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Original Article

Bevacizumab reduces toxicity of reirradiation in recurrent high-grade glioma

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ABSTRACT

Purpose: The role of bevacizumab (BEV) in the setting of reirradiation (reRT) of malignant glioma recurrences is poorly defined. At our institution, reRT plus BEV was routinely used until its disapproval for glioma treatment by the European Medical Agency. Accordingly, reRT was applied without the addition of BEV since 2017. Here we present for the first time outcome and toxicity profiles of reRT plus BEV and reRT alone for malignant glioma recurrences.

Patients and methods: All adult patients consecutively undergoing reRT of a recurrent malignant glioma (37 anaplastic astrocytoma, WHO III; 124 glioblastoma, WHO IV) between 2007 and 2017 were included. In one group of patients, BEV (10 mg/kg bodyweight) was applied concomitantly on days 1 and 15 of reRT. Radiation toxicity referred to clinically significant toxicities of proven symptomatic radionecrosis (RN) and symptomatic oedema (SE) requiring steroid treatment for more than six weeks after reRT. Post-recurrence survival (PRS) and freedom from RN/SE were estimated with the Kaplan–Meier method. Prognostic factors were obtained from proportional hazards models.

Results: BEV plus reRT was applied in 124 and reRT alone in 37 patients. Both groups were comparable in terms of their patient-, tumour-, and RT/reRT-related variables. PRS was independent from the applied reRT protocols. RN/SE was less frequently seen after reRT plus BEV absolutely (27/124 (21.8%) vs. 14/37 (37.8%) patients; $p = 0.025$) and over time (1-year RN/SE rate: 23.9% vs. 54.1%; $p = 0.013$). The unadjusted and adjusted hazard ratio for RN/SE was doubled in case of reRT alone. Absence of BEV remained the only risk factor for RN/SE in multivariate models ($p = 0.026$).

Conclusion: Concomitant BEV effectively reduces treatment toxicity of reRT and should be reconsidered in future reRT protocols.

The role of bevacizumab (BEV) in the setting of salvage reirradiation (reRT) concepts of malignant glioma recurrences still remains a controversial issue. So far, no study has compared the toxicity and outcome profiles of reRT plus BEV and reRT alone. We had routinely applied reRT in combination with BEV until the European Medical Agency (EMA) has disapproved the use of BEV for glioma treatment (which was triggered by the negative results of both the RTOG 0825 [6] and the AVAglio trial [7]). Thereafter, reRT alone was used at our institution since 2017. Indication profiles for reRT plus BEV and reRT alone, however, did not change over time. We here present for the first time outcome and toxicity profiles of reRT alone as compared to reRT plus BEV for malignant glioma recurrences after previously applied multimodal treatment. The provided data might be used as a reference for risk and efficacy assessments of further studies.

Methods

Patients

The prospective institutional database of the Department of Radiation Oncology of the University Hospital of the LMU Munich was searched for all adult patients with recurrent malignant glioma undergoing reRT with or without concomitant BEV between April 2007 and December 2017. The study was reviewed and approved by the local Institutional Review Board of Ludwig-Maximilians-University Munich (approval number 620-15).

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Radiation treatment protocols

At first irradiation treatment, patients received conventional fractionation with 30 fractions of 2 Gy in 6 weeks or hypofractionation with 15 fractions of 2.67 Gy. The latter scheme was preferred for the elderly subpopulation (>65–70 years of age) [1,2]. Concomitant and adjuvant temozolomide chemotherapy was given in the majority of cases [2–4]. ReRT was usually applied as a second line salvage treatment concept (after failure of extensive salvage chemotherapy and/or surgical treatment). Only selected patients with mostly relatively small sized tumour volumes and/or an unfavourable molecular-genetic profile (i.e. an unmethylated *MGMT* promoter) were considered candidates for first-line salvage reRT. Generally, patients had to have a localized, recurrent (progressive) malignant glioma (WHO grades III–IV), and a Karnofsky Performance Score (KPS) of at least 70. A minimal time interval of 6 months calculated from the end of the initial RT was required. Treatment decision in favour of reRT was made by the interdisciplinary tumour board of the Neuro-Oncology Cancer Center of the Ludwig-Maximilians-University. Radiation treatment was classified as reRT if the recurrent volume had been in parts located within the 80–90% isodose line of the initial RT field. The reRT risk score (RRRS) was calculated for all patients as recently published and used for risk assessment [7]. Patients received reRT without simultaneous integrated boost (SIB) with a median dose of 36 Gy (range: 30.6–46 Gy) in 1.8/2 Gy fractions. Another group received 2.2–2.4 Gy fractions (30.6–46 Gy), occasionally with a SIB, according to the physician's preference. The respective fractionation schemes and prescribed dose were selected according to tumour size, tumour location, previous dose distribution, and the date of the initial RT. The equivalent total dose (EQD) in 2-Gy fractions was calculated as described by Fowler et al. [5].

