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Maya Christine Rottler geb. Flieger

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Berichterstatter:	Prof. Dr. med. Dipl.-Phys. M. Niyazi
Mitberichterstatter:	PD Dr. med. Bogdana Suchorska
	Prof. Dr. med. Nathalie Albert
	Prof. Dr. med. Niklas Thon
Dekan:	Prof. Dr. med. Thomas Gudermann
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München, 12.01.2023 Maya Rottler

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Abkürzungsverzeichnis

CT	Computertomografie
GBM	Glioblastom
GTV	Gross tumor volume
Gy	Gray
HGG	high grade glioma
HR	hazard ratio
IDH 1/2	Isocitrat-Dehydrogenase
IMRT	Intensitätsmodulierte Radiotherapie
KPS	karnofsky performance status
MGMT	O6-Methylguanin-DNA-Methyltransferase
MRT/ MRI	Magnetresonanztomografie
NOA-Studien	Studien der Neuroonkologische Arbeitsgemeinschaft
PFS	progression free survival
PRS	post recurrence survival
PR-PFS	post recurrence progression free survival
PTV	planning target volume
RT	Radiotherapie
TMZ	Temozolomide
VEGF	vascular endothelial growth factor
WHO	world health organization

Publikationsliste

Publikation I

Titel: Re-irradiation and bevacizumab in recurrent high-grade glioma: an effective treatment option

Autoren: Maya Flieger, Ute Ganswindt, Silke Birgit Schwarz, Friedrich-Wilhelm Kreth, Jörg-Christian Tonn, Christian la Fougère, Lorenz Ertl, Jennifer Linn, Ulrich Herrlinger, Claus Belka, Maximilian Niyazi

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Einleitung

Das maligne Gliom

Glioblastome sind die häufigsten hirneigenen bösartigen Tumorerkrankungen bei Erwachsenen. Der Erkrankungsgipfel liegt zwischen dem 60. und 70. Lebensjahr. Die Mehrheit der Glioblastome sind sporadische Fälle, jedoch kann es bei selten erblichen Erkrankungen zu einer familiären Häufung kommen. Prognosebestimmend sind im Wesentlichen therapieunabhängige Faktoren wie Alter, Allgemeinzustand des Patienten und initialer neurologischer Status. Unbehandelt liegt das mittlere Überleben bei wenigen Monaten.
Die häufigste Lokalisation befindet sich in den Großhirnhemisphären sowie in den Stammganglien. Klinisch äußern sich diese Tumore nach kurzer Krankheitsgeschichte meist mit Zeichen eines erhöhten intrakraniellen Drucks durch Kopfschmerzen, Übelkeit, Erbrechen, Schwindel sowie fokal neurologischen Defiziten.
Auf Grund der subklinischen Tumoraussaat, die sich weder CT- noch MRT-morphologisch klar abgrenzen lässt, ist eine komplette Resektion nicht möglich.
Seit 2016 liegt eine Aktualisierung der WHO-Klassifikation vor, bei der auch molekulare Parameter zur differenzierten Einteilung der Gliome herangezogen werden (34). Darin stellt ein wichtiger prognostischer und prädiktiver Marker die Methylierung des Promoters für die O6-Methylguanin-DNA-Methyltransferase (MGMT) dar. Mutationen in der Isocitrat-Dehydrogenase 1 und/oder 2 sind charakteristisch für niedrigmaligne oder anaplastische Gliome. Eine IDH1-Mutation in einem Glioblastom legt eine Entdifferenzierung aus einem niedrigmalignen Gliom nahe. IDH1-mutierte Tumore mit einer Kodeletion des Chromosoms 1p und 19q haben eine oligodendrogliale Herkunft. Als neue Entität wurde das diffuse Mittelliniengliom mit einer Mutation im Histon 3 beschrieben.

Therapie bei Erstdiagnose

Trotz der multimodalen und aggressiven Therapie in der primären Erkrankungssituation, bestehend aus Operation, Chemotherapie und Strahlentherapie, ist eine Kuration nicht möglich. Beim Auftreten eines Rezidivs stellt sich erneut die Frage nach der richtigen multimodalen Therapie. Insbesondere die hohe Rate an lokalen Rezidiven stellt die behandelnden Ärzte vor besondere Herausforderungen.

