CT-Guided Interstitial HDR Brachytherapy for Recurrent Glioblastoma Multiforme

Long-Term Results

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Background and Purpose: Recurrences of glioblastoma multiforme (GBM) within previously irradiated volumes pose a serious therapeutic challenge. This retrospective study evaluates the long-term tumor control of recurrent GBM treated with interstitial high-dose-rate brachytherapy (HDR-BRT).
Patients and Methods: Between 1995 and 2003, 84 patients were treated for recurrent cerebral GBM located within previously irradiated volumes. All patients had received adjuvant external radiotherapy following primary surgery, with a focal dose up to 60 Gy. The median recurrent tumor volume was 51 cm^3 (3–207cm^3), and the HDR-BRT consisted of an afterloading ^{192}Ir implant which delivered a median dose of 40 Gy (30–50 Gy). Catheter implantation was implemented using interactive computed tomography (CT) guidance under local anesthesia and sedoanalgesia.
Results: After a median follow-up of 61 months, 5/84 patients (6%) were alive. The median post-BRT survival was 37 weeks, and the median overall survival 78 weeks. Moderate to severe complications occurred in 5/84 cases (6%).
Conclusion: For patients with recurrences of GBM within previously irradiated volumes, CT-guided interstitial HDR-BRT is a feasible treatment option that can play an important role in providing palliation.

Key Words: Recurrent glioblastoma multiforme · HDR brachytherapy · CT-based planning

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CT-gestützte interstitielle HDR-Brachytherapie bei Glioblastoma-multiforme-Rezidiven. Langzeitergebnisse

Hintergrund und Ziel: Glioblastoma-multiforme-(GBM-)Rezidive innerhalb vorbestrahlter Volumina stellen eine therapeutische Herausforderung dar. Ziel dieser Studie ist die Vorstellung der CT-gestützten interstitiellen High-Dose-Rate-Brachytherapie (HDR-BRT) bei der Behandlung zerebraler GBM-Rezidive.
Patienten und Methodik: Von 1995 bis 2003 wurden insgesamt 84 Patienten mit rezidiviertem GBM mittels interstitieller HDR-BRT behandelt. Alle Patienten waren voroperiert und hatten im Rahmen der Primärtherapie eine adjuvante perkutane Teilhirnbestrahlung bis 60 Gy erhalten. In der Rezidivsituation erhielten alle eine fraktionierte interstitielle ^{192}Ir-HDR-BRT bis zu einer medianen Gesamtdosis von 40 Gy (30–50 Gy). Die Implantation der BRT-Katheter wurde bei einem medianen Tumorvolumen von 51 cm^3 (3–207 cm^3) unter CT-Kontrolle in Sedoanalgesie und Lokalanästhesie durchgeführt.
Ergebnisse: Bei einer medianen Nachbeobachtung von 61 Monaten betrug das mediane Überleben 37 Wochen vom Zeitpunkt der Brachytherapie sowie 78 Wochen ab Diagnosestellung. Moderate bis schwerwiegende Komplikationen ereigneten sich in 5/84 Fällen (6%).
Schlussfolgerung: Die CT-gestützte interstitielle HDR-BRT ist ein wertvolles Instrument für die palliative Behandlung von Patienten mit rezidiviertem GBM.

Schlüsselwörter: Rezidiviertes Glioblastoma multiforme · HDR-Brachytherapie · CT-gestützte Behandlungsplanung

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Introduction

Glioblastoma multiforme (GBM World Health Organization [WHO] grade 4) ranks among the most aggressive tumors in oncology. The current treatment procedure consists of surgical resection to the extent that is safely feasible, followed by fractionated radiotherapy (RT) up to 60 Gy with concomitant administration of temozolomide [54].

Despite this multimodal approach [16, 27], the median survival remains disappointingly short, about 10 months in most reports, and less than 5% of patients survive more than 5 years after resection and RT [41], suggesting, among other things, that there is clinical heterogeneity in GBM radiosensitivity [6, 10, 22]. However, the efficacy of irradiation is not only limited by the inherent radioresistance of glioma cells, but also by the radiosensitivity of surrounding healthy brain tissue [6, 10].

Although focal dose escalation beyond 60 Gy is feasible using advanced technologies [40], the predominant failure pattern remains local [2, 14, 49]. In recurrences of GBM within previously irradiated volumes, low-dose-rate brachytherapy (LDR-BRT) is an applied method to deliver additional dose while sparing healthy tissue [33, 45]. To the best of our knowledge, our analysis is the largest study reporting clinical experience on the use of interstitial high-dose-rate brachytherapy (HDR-BRT) in the treatment of recurrent GBM.