ReRT was applied as 3D conformal or as intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT), if organs at risk, such as the optic nerve were close to the target volume. Target volume delineation was based on the gross tumour volume (GTV) consisting of all gadolinium positive areas in the gadolinium contrast-enhanced T1-sequence of magnetic resonance imaging (MRI). Clinical target volume (CTV) referred to the GTV with an expansion of 5 mm and subsequent correction for anatomical borders. The planning target volume (PTV) referred to the CTV with an additional isotropic 3 mm margin. Immobilization was achieved by thermoplastic mask systems (IT-V, Innsbruck, Austria). Radiation treatment planning was carried out on an Oncentra External Beam® treatment planning system (Elekta Instrument AB Stockholm, 10,393 Stockholm, Sweden) and on Monaco® (Elekta Instrument AB Stockholm, 10,393 Stockholm, Sweden) for IMRT and VMAT plans. A representative example is given in Fig. 1.

Suspected tumour progression before reRT was verified according to the RANO criteria [6]. In selected patients with inconclusive imaging, ^{18}F-fluoroethyltyrosine (^{18}F-FET) positron emission tomography (PET) was added to the diagnostic workup. In cases with remaining uncertainties, patients underwent minimal-invasive stereotactic biopsy before reRT [7,8]. Tumour grading was performed according to the World Health Organization (WHO) classification. The status of molecular biomarkers was re-defined if considered necessary.

Anti-oedematous therapy was performed with dexamethasone starting with a cumulative dose of 4–12 mg applied two or three times per day during treatment, respectively, and reduced slowly at the end of treatment every 3 days at steps of 4, 2 and 1 mg, respectively. Prolonged dexamethasone use was defined as treatment durations of more than 6 weeks after reaching the nadir dose.

Concomitant and maintenance bevacizumab treatment protocol

BEV was concomitantly applied on days 1 and 15 of reRT in one group of patients. BEV maintenance treatment started two weeks after reRT and was applied in two week intervals for another six cycles. BEV dosage was 10 mg per kg bodyweight [9,10]. Decision in favour of BEV maintenance was influenced by the preference of the treating radiation oncologist. A recent history of arterial thromboembolism, poorly controlled hypertension, intracranial bleeding, and/or wound healing disorders was considered a contradiction for BEV treatment [11].