Die Behandlung von Glioblastomen bei Erstdiagnose umfasst zumeist eine Resektion. Zum einen wird hierdurch eine histologische Sicherung erzielt, zum anderen wird eine möglichst komplette Tumorresektion angestrebt. Das Resektionsausmaß konnte als unabhängiger prognostischer Faktor identifiziert werden. In der NOA-1-Studie zeigten Patienten mit einer Tumorresektion eine signifikant erhöhte Überlebensrate gegenüber Patienten, die lediglich eine bioptische Sicherung erhalten hatten (63).
Der aktuelle Therapiestandard sieht eine anschließende Radiotherapie oder kombinierte Radiochemotherapie vor. Bei inoperablen Befunden wird eine primäre Radiotherapie oder Radiochemotherapie durchgeführt. Bei Patienten über 65 Jahren, deren Tumor eine MGMT-Promotor-Methylierung aufwies, konnte in der NOA-08-Studie auch eine alleine Chemotherapie bei Erstdiagnose als Therapiealternative zu einer alleinigen Radiotherapie gezeigt werden (65).
In der primären Situation hat sich eine Radiochemotherapie mit Temozolomid bis 60 Gy in 2 Gy Einzeldosen als aktueller Standard etabliert (57). Auch hypofraktionierte Schemata mit höheren Einzeldosen und verkürzter Therapiedauer sind möglich (64).

Therapie eines Rezidivs

Im Falle eines Rezidivs ergeben sich verschiedene Therapieoptionen. Diese müssen individuell und interdisziplinär abgewogen werden. Eine erneute radikale Resektion ist auf Grund des infiltrativen Wachstums des Glioblastoms meist nicht ohne ein hohes Morbiditätrisiko durchführbar. Dennoch kann sie bei sehr hohem Karnofsky-Index erwogen werden.
Bezüglich der radioonkologischen Therapien ergeben sich mehrere Optionen. (46). Eine Einzeit-Stereotaxie ist unter Umständen möglich, kann aber bei großen Tumoren mit einem erhöhten Risiko für Nebenwirkungen einhergehen. Eine fraktionierte Stereotaxie hingegen kann häufig auch in eloquenter Lage des Tumors und größeren Tumorvolumina mit einer adäquaten Effektivität durchgeführt werden. Auch eine erneute Re-Bestrahlung mit Temodal mit kompromittierter Gesamtdosis ist effektiv und wird gut toleriert. Da Glioblastomrezidive meist ein lokalisierter Prozess sind, ist auch eine Brachytherapie durchführbar.
Auch stehen verschiedene systemische Therapien zur Verfügung. Hier sind die hohe Chemotherapieresistenz und die geringe Bioverfügbarkeit der meisten Medikamente im ZNS zu beachten. Insgesamt war zumeist eine Dosislimitation durch die Hämatotoxizität gegeben.

Eine Radioimmuntherapie, bei der radioaktiv markierte Antikörper lokal appliziert werden und sich so gegen die Tumorzellen richten sollen, ist aktuell noch hoch experimentell. Insgesamt sollte eine lokale Therapie bevorzugt werden, wenn diese möglich ist (46).