Patients and Methods

Between 1995 and 2003, 84 patients were treated with computed tomography-(CT-)guided interstitial ^{192}Ir-HDR-BRT for recurrent cerebral GBM. The study population's characteristics are described in Table 1.

All patients had received previous surgery as primary treatment for initial histology-proven GBM (WHO grade 4), and gross total resection was performed in 58/84 (69%) and subtotal resection in 26/84 patients (31%). All patients were given postoperative partial-brain irradiation with a focal dose up to 60 Gy, and the median interval from the date of surgery until the start of RT was 24 days (6–58 days). 17 patients (20%) received chemotherapy either as part of their initial treatment or for recurrent disease. No patient received chemotherapy planned in conjunction with BRT, and no case of secondary GBM was included. Recurrence histology was determined by review of previously resected material and increasing volume of gadolinium-enhancing lesion(s) on serial post-RT magnetic resonance imaging (MRI) scans.

Survival distribution was estimated using the Kaplan-Meier product limit method [25]. Variables were analyzed as dichotomous, and univariate analysis was performed to examine the differences between potentially prognostic subgroups [34].

Implantation Technique

Catheter implantation was performed with neurosurgical assistance using CT guidance [28, 29] under local anesthesia (20–40 ml lidocaine 2%) and sedoanalgesia (30–100 mg i.v. meperidine and 2–5 mg i.v. midazolam). Prophylactic premedication consisted of 40 mg i.v. dexamethasone and 250 mg i.v. phenytoin. Implantation technique of choice was transcranial insertion utilizing a Perspex template sutured to the scalp without requirement of a stereotactic frame [29] (Figure 1). Positional control of the first catheter was obtained by generating contrast-enhanced CT images with the catheter in situ, and this procedure was repeated for all subsequent applicators. Thus, maximum insertion depth, direction and position of the catheters were estimated by interactive CT scanning [28, 29, 55].

Table 1. Patient characteristics. BRT: brachytherapy.

Tabelle 1. Patientenmerkmale. BRT: Brachytherapie.

Number of patients	84
Age	Median 57 years (17–78 years) 20/84 (24%) patients ≤ 50 years 64/84 (76%) patients > 50 years
Ratio male/female	54/30
Tumor volume	Median 51 cm^3 (3–207 cm^3) 24/84 (29%) patients ≤ 30 cm^3 60/84 (71%) patients > 30 cm^3
Tumor sites	
• Frontal	43/84 (51%)
• Parietal	12/84 (14%)
• Temporal	23/84 (27%)
• Occipital	2/84 (2%)
• Corpus callosum	4/84 (6%)
Pre-BRT Karnofsky Performance Score	Median 80 (50–100)

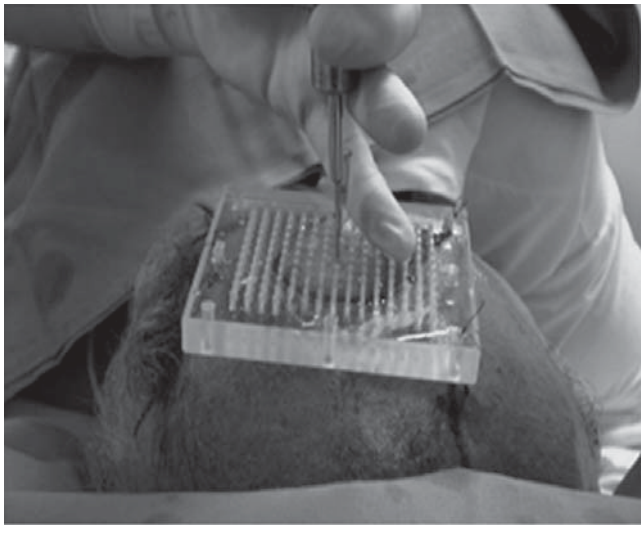
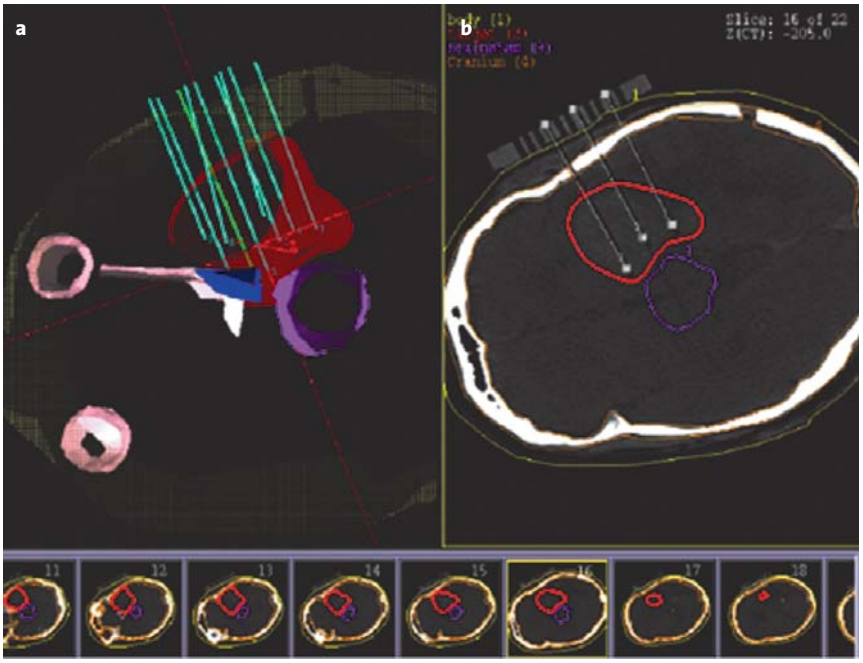