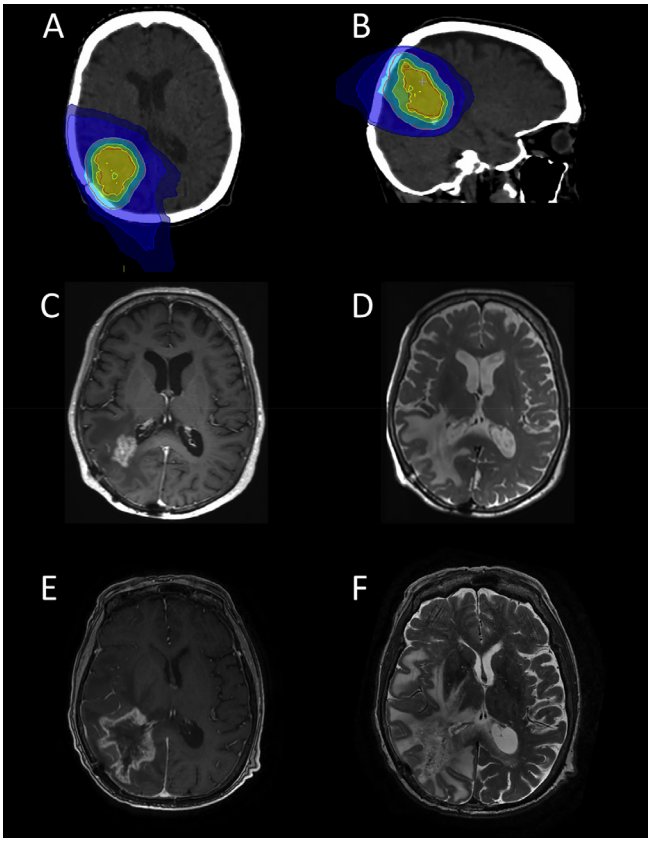

Fig. 1. 75 year old, female patient with recurrent glioblastoma treated with reRT without bevacizumab. Representative axial (A) and sagittal (B) plane of a VMAT plan of reRT [PTVboost (red), 43.2 Gy isodose line (yellow), 41.04 Gy isodose line (green), PTV (red), 34.2 Gy isodose line (light blue), 20 Gy isodose line (blue), 15 Gy isodose line (dark blue)]. Representative axial planes in CE-T_1 and T_2 MRI sequences before reRT (C and D) and four months after reRT (E and F) with symptomatic radionecrosis resulting in left-sided hemiparesis despite high-dose dexamethasone therapy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Treatment and follow-up schedule

Gadolinium contrast-enhanced MRI was performed six weeks after completion of reRT and in 3 months intervals thereafter. Treatment response was assessed according to the RANO criteria [6]. In case of suspected pseudoprogression additional ^{18}F-FET PET and/or subsequent stereotactic biopsy were used to detect/rule out tumour progression.

Toxicity evaluation

A symptomatic radionecrosis (RN) was assumed in case of adverse events of at least CTCAE v5.0 grade 2 (Common Terminology Criteria for Adverse Events). RN suspicion was based on typical MRI morphological findings on contrast-enhanced (CE) T1 sequences, such as the appearance of a spreading wavefront, spread to the contralateral hemisphere and/or multiple foci with discrete contrast enhancement only [12–15] and/or additional dynamic ^{18}F-FET PET findings, typically exhibiting increasing time

activity curves in case of a RN [16–18]. If considered necessary by the interdisciplinary tumour board, a stereotactic, mostly PET-guided, biopsy was initiated in uncertain cases to rule out tumour progression and to verify the suspicion of radionecrosis. The detection of necrotic tissue, the lack of viable tumour tissue, and low proliferation indices (Ki-67 labelling index in the range of 1%) strongly pointed to the diagnosis of radionecrosis. Structural and molecular imaging and histological findings were analysed by the respective experts and presented and discussed in the tumour board.

Patients, who had no typical signs of either RN or tumour progression, but remained highly symptomatic (e.g. suffering from severe headache, drowsiness, paresis, etc.) longer than 6 weeks after reRT due to persistent symptomatic oedema despite steroid treatment (as demonstrated by T2-weighted follow up MRI) were classified as symptomatic oedema (SE) patients. All SE patients had to stabilize/improve clinically over time to rule out tumour progression. The SE diagnosis was also determined by the tumour board.

Statistics

The distribution of continuously (categorical) scaled variables were analysed with the Mann–Whitney *U* test or (Fisher's exact test/chi-square statistics). Post-recurrence survival (PRS), post-recurrence progression-free survival (PR-PFS), RN- and RN/SE-free survival was analysed with the Kaplan–Meier method and referred to the date of reRT initiation. Overall survival was calculated from the date of initial RT treatment at first diagnosis. Risk factors were obtained from proportional hazards models. For multivariate analyses, a stepwise backward selection process employing a likelihood-ratio test was used. For further validation, an additional complementing propensity score matching analysis was performed.

