Hypofractionated Reirradiation for Recurrent Malignant Glioma

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Background and Purpose: Treatment options for recurrent high-grade glioma after a complete course of radiotherapy comprise surgery, reirradiation and chemotherapy but the efficacy of any of the given salvage treatments is limited. In order to further define the role of short-term radiotherapy as retreatment option for selected patients, we analyzed outcomes after treatment with a hypofractionated radiation.

Patients and Methods: Treatment outcomes (overall survival and treatment-associated toxicity) were analyzed retrospectively in 31 patients treated between 1994 and 2007. Hypofractionated radiotherapy was performed after three-dimensional CT planning with a median total dose of 20 Gy in a single department.

Results: With a median interval of 20 months from primary radiotherapy, two grade III and 29 grade IV tumors were reirradiated. Pretreatment consisted of surgery and involved-field radiotherapy (median 59 Gy). 77% of the patients received additional chemotherapy before the second course of radiotherapy, and 48% were treated after secondary resection. The median overall survival after hypofractionated radiotherapy was 10.2 months, and the median overall survival time after primary diagnosis 30.9 months. No severe toxicity was observed.

Conclusion: Hypofractionated reirradiation with 20 Gy given over 1 week is a practicable and well-tolerated treatment option for patients with recurrent malignant glioma. The overall survival was comparable to the reported outcomes from other series including those with longer treatment protocols.

Key Words: Recurrent malignant glioma · Reirradiation · Hypofractionation

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Hypofraktionierte Rebestrahlung bei rezidivierten malignen Gliomen

Hintergrund und Ziel: Die aktuellen Behandlungsoptionen bei Rezidiv eines vorbestrahlten hochmalignen Glioms beinhalten Operation, Strahlentherapie und Chemotherapie. Allerdings ist die Wirksamkeit der gegebenen Salvage-Behandlungen begrenzt. Um die Rolle einer kurzzeitigen Rebestrahlung bei ausgewählten Patienten weiter zu definieren, wurden Krankheitsverläufe bei Patienten nach Behandlung mit einem kurzzeitigen hypofraktionierten Bestrahlungskonzept analysiert.

Patienten und Methodik: Die Verläufe (Gesamtüberleben und Toxizität) von 31 zwischen 1994 und 2007 behandelten Patienten wurden retrospektiv analysiert. Die hypofraktionierte Strahlentherapie wurde nach dreidimensionaler CT-Planung mit einer mittleren Gesamtdosis von 20 Gy in einer einzelnen Abteilung durchgeführt.

Ergebnisse: Bei zwei Grad-III- und 29 Grad-IV-Tumoren wurde mit einem mittleren Abstand von 20 Monaten nach der primären Strahlentherapie eine Rebestrahlung durchgeführt. Die Vorbehandlung bestand in Operation und Involved-Field-Strahlentherapie (Median 59 Gy). 77% der Patienten erhielten vor dem zweiten Strahlentherapiekurs zusätzlich eine Chemotherapie, und 48% wurden nach erneuter Resektion behandelt. Das mittlere Gesamtüberleben nach hypofraktionierter Strahlentherapie betrug 10,2 Monate und das mittlere Gesamtüberleben nach Primärdiagnose 30,9 Monate. Schwere Toxizitäten wurden nicht beobachtet.

Schlussfolgerung: Die hypofraktionierte Rebestrahlung mit 20 Gy über eine Woche ist eine praktikable und gut verträgliche Behandlungsform für Patienten mit Rezidiv eines hochgradigen malignen Glioms. Das Gesamtüberleben war mit den in der Literatur berichteten Resultaten anderer Serien einschließlich jener mit längeren Bestrahlungsprotokollen vergleichbar.

Schlüsselwörter: Rezidiviertes Glioblastom · Rebestrahlung · Hypofraktionierung

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Introduction

The diagnosis of malignant glioma is usually associated with an extremely poor prognosis. The inclusion of temozolomide into the primary treatment setting for malignant brain tumors improved local control and survival rates. The EORTC/NCIC study (22981/CE.3) revealed that concomitant and adjuvant temozolomide was associated with a significant increase of overall survival from 12.1 to 14.6 months [39].

Despite this clear improvement, tumor recurrence was observed in about 90% of the cases within 2 years after diagnosis for many tested adjuvant chemotherapies [17, 20, 31, 39].