Figure 1. Implantation of flexible catheters in CT-guided Perspex template technique. Trepanation of the skull bone and dura mater through the template holes.

Abbildung 1. Implantation flexibler Katheter in CT-gestützter Plexiglas-Template-Technik. Trepanation der Schädelkalotte und der Dura mater durch die Template-Lochung.



Figures 2a and 2b. Interstitial brachytherapy implant of a right temporal-located glioblastoma multiforme recurrence. 3-D view (a) and representative 2-D view (b) of the reconstructed catheters and contoured anatomy of the same implant.

Abbildungen 2a und 2b. Interstitielles Brachytherapieimplantat bei rechtsseitig temporal lokalisiertem Glioblastoma-multiforme-Rezidiv. 3-D- (a) und repräsentatives 2-D-Bild (b) der Applikatorkonstruktion sowie der anatomischen Konturierungen des gleichen Implantats.

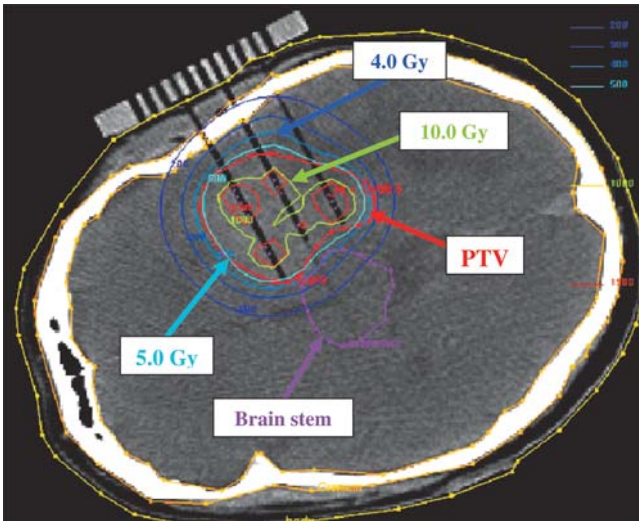


Figure 3. Example of the brachytherapy implant described in Figure 2. 2-D view on a transverse CT plane showing the catheter geometry as well as the PTV (red) with isodose lines and the brain stem (pink) as organ at risk. The reference dose is 5.0 Gy and represents the 100% isodose (light blue).

Abbildung 3. Brachytherapieimplantat aus Abbildung 2. Axiales CT-Schnittbild mit Wiedergabe der Applikatorgeometrie sowie Darstellung des PTV (rot) mit Isodosenverteilung und des Hirnstamms (rosa) als kritischer Struktur. Die Referenzdosis beträgt 5,0 Gy und entspricht der 100%-Isodose (hellblau).

Brachytherapy Planning and Treatment

Tumor demarcation with planning target volume (PTV) delineation for CT-based planning [3, 28, 29, 55] was originally performed using PLATO IPS (Nucletron, Veenendaal, The Netherlands) and, since 1999, the Exomio/ProSoma three-dimensional (3-D) planning system (Medcom, Darmstadt, Germany). Catheter reconstruction and final treatment planning with 3-D dose optimization were conducted by Plato BPS (Nucletron, Figure 2). Active source dwell positions were selected along the catheters to ensure placement inside the PTV and source location below the PTV surface (Figure 3). PTV coverage was defined as the proportion of the PTV receiving 100% of the prescribed dose, and the prescribed fractional dose of 5.0 Gy as the mean dose value on the PTV surface, representing also the 100% isodose line (Figure 4). The entire implantation/planning/optimization procedure required about 45–75 min by enabling the subsequent onset of BRT.