Results

Patients

161 consecutively treated patients (107 male and 54 female) with recurrent malignant glioma (WHO grade III: 37 patients, grade IV: 124 patients) underwent reRT. Initial treatment consisted of tumour resection/biopsy plus chemoradiotherapy. First line salvage therapy included tumour resection ($n = 42$) and/or chemotherapy ($n = 81$). ReRT was applied as second line salvage treatment in 102 patients of this series. At the time of reRT, median age was 51 years. 85/151 tumours were *MGMT* promoter methylated and 26/107 tumours exhibited an *IDH* mutation. A *1p/19q* co-deletion was seen in 29/115 tumours. 32 patients exhibited favourable, 96 intermediate, and 33 poor reRT risk scores [19]. Overall, the median PTV was 118.1 cm^3 (range 22.6–385.5 cm^3) and the median prescribed dose 36 Gy (range 36–48.4 Gy). The estimated median EQD2 for the normal brain and the tumour was 36 Gy (range 29.4–52.4 Gy; $EQD_{3/2}$) and 36 Gy (range 30.1–48.0 Gy; $EQD_{10/2}$), respectively.

ReRT plus BEV treatment was applied in 124 patients. This included 77 (62.0%) patients with concomitant BEV only and 47 (38.0%) with additional BEV maintenance treatment. Both BEV groups did not differ with respect to patient-, tumour- and treatment-related factors (data not shown). Thirty-seven patients underwent reRT alone. Concomitant temozolomide chemotherapy was given in 6 patients of the reRT alone subgroup indicating the only significant difference to the combined treated subgroup (Table 1).

Survival analyses

For the entire study population, median follow-up after reRT was 44 months (95%-CI 8.8–79.2). Median PR-PFS and median PRS were 5 months (95%-CI 4.4–5.6) and 9 months (95%-CI 7.8–10.2), respectively. PR-PFS and PRS were not influenced by the different reRT protocols, i.e. patients receiving reRT alone or reRT with either concomitant or concomitant and maintenance BEV exhibited similar outcome scores (median PR-PFS 5 vs. 5 months, $p = 0.734$; median PRS 9 vs. 9 months, $p = 0.478$). Median overall survival was 38 months (95%-CI 31.5–44.5) and also similar among subgroups (data not shown).

Treatment toxicity

Overall, a symptomatic RN was documented in 11 patients. RN was diagnosed by clinical assessment in combination with MRI alone in 3 patients, by additional ^{18}F-FET PET in 3 patients, and by MRI/^{18}F^{18}F-FET PET guided stereotactic biopsy in 5 patients. RN-related toxicity occurred more often after reRT alone than after combined treatment [5/37 (13.5%) vs. 6/124 (4.8%), $p = 0.078$]. The overall toxicity related to both, RN and SE (RN/SE) was 37.8% (14/37) after reRT alone and 21.8% (27/124) after the combined treatment ($p = 0.025$). Patients with concomitant BEV with and without maintenance BEV exhibited similar toxicity rates (RN: 6.4% (3/47) vs. 3.9% (3/77), $p = 0.672$; RN/SE: 17.0% (8/47) vs. 24.4% (19/77), $p = 0.375$). The median time interval between the end of primary RT and the beginning of reRT was 9 months for patients with RN, 17 months for patients with RN/SE, and 18 months for patients without RN or RN/SE. The differences were not statistically significant ($p = 0.545$; $p = 0.876$). The respective median prescribed doses were 41.6 Gy (range 36–48 Gy) for patients with RN, 36 Gy (range 30–48 Gy) for patients with RN/SE, and 36 Gy (range 30–48.4 Gy) for patients without major toxicity. The difference was significant for RN, but not for RN/SE ($p = 0.02$; $p = 0.699$). The 1-year risk for RN or RN/SE was 23.9% after combined treatment and 54.1% after reRT alone (Fig. 2, $p = 0.013$).

Prognostic models

An overview of the univariate and the multivariate risk models is given in Table 2 for RN/SE and in Table 3 for RN. Univariately, the absence of BEV treatment was significantly associated with an increased risk for RN/SE. Sex, age, KPS, WHO grade at initial diagnosis, time to reRT, *MGMT* methylation status, *IDH1/2* mutational status, PTV volume, prescribed dose, and BEV maintenance therapy were not significantly associated with the occurrence of RN/SE. Univariately, the absence of concomitant BEV ($p = 0.018$) and a higher total radiation dose ($p = 0.001$) were significant predictors for RN.