In case of recurrence, the treatment options are limited because of the sensitivity of the surrounding normal tissues and putative treatment resistances after intensive pretreatment. Nevertheless several sets of data indicate that in certain patients retreatment will result in additional survival time and stabilization of neurologic deterioration [16, 28, 29]. Whenever possible, a second resection should be attempted, bearing the inherent risk of functional losses in mind. Thus only patients with well-accessible tumors and a good performance status might be subjected to this approach [3, 15, 27]. The efficacy of chemotherapy has been tested in many different settings with only modest beneficial effects [5, 30, 44–46].

Although the standard pretreatment generally prohibits the use of a second fully dosed radiotherapy course, reirradiation has been shown to be of value after local relapse. In this regard, several different modalities of percutaneous radiotherapy or brachytherapy for retreatment of glioblastomas have been investigated. In general, all data consistently show that, whenever employed cautiously, reirradiation is feasible and most likely prolongs survival [1, 4, 7, 8, 11, 13, 14, 21, 24, 34, 35, 38, 40–42].

Since the life expectancy of these patients is clearly limited, it is advisable to employ short-term treatment approaches [32, 33]. From 1994 onward, all patients clinically considered to benefit from a retreatment course were treated with a hypofractionated radiotherapy protocol in our department. Outcome and toxicities were now evaluated retrospectively.

Patients and Methods

Patients

This retrospective analysis includes patients treated between March 1994 and September 2007 at the University of Tübingen, Germany. All patients had prior histological diagnosis of malignant glioma, prior radiotherapy and a clear evidence of recurrence or progression by cranial computed tomography (CCT) or magnetic resonance imaging (MRI). The Karnofsky Performance Score (KPS) had to be ≥ 60. All treatment decisions were based on interdisciplinary counseling.

Treatment

Hypofractionated radiotherapy was generally applied with a 6-MV linear accelerator. In all but four cases treated with an intensity-modulation radiotherapy (IMRT) approach, conventional three-dimensional planning was performed. In order to achieve an accurate daily repositioning, an individual immobilization mask was manufactured for each patient. Treatment planning was performed three-dimensionally with the Helax-TMS (Nucletron), OTP (Nucletron), Xknife (Radionics), or the Hyperion System (UKT) for IMRT.

Planning target volume (PTV) definition was based on contrast-enhanced CT or MR images or both with a slice thickness of 3 mm. The PTV included the gross tumor volume, defined as area of contrast enhancement on the CT or MR scans, and a safety margin of 3–10 mm depending on localization of the lesion and the estimated exposure of the organs at risk according to the ICRU report 50/62. In 24 patients, irradiation was accompanied by prophylactic dexamethasone treatment in a median daily dose of 12 mg (3–32 mg).

Statistical Analysis

For statistical analysis, we used the JMP software (SAS Institute Inc.). The primary endpoint was overall survival after reirradiation starting from the beginning of reirradiation. It was calculated using the Kaplan-Meier method considering death an event and taking patients alive at last follow-up as censored. Secondary endpoint was the time of survival from the initial diagnosis.

Subgroup analysis of prognostic factors was performed by comparing survival curves with the log-rank test. Significance level was $p \leq 0.05$. Prognostic factors were further evaluated in a univariate and multivariate stepwise Cox regression analysis.

Results

Patient Characteristics

31 patients (21 male, ten female) were treated. The median age at primary diagnosis was 50 years (16–74 years). The last available histological grading revealed a WHO grade III tumor in two and a WHO grade IV tumor in 29 cases.

All patients had received previous involved-field external-beam radiotherapy (6-MV linear accelerator) with a median dose of 59 Gy (39–60 Gy) following macroscopic complete resection (70%), partial resection (23%), or biopsy (7%).

48% of patients underwent further surgery before reirradiation resulting in macroscopic complete resection in 74% at any time before the second radiation course. Six patients received local surgical procedures after reirradiation.

24 patients received chemotherapy before reirradiation, 15 of them as concomitant radiochemotherapy. Five of the remaining seven chemo-naive patients underwent chemotherapy after reirradiation, and eight patients were given additional chemotherapy after reirradiation. A total of 17 patients received second- or third-line chemotherapy during the course of their disease. In general, predominantly used chemotherapeutics were temozolomide (23), lomustine/procarbazine/vincristine (12) or nimustine/teniposide (16).