All patients received 5.0 Gy twice a day over consecutive days with an interval of at least 6 h to a total dose of 30 Gy in 16/84 (20%), 40 Gy in 55/84 (65%), and 50 Gy in 13/84 implants (15%), with a median dose value of 40 Gy. Median tumor volume was 51 cm^3 (3–207 cm^3), and median catheter number seven (one to 21). During treatment, all patients received prophylactic antibiotics, and corticosteroids were administered to improve neurologic function or relieve symptoms of increased intracranial pressure. Catheters were removed successional to the last BRT fraction and patients thereupon evaluated at intervals of 8 weeks with CT and MRI scans (Figure 5). The median hospitalization time amounted to 6.5 days (6–9 days).

As recommended [37], reported doses were specified by D_{90} and D_{100} as determined by the corresponding dose-volume histogram. Similarly, dose heterogeneity was specified by V_{100}, V_{150}, and V_{200}. The mean values for our series were: D_{90} = 5.2 Gy (4.2–6.1 Gy); D_{100} = 4.2 Gy (3.6–4.9 Gy); V_{100} = 93.8% (90–98%); V_{150} = 66.1% (60–71%); and V_{200} = 41% (30–47%).

Results

Survival

Overall survival was defined as the time from primary surgery to the time of death or last follow-up. After a median follow-up of 61 months, 5/84 patients (6%) were alive, and the median overall survival was 78 weeks, ranging from 13 weeks to 914 weeks.

Survival after interstitial HDR-BRT (post-BRT survival) was defined as the time from BRT to the time of death or last

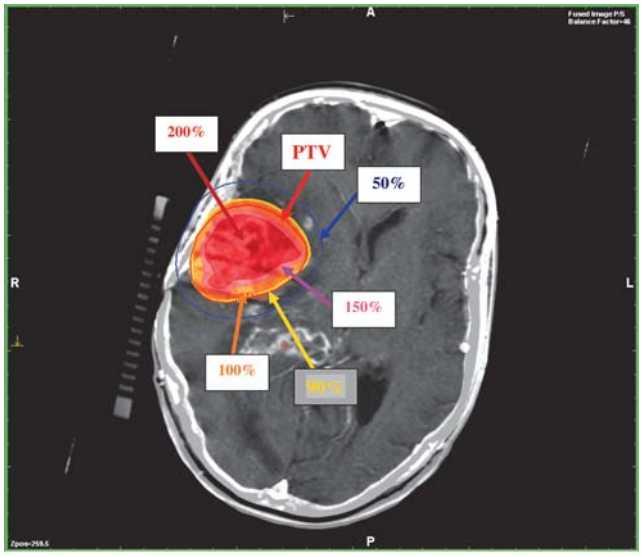


Figure 4. Isodose distribution of an ipsilateral temporal implant in a case of bifocal recurrence after ProSoma-based CT/MR image fusion. The color gradation represents: red = 200% isodose = 10.0 Gy, pink = 150% isodose = 7.5 Gy, orange = 100% isodose = 5.0 Gy, yellow = 90% isodose = 4.5 Gy, and blue = 50% isodose = 2.5 Gy. The respective target volume is denoted as red-delineated PTV.

Abbildung 4. Darstellung der Isodosenverteilung eines ipsilateralen temporalen Implantats bei bifokalem Rezidivmuster anhand ProSoma-basierter CT/MRT-Bildfusion. Die Farbskalierung entspricht: rot = 200%-Isodose = 10,0 Gy, rosa = 150%-Isodose = 7,5 Gy, orange = 100%-Isodose = 5,0 Gy, gelb = 90%-Isodose = 4,5 Gy und blau = 50%-Isodose = 2,5 Gy. Das jeweilige Zielvolumen ist als rot dargestelltes PTV markiert.

follow-up. Median post-BRT survival was 37 weeks, ranging from 8 weeks to 97 weeks.

Prognostic Factors for Survival

At the time of BRT, the Karnofsky Performance Score (KPS) distribution was as follows: KPS 100, n = 23; KPS 90, n = 9; KPS 80, n = 19; KPS 70, n = 18; KPS 60, n = 8; and KPS 50, n = 7. Regarding tumor volume, 24 patients had lesions ≤ 30 ml and 60 patients lesions > 30 ml. Partitioned by age, 20 patients were ≤ 50 years and 64 patients > 50 years.