For multivariate analysis, only the endpoint RN/SE was used due to the small number of events. Absence of concomitant BEV remained the only significant predictor for RN/SE after adjustment for the effects of all other variables tested in the model ($p = 0.026$). The unadjusted and adjusted hazard ratio for the risk of RN/SE after reRT alone was 2.2 (95%-CI 1.146–4.220) and 2.137 (95%-CI 1.096–4.166), respectively (Table 2). Sixty-two patients could be included in a propensity score matching analysis model, which supported the results of the overall risk model; absence of BEV was a risk factor for RN/SE in the univariate ($p = 0.045$) and multivariate models ($p = 0.058$). Overall, patients with RN/SE did not have shorter PRS ($p = 0.403$). In contrast, patients with RN alone experienced longer PRS than patients without RN (mean: 32.9 months (95%-CI 18.4–47.5) vs. 9 months (95%-CI 7.7–10.3) ($p = 0.006$)).

Favourable predictors for PRS were a higher KPS at beginning of reRT ($p = 0.02$), a methylated *MGMT* promoter ($p = 0.05$), and a mutated *IDH1* status ($p = 0.033$). BEV treatment did not gain prognostic impact.

Bevacizumab related toxicities

BEV related CTCAE grades ≥III toxicity within 6 months after last BEV therapy was detected in 12/124 cases (9.7%; 3 cases with

Table 1
Characteristics of patients with recurrent malignant glioma undergoing reirradiation with/without bevacizumab treatment.

Characteristic	All patients (n = 161) N (%) or median (range)	ReRT with BEV (n = 124) N (%) or median (range)	ReRT without BEV (n = 37) N (%) or median (range)	p-Value
Sex				
Male	107 (66.5%)	85 (68.5%)	22 (59.5%)	ns (p = 0.326)
Female	54 (33.5%)	39 (31.5%)	15 (40.5%)	
Median Age in years (range)	51 (18–81)	50.5 (18–81)	51 (30–75)	ns (p = 0.576)
Median KPS (range)	80 (40–100)	80 (40–100)	80 (50–100)	ns (p = 0.100)
WHO grade at initial diagnosis				
WHO grade II	15 (9.3%)	10 (8.1%)	5 (13.5%)	ns (p = 0.761)
WHO grade III	35 (21.7%)	30 (24.2%)	5 (13.5%)	
WHO grade IV	111 (68.9%)	84 (67.7%)	27 (73.0%)	
WHO grade at recurrence				
WHO grade IV	124 (77.0%)	95 (76.6 %)	29 (78.4%)	ns (p = 0.831)
WHO grade <IV	37 (23.0%)	29 (23.4 %)	8 (21.6%)	
MGMT promotor status				
MGMT methylated	87 (54.0%)	63 (50.8%)	24 (64.9%)	ns (p = 0.114)
MGMT unmethylated	64 (39.8%)	54 (43.5%)	10 (27.0%)	
Unknown MGMT status	10 (6.2%)	7 (5.6%)	3 (8.1%)	
IDH1/2 mutational status				
IDH1/2 mutated	26 (16.2%)	17 (13.7%)	9 (24.3%)	ns (p = 0.307)
IDH1/2-wildtype	81 (50.3%)	62 (50.0%)	19 (51.4%)	
Unknown IDH1/2 status	54 (33.5%)	45 (36.3%)	9 (24.3%)	
1p/19q status				
Codeletion	11 (6.8%)	6 (4.8%)	5 (13.5%)	ns (p = 0.694)
Partial deletion	29 (18.0%)	19 (15.3%)	10 (27.0%)	
No deletion	75 (46.6%)	61 (49.2%)	14 (37.8%)	
Unknown 1p/19q status	46 (28.6%)	38 (30.6%)	8 (21.6%)	
Median interval between RT and reRT in months (range)	18 (4–265)	17 (4–265)	18 (5–182)	ns (p = 0.313)
PTV volume (cm^3)	118.06 (22.55–385.5)	117.45 (22.55–385.5)	122.46 (43.39–293.51)	ns (p = 0.603)
Highest dose per fraction including SIB (Gy)	2.0 (1.8–5.0)	2.0 (1.8–2.6)	2.0 (1.8–5.0)	ns (p = 0.300)
Prescribed dose (Gy)	36.0 (30.0–48.4)	36.0 (30.0–48.4)	36.0 (30.0–43.2)	ns (p = 0.912)
$EQD_{3/2}$ (Gy)	36.0 (30.0–49.6)	36.0 (29.4–52.4)	36.0 (29.4–48.0)	ns (p = 0.290)
$EQD_{10/2}$ (Gy)	36.0 (30.0–48.4)	36.0 (30.0–49.6)	36.0 (30.1–44.6)	ns (p = 0.658)
Concomitant TMZ chemotherapy	6 (3.7%)	0	6 (16.2%)	**p < 0.001**
Risk group				
Good	32 (19.9%)	25 (20.2%)	7 (18.9%)	ns (p = 0.254)
Intermediate	96 (59.6%)	77 (62.1%)	19 (51.4%)	
Poor	33 (20.5%)	22 (17.7%)	11 (29.7%)	
Radiation necrosis	11 (6.8%)	6 (4.8%)	5 (13.5%)	
Radionecrosis and/or symptomatic oedema	42 (25.5%)	27 (21.8%)	14 (37.8%)	

