 years in a single tertiary-care center. Wien Klin Wochenschr 115: 389–397
7. Buckner JC (2003) Factors influencing survival in high-grade gliomas. Semin Oncol 30 [6 Suppl 19]: 10–14
8. Fazeny-Dorner B, Veitl M, Wenzel C, et al (2003) Second-line chemotherapy with dacarbacine and fotemustine in nitrosourea-pretreated patients with recurrent glioblastoma multiforme. Anticancer Drugs 14: 437–442
9. Tatter SB (2002) Recurrent malignant glioma in adults. Curr Treat Options Oncol 3: 509–524
10. The Medical Research Council Brain Tumour Working Party (2001) Randomized trial of procarbazine, lomustine, and vincristine in the adjuvant treatment of high grade astrozytoma: a medical research council trial. J Clin Oncol 19: 509–518
11. Hau P, Baumgart U, Pfeifer K, et al (2003) Salvage therapy in patients with glioblastoma: is there any benefit? Cancer 98: 2678–2686
12. Kaplan EL, Meier P (1958) Non parametric estimation for incomplete observations. J Am Stat Ass 53: 457–481
13. Kim HK, Thornton AF, Greenberg HS, et al (1997) Results of re-irradiation of primary intracranial neoplasms with three-dimensional conformal therapy. Am J Clin Oncol 20: 358–363
14. Vitanovics D, Sipos L, Afra D (2002) BCNU-DBD chemotherapy of recurrent supratentorial anaplastic astrocytomas and glioblastomas. Neoplasma 49: 342–345
15. Brada M, Hoang-Xuan K, Rampling R, et al (2001) Multicenter phase II trial of temozolamide in patients with glioblastoma multiforme at first relaps. Ann Oncol. 12: 259–266
16. Yung WK, Prados MD, Yaya-Tur R, et al (1999) Multicenter phase II trial of temozolamide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. Temodal Brain Tumor Group. J Clin Oncol 17: 2762–2771
17. Mühlbauer M, Gebhart E, Pfisterer W, et al (2002) Microsurgery for glioblastoma preserves short-term quality of life both in functionally impaired and independent patients. Wien Klin Wochenschr 114: 886–873
18. Nieder C, Grosu AL, Molls M (2000) A comparison of treatment results for recurrent malignant gliomas. Cancer Treat Rev 26: 397–409
19. Vordermark D, Kolbl O, Ruprecht K, et al (2005) Hypofractionated stereotactic re-irradiation: treatment option in recurrent malignant glioma. BMC Cancer 5: 55
20. Arcicasa M, Roncadin M, Bidoli E, et al (1999) Reirradiation and lomustine in patients with relapsed high-grade gliomas. Int J Radiat Oncol Biol Phys 43: 789–793
21. Bhatnagar A, Heron DE, Kondziolka D, et al (2002) Analysis of repeat stereotactically radiosurgery for progressive primary and metastatic CNS tumors. Int J Radiat Oncol Biol Phys 53: 527–532
22. Combs SE, Ahmadi R, Schulz-Ertner D, et al (2005) Recurrent low-grade gliomas: the role of fractionated stereotactically re-irradiation. J Neuroncol 71: 319–323
23. Veninga T, Langendijk HA, Slotman BJ, et al (2001) Reirradiation of primary brain tumours: survival, clinical response and prognostic factors. Radiother Oncol 58: 127–137
24. Bauman GS, Sneed PK, Wara WM, et al (1996) Reirradiation of primary CNS tumors. Int J Radiat Oncol Biol Phys 36: 433–441
25. Lindvall P, Bergstrom P, Lofroth PQ, et al (2005) Hypofractionated conformal stereotactic radiotherapy alone or in combination with whole-brain radiotherapy in patients with cerebral metastases. Int J Radiat Oncol Biol Phys 61: 1460–1466
26. Holdhoff M, Kreuzer KA, Appelt C, et al (2005) Imatinib mesylate radiosensitizes human glioblastoma cells through inhibition of platelet-derived growth factor receptor. Blood Cells Mol Dis 34: 181–185
27. Rich JN, Reardon DA, Peery T, et al (2004) Phase II trial of gefitinib in recurrent glioblastoma. J Clin Oncol 22: 133–142

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