The survival rates after HDR-BRT were not significantly different according to the following variables: tumor volume (≤ 30 ml vs. > 30 ml; Figure 6), KPS (≤ 80 vs. > 80), and age (≤ 50 years vs. > 50 years). We also conducted subgroup analyses of patients treated with different doses. Among patients who received total doses of 30 Gy, 40 Gy, or 50 Gy, there was no statistically significant difference in post-BRT survival (Figure 7).

Acute and Late Toxicity

5/84 patients (6%) developed moderate to severe complications. Among those, two developed intracerebral bleeding after catheter implantation and one of them died due to massive hemorrhage. One patient developed bacterial meningitis post explantationem, and was treated successfully with antibiotics. Another two appeared to suffer the consequences of symptomatic focal radiation necrosis, which was diagnosed by thallium single-photon emission CT (one patient) and MR spectroscopy (one patient) with a mean latent interval of 3.5 months (2–5 months). Both were managed conservatively by corticosteroid therapy.

The median KPS of the entire patient population was 80 (50–100) at the time of BRT. At each of the first three 8-week evaluation periods, the median KPS was 80 (50–100), 80 (50–100), and 70 (50–100), respectively. Therefore, there was no severe deterioration regarding function in the 6 months immediately following BRT.

Discussion

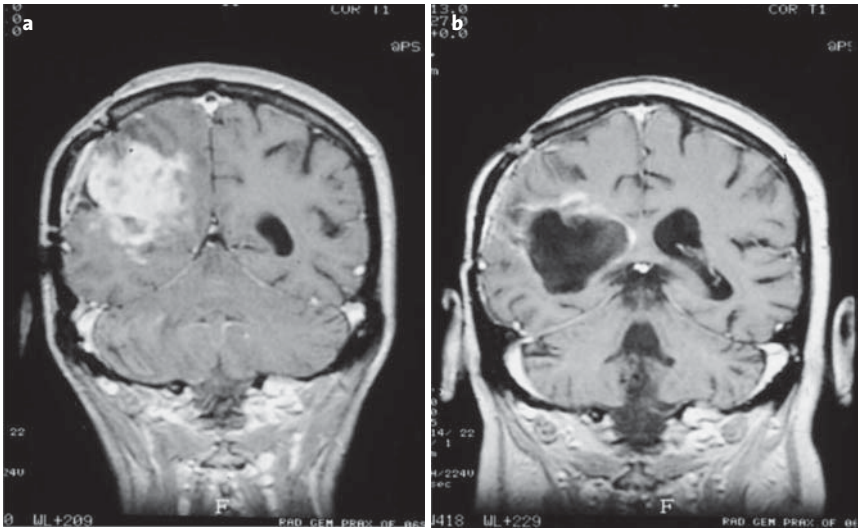
Despite significant advances in oncologic disciplines, less than 5% of GBM patients survive more than 5 years after resection and adjuvant treatment [41]. Patients who have recurrent lesions succumb to their disease [41], and retreatment with any existing modality is a challenging task for the clinicians.

Surgery, if attempted, and usually in combination with other regimens, has limited success [4, 21, 22, 32, 43, 48], while the risk for mortality and postoperative morbidity is high. Barker et al. [4], in a selected group of patients, achieved a median survival of 36 weeks after reoperation combined with various following therapies, whereas Dirks et al. [18] reported a median survival of 19 weeks for solely surgical treatment. Likewise, chemotherapy as sole treatment for recurrent GBM [7, 8, 11, 17, 24, 38, 44] gives predominantly unsatisfactory results (Table 2). Boiardi et al. [7] achieved a median survival of 44 weeks after systemic temozolomide and local mitoxantrone administration, following reoperation, while Newlands et al. [39] reported a median survival of 24 weeks among patients treated solely with temozolomide.

Above success rates of surgery and chemotherapy in the treatment of recurrent GBM support the importance of reirradiation as a therapeutic option, and stereotactic radiosurgery (SRS), as well as BRT, should be considered the most appropriate techniques to deliver additional high doses while maximally sparing normal tissue.

Hudes et al. [23] treated 20 patients with 24–35 Gy (3.0–3.5 Gy/fraction) achieving a post-SRS median survival of 42 weeks. Similar results were reported by other investigators with median survival varying between 34 and 41 weeks [30, 50]. However, these data should be evaluated conditionally since SRS is not recommended for recurrent lesions > 40 mm in diameter [26, 46, 47] and the fulfillment of this restriction immensely limits patient's eligibility for treatment.