Significant parameters in bold.

2 toxicities) including myelosuppression (n = 2) treated with G-CSF, thrombosis requiring antithrombotic agents (n = 5), infection treated with antibiotic therapy (n = 6), gastrointestinal bleeding (n = 1) and wound healing disorders (n = 1) requiring surgical intervention.

Discussion

The efficacy of BEV for the treatment of RN after RT has been recently demonstrated in a double-blind, placebo-controlled trial [29]. Whether BEV might additionally also prevent radiation toxicity, particularly within the context of reRT strategies of malignant glioma recurrences, remains unclear. Preliminary, mostly small sized prospective and retrospective studies have provided divergent conclusions and differed in their indication profiles and reRT protocols [9–11,20,21]. Moreover, most studies have predominantly focused on treatment efficacy rather than treatment toxicity. Determination of treatment toxicity, however, is of utmost interest when it comes to evaluate the pros and cons of a salvage treatment concept for recurrent malignant glioma patients. In a recently published consensus article on reRT treatment, no clear evidence could be provided with respect to selection criteria, timing, and treatment protocols. More specifically, no consensus has been achieved regarding systemic therapy concomitant to reRT for recurrent glioma patients [5].

In the present study, we have analysed and compared two reRT treatment protocols (with/without BEV) for malignant glioma recurrences. Both groups were comparable regarding their patient-, tumour-, and reRT-related parameters, but only the group of the initial observation period had received additional BEV. The change of the reRT protocol over time was triggered by the EMA disapproval of BEV in 2017 [22]. The disapproval was mainly explained by the limited antineoplastic efficacy of BEV in first-line glioma treatment as detected in more recently published phase III studies [23,24]. The current study was conducted to analyse for the first time the potential protective effect of BEV in case of a reRT setting of malignant glioma recurrences, rather than its antineoplastic effects. Ironically, this has become possible due to the EMA disapproval.

We have used two endpoints for estimation of reRT toxicity. We have focused on the frequency of both RN and SE. The latter end-