Before commencing reirradiation, the median KPS was 90 (60–100). Patient and tumor characteristics are summarized in Tables 1 and 2.

Treatment Evaluation and Toxicity

The PTV for retreatment was found to be inside or closely adjacent to the initial PTV in the majority of cases. We analyzed the region of recurrence according to the suggestions by Lee et al. who described "in field", "border" and "outside" to be whenever > 80%, 20–80% or < 20% of the recurrent tumor was found within the 95% isodose, respectively [23]. In our series recurrence was a true in-field relapse in 69% of the cases, whereas in 10% of the cases recurrence occurred in the border area, and in 21% of the cases a "outside" relapse was detectable (Figure 1). The median time interval between first treatment and salvage radiotherapy was 18 months (3–109 months). We applied a median total dose of 20 Gy (20–25 Gy), using a single dose of 5 Gy (4–5 Gy). The median size of reirradiation PTV was 52.7 ml (0.9–277 ml). Further information concerning treatment planning and fractionation is given in Table 3.

Hypofractionated reirradiation was well tolerated by all of the patients and no severe acute toxicity in regard to the neurologic or general health status was observed. Minor effects of hypofractionated reirradiation were headache and nausea. No clinical signs leading to the suspicion of radiation necrosis were reported. However, the real incidence rate of radiation necrosis can only be obtained by pathologic examination. In eight patients a secondary resection was performed after reirradiation, with a location of the resection generally not completely matching the reirradiated areas. In six cases the resection area was adjacent to the retreatment area with necrosis being detectable in two cases.

Table 1. Patient characteristics.

Tabelle 1. Patientencharakteristika.

Median age at primary diagnosis [years (range)]	50	(16–74)
Sex [n (%)]		
• Male	21	(68)
• Female	10	(32)
Initial surgical procedure [n (%)]		
• Gross total resection	22	(71)
• Subtotal resection	7	(23)
• Biopsy	2	(6)
Initial radiotherapy		
• Median overall dose [Gy (range)]	59	(39–60)
• Median single dose [Gy (range)]	2	(1.5–3)
• Concomitant chemotherapy [n (%)]	15	(48)
Salvage therapy before hypofractionated reirradiation [n (%)]		
• Surgery	15	(48)
• Chemotherapy	18	(59)
Median Karnofsky Index at hypofractionated reirradiation [KI (range)]	90	(60–100)

Table 2. Tumor characteristics.

Tabelle 2. Tumorcharakteristika.

	Initial n (%)	Last available n (%)
Histology		
Oligoastrocytoma	2 (6)	1 (3)
Astrocytoma	3 (10)	1 (3)
Glioblastoma	26 (84)	29 (94%)
Grading		
WHO grade I	0 (0)	0 (0)
WHO grade II	1 (3)	0 (0)
WHO grade III	4 (13)	2 (6)
WHO grade IV	26 (84)	29 (94)