Bevacizumab

Bevacizumab ist ein humanisierter monoklonaler Antikörper gegen VEGF-A. Als Wirkmechanismus wird einerseits eine Hemmung der Tumorneoangiogenese und andererseits eine Normalisierung der tumorbedingten Hypoxie postuliert, wodurch die Radiotherapie besser wirksam wird. Auch eine direkte Wirkung auf die Tumorzellen wird diskutiert, da bei hohen Leveln an Bevacizumab auch ohne vaskuläre Regression eine Verkleinerung des Tumors gesehen werden konnte. Auch wird VEGF-A als ein Faktor für die Zellmigration vermutet, die mit Bevacizumab reduziert werden kann.
Glioblastome exprimieren VEGF, was durch eine Radiotherapie als Reaktion der Tumorzellen deutlich erhöht wird. Somit soll durch VEGF-Inhibition eine verbesserte Wirkung auch der konkomitanten Bestrahlung erreicht werden.
Da die Tumorgefäße deutlich brüchiger sind als gesunde Blutgefäße, kommt es vermehrt zu einem Austritt intravasaler Flüssigkeit ins Hirngewebe. Durch eine Normalisierung der Angiogenese kommt es somit zu einer Reduktion des vasogenen Hirnödems (24).
Die häufigsten Nebenwirkungen der Therapie mit Bevacizumab sind Wundheilungsstörungen, Bluthochdruck sowie Blutungen und thrombembolische Ereignisse. Insbesondere bei der Kombination von Radiotherapie und Bevacizumab in der neoadjuvanten Therapie bei Rektumkarzinom wurden Wundheilungsstörungen sowie gastrointenstinale Blutungen beschrieben. Bei thorakalen Bestrahlungen scheint das Risiko für Fisteln erhöht zu sein.
Bezüglich der konkomitanten Applikation von Bevacizumab zur Re-Bestrahlung bei Glioblastomen konnte von Gutin et al. die sichere und effektive Anwendung gezeigt werden (19).
In verschiedenen anderen Studien wurde Bevacizumab in Kombination mit Irinotecan oder Etoposid getestet, um synergistische Effekte an der normalisierten Tumorvaskularisation zu erzielen. Bei Versagen einer Bevacizumabhaltigen Therapie zeigten sich weitere Bevacizumabhaltige Therapieregime als wenig effektiv.

Die Einzelarbeiten

In den beiden hier vorgestellten Arbeiten wurden die Daten des klinikeigenen Kollektivs an Patienten mit Glioblastomrezidiv nach erneuter Bestrahlung ausgewertet. Zur Optimierung der Wirkung der Radiotherapie wurde eine konkomitante systemische Therapie mit Bevacizumab appliziert.
Das ausgewertete Kollektiv betrachtet 71, respektive 88 Patienten, die zwischen 2004 und 2013 an einem Gliobastomrezidiv behandelt wurden. Der größte Anteil der Patienten erhielt die konkomitante Gabe von Bevacizumab zur Radiotherapie. Auch weiterhin ist dies das größte monoinstitutionelle Kollektiv, das sowohl mit Re-Bestrahlung als auch mit Bevacizumab behandelt wurde.
Ziel der ersten Publikation „Re-irradiation and bevacizumab in recurrent high-grade glioma: an effective treatment option“ war an einer großen Patientenkohorte die Sicherheit und Effektivität der kombinierten Therapie zu überprüfen. Hier zeigte sich, dass in dieser Kohorte kein erhöhtes Risiko für Nebenwirkungen bestand. Nur eine sehr geringe Anzahl von höhergradigen Nebenwirkungen traten auf, die nicht alleinig auf Bevacizumab oder die Kombination mit Re-Bestrahlung zurückgeführt werden konnten. Gleichzeitig konnte gezeigt werden, dass sowohl das Überleben nach dem Rezidiv (post recurrence survival, PRS) als auch das progressionsfreie Überleben nach Rezidiv (post recurrence progressions free survival, PR-PFS) im Falle der multimodalen Therapie signifikant erhöht waren gegenüber einer alleinigen Re-Radiotherapie.
In der primären Situation hatte sich die Tumorgröße als prognostischer Faktor gezeigt (64). Dies konnte sich bei der Re-Bestrahlung nicht bestätigen (44). In einer Subgruppenanalyse zeigte sich, dass Patienten mit einer MGMT-Methylierung von der kombinierten Therapie profitieren, da sowohl PRS als auch PR-PFS signifikant erhöht waren.
Die zweite Publikation „Validation of the prognostic Heidelberg re-irradiation score in an independent mono-institutional patient cohort“ beschäftigt sich mit der Validierung des Heidelberger Re-Bestrahlungsscores, in der Literatur inzwischen auch als Combs-Score bekannt (8). Combs et al. hatten 2013 ihr in Heidelberg behandeltes Kollektiv an Patienten mit Glioblastomrezidiv nach prognostischen Faktoren ausgewertet. In ihrer Kohorte ergab der aus Histologie, Alter bei Rezidiv und Intervall zwischen den Bestrahlungsserien gebildete Score eine prognostische Einteilung der Patienten zur Einschätzung des Benefits der Patienten an einer Re-Bestrahlung. An einer unabhängigen Kohorte sollte dieser Score überprüft werden. 88 Patienten, die bis 2013 ein zweites Mal