Although a considerable number of anatomic sites have been treated successfully with HDR-BRT and there is no significant medical or radiobiological evidence against its use in central nervous system lesions [29, 36, 58], LDR is still consid-



Figures 5a and 5b. MRI scans of a right parietal-located glioblastoma multiforme recurrence before (a) and 4 months after (b) interstitial HDR-BRT.

Abbildungen 5a und 5b. MRT-Schnittbilder eines rechts parietal lokalisierten Glioblastoma-multiforme-Rezidivs vor (a) und 4 Monate nach (b) interstitieller HDR-BRT.

ered the standard modality in recurrent GBM. Results from several studies using LDR are summarized in Table 3.

Patients with reoperation prior to, or after BRT for recurrent GBM, show better survival compared to similar patients that did not undergo repeated surgery [5, 20, 21, 22, 32, 43, 45, 50, 52]. The latter is important for interpretation of the reported LDR studies, since a large number of patients (30–56%) were offered reoperation after [5, 13, 20, 35, 43, 45, 50, 52], or had undergone repeated surgery (45–100%) prior to BRT [5, 22, 32, 43, 52]. In addition, eligibility criteria were confined to unifocal disease, no involvement of upper brain stem or corpus callosum, absence of ventricular or subependymal invasion, well-circumscribed lesions, and KPS of ≥ 70. Thus, these trials were limited to mainly operable and cautiously selected recurrences of GBM.

Our patients were considered by neurosurgical assessment nonsurgical candidates for complete resection or spacious debulking after interstitial BRT and only a minority (23%) could be offered tumor debulking prior to BRT. Furthermore, our series included patients with multifocal disease, diffuse margins, corpus callosum or leptomeningeal involvement, and KPS of < 70. Only 20% had been treated with systemic chemotherapy prior to BRT and the median tumor volume was 51 cm^3 (3–207 cm^3), whereas in known LDR and SRS trials it varied between 17–47 cm^3 and 6–33 cm^3, respectively. In spite of the notably large tumor size and the expanded eligibility criteria, our results are encouraging: median post-BRT survival of 37 weeks, no deterioration of the pre-BRT KPS, and a rate of moderate to severe complications of 6%. In LDR studies, this rate was up to 26% and even higher when BRT was combined with hyperthermia [5, 9, 22, 43, 50, 52]. Symptomatic radionecrosis was diagnosed in two patients (2.5%), whereas in studies reporting results of

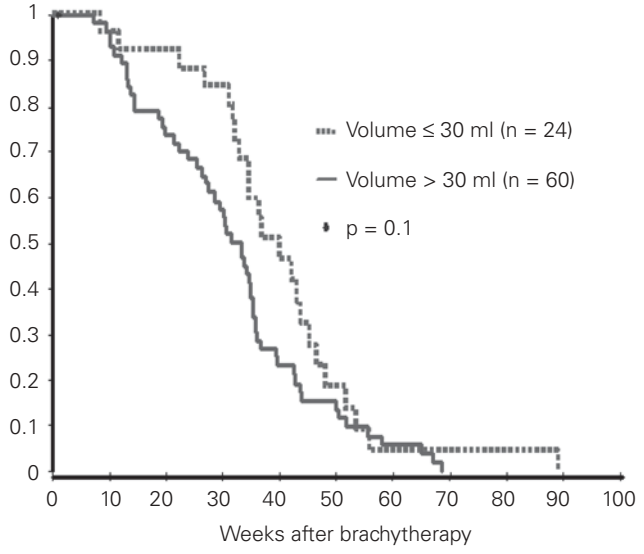


Figure 6. Postbrachytherapy survival according to pretreatment tumor volume.

Abbildung 6. Überleben vom Zeitpunkt der Brachytherapie an in Abhängigkeit vom Tumorvolumen.

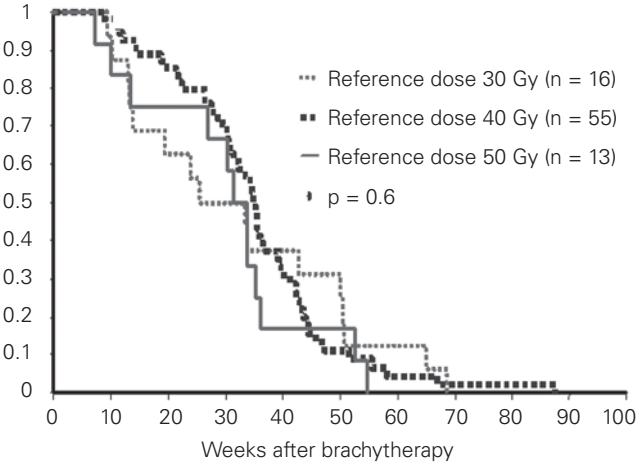


Figure 7. Postbrachytherapy survival according to reference total dose.