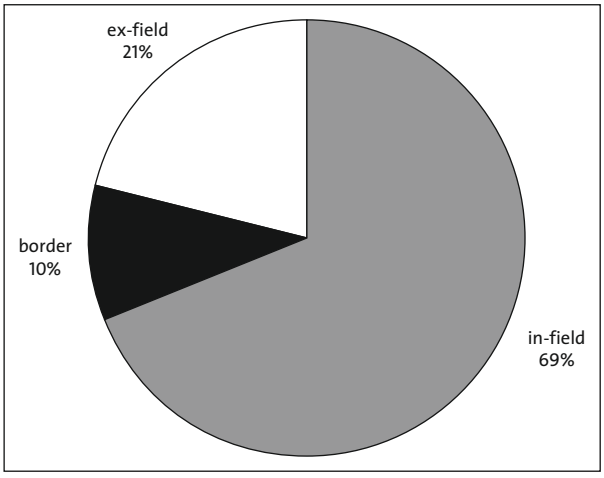


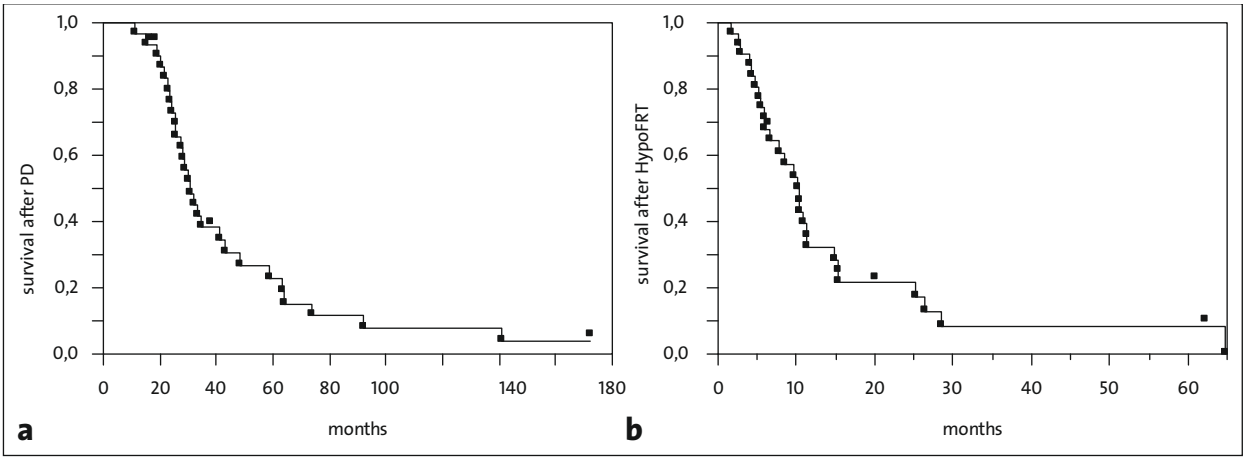
Figure 1. Location of tumor recurrence.

Abbildung 1. Ort des Rezidivs.

Table 3. Treatment details of hypofractionated reirradiation. PTV: planinng target volume.

Tabelle 3. Behandlungsdetails der hypofraktionierten Rebestrahlung. PTV: Planungszielvolumen.

Median age at hypofractionated reirradiation [years (range)]	52	(17–76)
Time from primary treatment to hypofractionated reirradiation [months (range)]	18	(3–109)
Hypofractionated reirradiation		
• Median PTV [ml (range)]	55	(0.9–277)
• Median total dose [Gy (range)]	20	(20–25)
• Median single dose [Gy (range)]	5	(4–5)
Fractionation schedules [n (%)]		
• 4 × 5 Gy	19	(61)
• 5 × 4 Gy	10	(32)
• 5 × 5 Gy	2	(7)



Figures 2a and 2b. Overall survival after primary diagnosis (a) and reirradiation (b).

Abbildungen 2a und 2b. Gesamtüberleben nach Primärdiagnose (a) und Rebestrahlung (b).

Table 4. Overall survival (OS) and treatment after hypofractionated reirradiation.

Tabelle 4. Gesamtüberleben (OS) und Behandlung nach hypofraktionierter Rebestrahlung.

Median OS [months (range)]		
• From primary diagnosis	30.9	(11–172)
• From hypofractionated reirradiation	10.2	(2–65)
6-month OS [% (range)]	72 ± 7	(58–83)
12-month OS [% (range)]	43 ± 7	(29–58)
Treatment after hypofractionated reirradiation [n (%)]		
• Surgery	6	(19)
• Chemotherapy	13	(42)
• Radiotherapy	3	(10)

Therapeutic Efficacy

The median overall survival in our cohort calculated from primary diagnosis was 30.9 months (11–172 months), with 12- and 24-month survival rates of 96% and 75%, respectively (Figure 2a, Table 4).

Median survival time from the start of reirradiation was 10.2 months (2–65 months). The survival rate at 6 months and 12 months after reirradiation was 72% and 43%, respectively (Figure 2b, Table 4). At the time of the last evaluation, four patients were still alive at 6, 9, 20, and 62 months after reirradiation, all with a histology of glioblastoma.

Younger age at primary diagnosis was confirmed to be of positive prognostic significance (Table 5). The survival for patients younger than the median age of 50 years was 11.3 months, whereas median survival for patients ≥ 50 years was 8.4 months (p = 0.07).