bestrahlt wurden, konnten ausgewertet werden. Der bedeutendste Unterschied zu der Heidelberger Kohorte war die zusätzliche konkomitante Therapie mit Bevacizumab bei 71 Patienten. Bei der Auswertung ergab sich keine statistische Signifikanz für die Faktoren des Heidelberger Scores. Als einzigen prognostischen Faktor für das PRS konnte die konkomitante Applikation von Bevacizumab zur Re-Bestrahlung ermittelt werden. Mögliche Gründe für dieses Ergebnis sind einerseits die konkomitante Applikation von Bevacizumab als auch der Einschluss größerer Rezidivtumore, da die Re-Bestrahlung mit Bevacizumab auch bei größeren Zielvolumina als sicher applizierbar erachtet wurde. Als weiterer Faktor mit Einfluss auf das Ergebnis muss die sehr heterogene Kohorte genannt werden. Alle Patienten hatten bereits diverse Vortherapien erhalten, unter anderem Brachytherapie, Re-Operationen sowie verschiedene Chemotherapieregime.

Die klinikeigene Datenbank umfasste 88 Patienten, die seit 05/2004 behandelt wurden. Eine systematische Erhebung des MGMT-Methylierungsstatus erfolgte erst nach 2006. Eine Nachbestimmung war insbesondere bei Patienten mit einer auswärtigen histologischen Sicherung nicht möglich, da nicht immer noch Tumormaterial vorhanden war.
Beim ersten Paper betrug das mediane Alter 53 Jahre, der mediane Karnofsky-Index betrug 80%. 34 Patienten hatten ein histologisch gesichertes Rezidiv, bei den übrigen Patienten erfolgte eine bildmorphologische Diagnose. 8,5 % der Patienten hatten bei Erstdiagnose ein Astrozytom WHO°II, das im Rezidiv malignisiert war. Vor der ersten Radiotherapie war bei 81,7% der Patienten einen totale oder subtotale Resektion erfolgt. 78,9% der Kohorte erhielten initial eine definitive oder adjuvante Radiochemotherapie mit Temozolomid. 12,7 % der Patienten erhielten vor der Re-Bestrahlung eine subtotale Resektion. Während der Re-Bestrahlung erhielten 57 Patienten Bevacizumab. Das mediane Follow-Up betrug 18 Monate.
Beim zweiten Paper betrug das mediane Alter 51 Jahre, der mediane Karnofsky-Index betrug 80%. Von den analysierten 88 Patienten erhielten 71 eine Re-Bestrahlung mit Bevacizumab, die restlichen 17 Patienten wurde lediglich re-bestrahlt. Bei 33% der Patienten betrug das Intervall zwischen der ersten und der zweiten Radiotherapie maximal 12 Monate. Das mediane Follow-Up verlängerte sich auf 30 Monate.
Das mediane Overall Survial betrug 32,5 Monate. Ein niedrigeres WHO-Grading war mit einem längeren Überleben assoziiert. So betrug das mediane Survival bei Patienten mit WHO°II-Tumoren bei Erstdiagnose 196,1 Monate, bei Patienten mit einem schon initial vorhanden Glioblastom lediglich 27,5 Monate.