Abbildung 7. Überleben vom Zeitpunkt der Brachytherapie an in Abhängigkeit von der applizierten Brachytherapiedosis.

^{125}I seed implantation, 40–50% manifested symptomatic focal radiation damage [21, 33, 59].

Among our patients, we did not observe KPS, tumor volume or age to be significantly associated with improved survival after BRT. This finding is not consistent with other studies showing that KPS, tumor volume and age are predictors of survival after reresection or reirradiation of recurrent GBM [1, 12, 15, 35, 38, 45, 51]. However, there are also series reporting KPS [43, 45], tumor volume [35, 43, 45, 50] or age [5] not to have a statistically significant impact on survival from implant.

Analysis of patients treated with increased dose, namely 50 Gy, suggests that doses > 40 Gy prescribed to the PTV surface confer no added survival benefit. This finding may be due to very specific characteristics of dose distribution within and beyond the PTV surface, which represents the 100% isodose line, in our CT-based interstitial HDR modality. When scrutinizing implant characteristics regarding to prescribed dose values (30 Gy vs. 40 Gy vs. 50 Gy), isodose partition within the PTV surface displays inward volume shares receiving gradually increasing high doses with near-surface values characteristically amounting to 50 Gy (160% isodose) in case of the 30-Gy total dose scheme. Considering that disease progression after BRT manifested mainly exteriorly, but scarcely marginal, to the PTV surface, it becomes conceivable that peripheral dose coverage is of particular importance. Attempting maximal tumor cell kill while minimizing the risk of toxicity (the two cases of symptomatic focal radionecrosis occurred in the 50-Gy total dose scheme), 40 Gy prescribed to the PTV surface appear to be an appropriate dose achieving therapeutic efficacy and constitute our ongoing intramural policy. In addition, since 2004 we introduced systematic CT/MRI image fusion (see Figure 4) as an integral part of our effort to improve target volume definition by more precise gross disease demarcation. However, potential selection bias and a relatively small patient number treated with 50 Gy (n = 13) as well as 30 Gy (n = 16) may also explain the lack of differences observed.

Table 2. Trials of conservative treatment in recurrent glioblastoma multiforme. PCV: Procarbazin, CCNU (Lomustin), Vincristin.

Tabelle 2. Studien konservativer Behandlungsmodalitäten bei Glioblastoma-multiforme-Rezidiven. PCV: Procarbazin, CCNU (Lomustin), Vincristin.

Authors	Treatment modality	Patients (n)	Median survival after chemotherapy (weeks)
	Sole chemotherapy		
Boiardi et al. [8]	"8-drugs-in-one-day" vs. PCV	35	26 vs. 24
Paulsen et al. [44]	Ifosfamide vs. temozolomide	20	24 vs. 21
Couldwell et al. [17]	Temozolomide	20	31
Brandes et al. [11]	Procarbazine + temozolomide	28	27

Table 3. Trials of brachytherapy in recurrent glioblastoma multiforme. HDR: high dose rate; ^{125}I: iodine-125; ^{192}Ir: iridium-192; LDR: low dose rate.

Tabelle 3. Brachytherapiestudien bei Glioblastoma-multiforme-Rezidiven. HDR: „high dose rate"; ^{125}I: Jod-125; ^{192}Ir: Iridium-192; LDR: „low dose rate".

Authors	Treatment modality	Patients (n)	Median survival after brachytherapy (weeks)
	Total resection plus placement of permanent ^{125}I seeds		
Patel et al. [43]	LDR-^{125}I seeds (120–160 Gy)	40	47
Larson et al. [32]	LDR-^{125}I seeds (150–500 Gy)	38	52
	Reoperation prior to and following LDR brachytherapy		
Scharfen et al. [45]	LDR-^{125}I (37–120 Gy)	66	49
Shrieve et al. [50]	LDR-^{125}I (38.7–63.6 Gy)	32	45
Gutin et al. [20]	LDR-^{125}I (57.4–120 Gy)	18	35
Boisserie et al. [9]	LDR-^{192}Ir (40–60 Gy)	19	56
Mayr et al. [35]	LDR-^{125}I (50–70 Gy)	28	37
	Total resection plus GliaSite Radiation Therapy System (GliaSite RTS)		
Chan et al. [15]	LDR-^{125}I (29.9–80 Gy)	24	36
	Sole HDR brachytherapy		
Kolotas et al. [29]	HDR-^{192}Ir (30–40 Gy)	31	29
Tselis et al.	HDR-^{192}Ir (30–50 Gy)	84	37