Although it seems reasonable to think that the size of the planning target volume could be of relevance, the statistical analysis using the PTV as a continuous variable did only reveal a tendency in favor of smaller volumes (Table 5). After arbitrarily dividing the patients into two groups with a PTV of > and < 30 ml as described before [22], a significant influence of the initial tumor volume was detectable (p = 0.01), with an overall survival rate of 9.7 and 25.2 months, respectively (Figure 3).

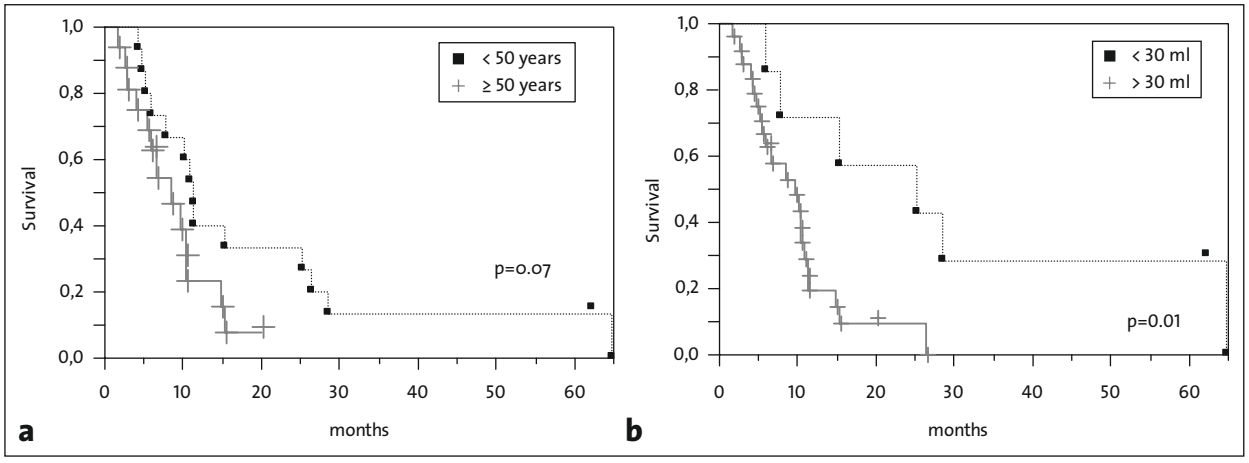
Additional factors influencing outcome after retreatment were KPS and a longer interval between the primary irradia-

Table 5. Prognostic factors for overall survival after hypofractionated reirradiation according to Cox regression analysis. PTV: planning target volume.

Tabelle 5. Prognostische Faktoren für das Gesamtüberleben nach hypofraktionierter Rebestrahlung gemäß Cox-Regressionsanalyse. PTV: Planungszielvolumen.

Variable	Univariate	Multivariate
Age at primary diagnosis (years)	< 0.01*	0.07
Complete resection before hypofractionated reirradiation (yes vs. no)	0.26	–
Concomitant chemotherapy (yes vs. no)	0.89	–
Chemotherapy before hypofractionated reirradiation (yes vs. no)	0.11	–
Salvage surgery before hypofractionated reirradiation (yes vs. no)	0.63	–
Karnofsky Performance Score	0.01*	0.29
Interval (months)	0.05*	0.47
PTV (ml)	0.08	–
Chemotherapy after hypofractionated reirradiation (yes vs. no)	0.07	–
Surgery after hypofractionated reirradiation (yes vs. no)	< 0.01*	0.07

*p ≤ 0.05



Figures 3a and 3b. Subgroup analysis: overall survival after reirradiation by age (a) and by PTV (b).

Abbildungen 3a und 3b. Subgruppenanalyse: Überleben nach Rebestrahlung nach Alter (a) und nach PTV (b).

tion series and the reirradiation (Table 5), whereas neither the initial use of radiochemotherapy or complete resection nor salvage surgery before reirradiation had a prognostic influence on survival after retreatment (Table 5).

Discussion

Despite the fact that the addition of concomitant temozolomide significantly improved survival times of high-grade gliomas, almost all patients ultimately recur locally [2]. Currently employed salvage therapies include surgical resection, salvage chemotherapy, and reirradiation by different modalities [16, 28, 29].