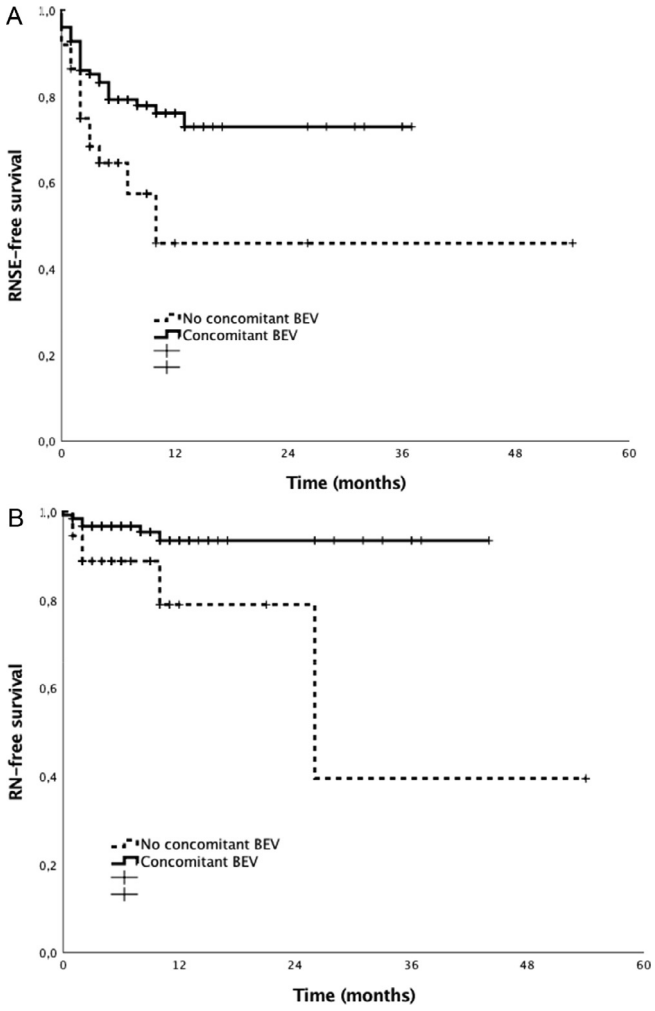

Fig. 2. RN/SE-free survival (A) and RN-free survival (B) stratified for concomitant BEV treatment to reRT.

point has been rarely analysed in the literature so far. Long term steroid application due to RT induced SE, however, is regarded as one of the major causes of treatment associated morbidity, e.g. possibly leading to steroid induced muscle waste and severe metabolic alterations. The latter might also trigger tumour proliferation and early tumour recurrence [25]. It could be argued that SE assessments might be biased/overestimated by effects of undetected tumour progression. However, this issue was nearly ruled out in the current series. Dynamic ^{18}F-FET PET imaging with TTPmin measurements in dynamic uptake analysis [26] and additional rebiopsy procedures, if considered necessary, were used to detect/rule out tumour progression. Outcome scores supported our diagnostic classification protocol, as the PRS was not different in patients with/without detected RN/SE. Using reRT alone, we observed higher frequencies of RN/SE-associated symptoms as compared to those undergoing combined treatment with BEV. The difference was statistically significant in univariate und multivariate risk models. We found a more than two-fold increase in the adjusted hazard ratio for RN and/or SE in case of reRT alone treatment.

Whereas risk factors of RN were both, the applied total dose and absence of BEV treatment in univariable models, absence of BEV treatment remained the only risk factor for RN/SE after adjustment for the effects of the other variables. Given the low frequency of RNs, we were not able to create multivariate risk models separately for this endpoint. More data are necessary to elucidate this important question. The additional impact of maintenance BEV remains undefined in this study. Patients receiving maintenance BEV did not do better than those undergoing concomitant treatment alone in terms of both their outcome scores and their risk profile. However, given the small sample size of the BEV maintenance subgroup, these results should be interpreted with caution. We did not find a significant impact of the reRT risk score in this series. Whether that should be related to the relatively small sample size, remains unknown and deserves further evaluation [19].

Table 3
Univariate cox-regression for radionecrosis (RN)-free survival.

Variable	RN-free survival cox regression (univariate, continuous)	Hazard ratio (95%-CI)
No BEV concomitant to reRT	**p = 0.018**	**3.969 (1.271–12.390)**
Sex	ns (p = 0.563)	0.680 (0.184–2.513)
Age	ns (p = 0.186)	1.033 (0.984–1.085)
KPS	ns (p = 0.982)	1 (0.957–1.044)
WHO grade at initial diagnosis		
WHO IV vs. II	ns (p = 0.111)	2.949 (0.781–11.131)
WHO IV vs. III	ns (p = 0.344)	0.366 (0.046–2.931)
MGMT methylation status	ns (p = 0.639)	0.749 (0.224–2.507)
IDH1/2 mutational status	ns (p = 0.780)	0.824 (0.211–3.215)
Interval from RT to reRT	ns (p = 0.167)	2.549 (0.675–9.624)
PTV volume	ns (p = 0.833)	1.001 (0.993–1.009)
Prescribed dose (Gy)	**p = 0.001**	**1.239 (1.092–1.407)**
BEV maintenance therapy	ns (p = 0.638)	0.731 (0.197–2.703)

Significant parameters in bold.