Our data report on patients treated between 1995 and 2003, a time period when alkylating agents were not yet standard treatment in patients with GBM. Compared to most recent data corroborating the administration of temozolomide concomitant as well as adjuvant to RT for GBM [54], our results endorse questions while relativizing the declared impact and emphasized scale of benefit for temozolomide. On this, Stupp et al. [54] reported a median overall survival of 14.6 months (58.4 weeks) for RT plus temozolomide in newly diagnosed GBM. By contrast, our series included only a minority of patients, namely 20%, who received systemic chemotherapy, partly consisting of temozolomide. However, our patients achieved a median overall survival of 78 weeks. It can be assumed that the additional median survival benefit of 20 weeks (78 weeks vs. 58.4 weeks) is certainly due to the applied interstitial BRT method. On the other hand, the fact that more than 80% of our patients did never receive temozolomide obviously had no negative impact on survival likened to the data by Stupp et al. [54].

Concerning the median overall survival time, our BRT method should also

be evaluated in comparison to series with implantation at initial diagnosis. Mayr et al. [35] reported a median overall survival of 40 weeks in patients with GBM who were treated at initial presentation, and Laperriere et al. [31] reported a 55-week median survival in 63 patients with also primarily implantation. Wen et al. [57] achieved a median survival of 72 weeks, whereas Videtic et al. [56] reported a median survival of 76 weeks in 53 GBM treated likewise at initial diagnosis.

Compared to modern experience in LDR for operable recurrences of GBM [35], the radiobiological advantages of our interstitial method, according to which patients received 40 Gy of HDR-^{192}Ir in 3.5 days administered as 5.0 Gy twice daily, relative to 50–70 Gy of LDR-^{125}I as administered by Mayr et al. [35], are evident after careful comparison of the two modalities. Assuming $\alpha/\beta = 10$ Gy for GBM [53], we calculate a biologically equivalent dose (BED) value of 60 Gy Equivalent (GyE) for our HDR scheme. Considering the method of Mayr et al. [35], and taking the average dose rate of 0.374 Gy/h, BED values in the range of 53–61 GyE, 63–73 GyE, and 74–85 GyE were calculated for total doses of 50, 60, and 70 Gy, respectively. Repair half-times ($T_{1/2}$) for GBM in the range of 0.5–2.0 h were at this assumed, in order to account for the variability of this parameter. Based on these data, our HDR schedule appears, at first glance, to be equivalent to the LDR scheme of 50–60 Gy. However, the treatment duration of the LDR scheme is 2–4 days longer than our schedule. Thus, if tumor repopulation occurs during a time frame of 3–8 days, it decreases the biological effectiveness of the LDR regimen and, consequently, the equivalence of our HDR scheme is probably shifted to LDR doses > 60 Gy. Furthermore, due to the faster increase in biological effectiveness of HDR when moving to higher isodoses (e.g., > 150%) compared to LDR, in the main/central part of the target volume the equivalent effect of our schedule could be achieved only with the higher doses of LDR (70-Gy total dose scheme). Assuming that, primary treatment(s) and hypoxic conditions resulted in decreased radiosensitivity, this will clearly favor the effectiveness of HDR.

Analysis of brachytherapy series is complicated by the highly selected nature of patients who undergo treatment, and the inherent variation of therapeutic interventions as well as histological tumor characteristics for recurrent gliomas, in particular, make comparison of such patient groups from different institutions unreliable. Typically, in most LDR studies [5, 22, 31, 35, 43, 45, 50, 52, 56, 57] patients had either an initial diagnosis of GBM and failure after primary treatment or biopsy-proven GBM after failure of treatment for a lower-grade astrocytoma. Furthermore, in those series patients were either implanted at initial diagnosis or at recurrence. To attempt to minimize such bias, in this study we included only patients with HDR-BRT for recurrences of primary histology-proven GBM.

Finally, possibilities offered by MRI technology and positron emission tomography (PET) [19] are promising in the area of BRT as the full potential of individually defining and evaluating tumor extent is exploited. In this regard MRI-guided interstitial BRT with PET-scan-assisted target volume definition will certainly gain future importance. In addition, advances in the field "molecular targeted" approved drugs [42] may also play an important role in the treatment of recurrent GBM.

Conclusion

Interstitial HDR-BRT can play an important role in the treatment of unresectable recurrent GBM. To achieve tumor control with a reasonably good chance of palliation and survival, a meaningful tumor dose, i.e., at least ≥ 30 Gy, should be delivered. By using CT-guided implantation, an osteoclastic craniotomy can be avoided while providing short treatment times.

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