In the present series of patients with recurrent high-grade glioma treated with short-term hypofractionated irradiation, a median survival time of 10.2 months was achieved. Comparison of overall survival and toxicity of the chosen treatment with results of different approaches using external-beam radiotherapy for reirradiation reported over the last years [1, 4, 8, 9, 11, 22, 25, 35, 36, 41–43] certainly remains difficult because of the variation in target definition, treatment technique, tumor volume, concomitant chemotherapy, and initial patient characteristics. However, considering the large median PTV of 50 ml and the high number of glioblastoma included, this is comparable to the earlier results. Conventionally fractionated total doses of 36 Gy up to 46 Gy were resulting in overall survival rates of 8 and 6.1 months, respectively [8, 41]. Two groups report on an overall survival of 8–10 months with a total dose of 30 Gy using a hypofractionated schedule with a single dose of 5 Gy [42, 43]. An association of longer overall survival times with prior rerersection as described before [4] was not seen in our series.

No severe acute toxicity was mentioned in the studies above. However, Shepard et al. found an increasing risk of late complication rate up to 36% using a single dose of 5 Gy, with total doses > 40 Gy as a significant predictor of complications [37]. Single doses of > 5 Gy were associated with higher toxicities after hypofractionated stereotactic radiotherapy in case of brain metastases [12], whereas hypofractionated stereotactic radiotherapy for recurrent malignant glioma maintained the quality of life for an acceptable period [11]. The delivered total dose in our study was below the dose where inacceptable toxicity in preradiated patients was reported [37]. Indeed, no severe toxicity was seen in our series, administering dexamethasone prophylactically in a fair number of patients.

A significant difference in survival depending on tumor volume with a separation at 30 ml was described before [6, 22]. In accordance with that, median survival tends to increase for a PTV below and above the median value of 30 ml amounting to 8.4 and 25.2 months, respectively.

With regard to the interval between first treatment and reirradiation, our patient collective shows a bias toward a better prognosis. In the literature, intervals from < 10 months [18, 22] to > 30 months [19, 41] appear. Veninga et al. found a median survival time of 6.1 and 16.2 months for an interval from 12 to 36 months and for an interval of > 36 months, respectively [41]. Another study separates treatment intervals of > 30 months as connected with longer survival [14]. In our series, the median time between first and second radiotherapy was 18 months, similar to Vordermark et al. and Voynov et al. [42, 43] with a tendency towards positive correlation of longer interval and survival after hypofractionated radiotherapy.

It must be noted that after reirradiation both chemotherapy and surgical interventions were performed for salvage treatment in 48% of patients. The patient alive after 62 months was treated with chemotherapy, repeated surgery, and irradiation. As previously reported [6, 42], the median survival in these intensely treated patients was significantly longer encouraging the stated benefit of aggressive salvage treatment in a subgroup of patients suffering recurrent glioblastoma.

Taken together, the current series suggests that hypofractionated external-beam radiotherapy implementing a fraction

schedule over 1 week leads to results comparable with other salvage therapies of recurrent malignant glioma in regard to toxicity and efficacy. Chemotherapy-based approaches are most frequently employed with similar overall survival times in the range of 5–11 months [5, 45]. However, it has to be taken into account that the use of salvage chemotherapy is associated with relevant, mostly bone marrow-related side effects [5]. Although surgical reintervention can be a suitable option in selected patients, there is also a considerable risk of morbidity and mortality and it should be combined with additional salvage treatment [3, 10, 26]. Other radiation-based approaches include radiosurgery as well as brachytherapy retreatments. Radiosurgery is only suitable for very selected patients with small lesions [36], and brachytherapy-based options are invasive, associated with neurologic toxicity and require highly experienced personnel [13, 21, 24, 34, 40].

The noninvasive approach with an individual mask fixation system will allow to treat also patients excluded from surgical interventions necessary for brachytherapy because of performance status or tumor location. Protracted radiotherapy with conventional fractions appears impractical considering the still palliative nature of all given treatment possibilities. On the other hand, the fractionation enables reirradiation of larger tumors in eloquent structures with acceptable toxicity as compared to the use of radiosurgery.

Conclusion

Until results from prospective trials consolidate the data obtained in the present analysis, decisions for salvage treatment will remain individual. However, because of the feasibility and low toxicity of this intervention, hypofractionated reirradiation may be offered to a substantial subgroup of patients rendering hospitalization unnecessary. The short duration of the treatment furthermore offers the possibility of combining it with concomitant or consecutive chemotherapy, e.g., temozolomide in a weekly schedule.

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