Table 2
Univariate and multivariate cox-regression for radionecrosis and/or symptomatic oedema (RN/SE)-free survival.

Variable	RN/SE-free survival univariate, continuous cox regression	Hazard ratio (95%-CI)	RN/SE-free survival multivariate, continuous cox regression (backward selection, LR test)	Hazard ratio (95%-CI)
No BEV concomitant to reRT	**p = 0.018**	**2.2 (1.146–4.220)**	**p = 0.026**	**2.137 (1.096–4.166)**
Sex	ns (p = 0.870)	0.947 (0.490–1.829)	–	–
Age	ns (p = 0.525)	0.992 (0.967–1.018)	excluded prior to last step	–
KPS	ns (p = 0.893)	0.998 (0.976–1.021)	–	–
WHO grade at initial diagnosis			–	–
WHO IV vs. II	ns (p = 0.167)	1.877 (0.769–4.579)		
WHO IV vs. III	ns (p = 0.490)	1.295 (0.622–2.697)		
MGMT methylation status	ns (p = 0.530)	0.816 (0.432–1.541)	–	–
IDH1/2 mutational status	ns (p = 0.185)	0.618 (0.304–1.258)	–	–
Interval from RT to reRT	ns (p = 0.599)	0.850 (0.464–1.559)	–	–
PTV Volume	ns (p = 0.655)	0.999 (0.994–1.004)	Excluded prior to last step	–
Prescribed dose (Gy)	ns (p = 0.376)	1.037 (0.957–1.123)	Excluded prior to last step	–
BEV maintenance therapy	ns (p = 0.085)	0.507 (0.234–1.099)	Excluded prior to last step	–

Significant parameters in bold.

Given sample size associated imbalances in the study groups of this series, we additionally performed a propensity score matching analysis, which supported the conclusions of the overall unmatched analysis. Apparently, selection bias to the disadvantage of the reRT alone group might be minor or does not exist. Given the small size of the reRT alone group, however, an underestimation of the hazard ratio for this group could not be excluded.

The predominant protective influence of BEV for developing RN and/or SE symptoms after reRT points to the importance of vessel-mediated mechanisms in reRT induced toxicity. Increased capillary permeability with consecutively reduced blood flow might significantly contribute to complications of reRT [27]. Continuous remodelling of the vasculature network during reRT apparently improves the risk profile of reRT. Our data, however, also demonstrate that BEV treatment could not completely prevent reRT toxicity.

The optimal time interval between initial RT and reRT remains unknown. In the current series a minimal time interval of 6 months was requested. Remarkably, those patients presenting with less or no toxicity at all were treated after a longer time interval. Nevertheless, the time interval was not statistically significant on univariate analysis and more data are necessary to elucidate its impact more appropriately. Previous studies on reRT with concomitant BEV were in line with our data: outcome was similar and the rate of RN was comparably low [28–31]. We were able to demonstrate, that malignant glioma patients undergoing reRT are highly selected and may experience longer overall survival than usually reported [3]. We did not find longer PRS after additional concomitant BEV treatment, stressing its limited impact on the prognosis of the disease.

Overall, there are certain limitations to our study design, specifically its non-randomized nature and the retrospective allocation of toxicities. Nevertheless, a natural form of randomization took place, as after the EMA decision patients formerly eligible for reRT plus BEV have been allocated to reRT alone explaining the well-balanced treatment groups of this study.

A strength of this study was the availability of dynamic molecular imaging and sophisticated minimal invasive stereotactic biopsy techniques to differentiate radiation toxicity from tumour progression. Accordingly, the occurrence of RN/SE was not associated with shorter PRS and did not represent tumour progression.

In summary, BEV therapy concomitant to reRT is associated with a significantly lower rate of RN and RN/SE compared to reRT alone in patients with recurrent malignant glioma. Therefore, BEV therapy concomitant to reRT is strongly advised for patients with recurrent glioma.

Declaration of Competing Interest

The authors declare that conflicts of interest do not exist.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.06.009.

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