Insgesamt war die Re-Bestrahlung in Kombination mit Bevacizumab gut verträglich. In der Kohorte traten drei Grad 2-Toxizitäten auf, eine Grad 3-Toxizität, zwei Grad 4-Toxizitäten sowie eine Grad 5-Toxizität. Letztere war eine Sigmaperforation bei vorbestehender Divertikulose nach langer Kortisoneinnahme. Trotz einer sofortigen Operation verstarb der Patient. Es konnten drei Radionekrosen beobachtet werden sowie eine Grad 1-Leukenzephalopathie, fünf Grad 2-Leukenzephalopathien sowie eine Grad 3-Leukenzephalopathie.
Das Postrecurrence survival (PRS) der gesamten Kohorte lag bei 7,8 Monaten, das Postrecurrence Progression Free Survival (PR-PFS) bei 4,9 Monaten.
Betrachtet man die Patienten, die nur radiotherapiert wurde sowie die, die die kombinierte Therapie bekommen hatten, so zeigt sich, dass keine Unterschiede bezüglich initialer WHO-Grad, MGMT-Status, Alter, Geschlecht, Tumorvolumen, Karnofsky-Index, zweiter Resektion sowie adjuvanter oder salvage Chemotherapie bestand. Somit konnte ein Bias ausgeschlossen werden. Auch wirkten sich diese nicht signifikant auf PRS und PR-PFS aus.
Bei Berücksichtigung der unterschiedlichen Therapieschemata zeigte sich, dass das PRS auch nach Analyse der 88 Patienten in der Gruppe mit Bevacizumab konkomitant zur Bestrahlung signifikant verbessert war (8 Monate vs 6 Monate). Eine frühe adjuvante Chemotherapie erbrachte eine nicht signifikante Verbesserung des PR-PFS, die bei mit Bevacizumab behandelten Patienten noch etwas ausgeprägter auftrat.
Der Heidelberger Score konnte nicht validiert werden. So hatte er in unserer Kohorte keinen Einfluss auf PRS oder PR-PFS. Die Überlebensraten waren in allen Subgruppen ungefähr gleich. Auch konnte kein Einfluss von Bevacizumab auf die Subgruppen des Heidelberger Scores ermittelt werden.
Zur Identifikation möglicher prognostischer und/oder prädiktiver Faktoren wurden uni- und multivariate Analysen durchgeführt. In der univariaten Analyse zeigte sich, dass Alter, Geschlecht, MGMT-Status, Zeitintervall zwischen den Bestrahlungen, Karnofsky-Index sowie eine Resektion vor Re-RT keinen signifikanten Einfluss hatten. Bevacizumab, eine adjuvante Chemotherapie sowie die Re-Bestrahlungsdosis hatten einen signifikanten Effekt auf das Überleben, beim PR-PFS waren lediglich Bevacizumab und adjuvante Chemotherapie signifikant. Die Größe des GTV in der Re-Bestrahlungssituation zeigte einen Trend bezüglich verlängertem PRS und PR-PFS.
Der einzige Faktor, der in der multivariaten Analyse signifikant blieb, war die Therapie mit Bevacizumab. Ein marginaler Einfluss auf das PRS konnte durch die adjuvante Chemotherapie festgestellt werden, sowie auf das PR-PFS durch den Karnofsky-Index.

Selbst bei Ausschluss der Patienten, die initial ein Low grade-Gliom hatten, blieb die Bevacizumab-Applikation ein signifikant prognostischer Faktor sowohl bezüglich PR-PFS und PRS.
Betrachtet man lediglich die Patienten mit einem Glioblastoma multifirme WHO° IV, so zeigte diese Kohorte keine Unterschiede in den Patientencharakteristika gegenüber der Gesamtkohorte, lediglich wurde häufiger Bevacizumab angewendet.

Zusammenfassung

Beide Paper konnten zeigen, dass in bestimmten Patientensubgruppen mit Gliobastomrezidiv eine Re-Bestrahlung mit Bevacizumab ein verlängertes Überleben ermöglichen kann. Gleichzeitig ist die kombinierte Therapie mit vertretbarer Toxizität durchführbar. So konnte im ersten Paper gezeigt werden, dass die Toxizitätsraten nicht höher sind als bei einer alleinigen Bevacizumab-Therapie oder bei Therapien mit anderen Chemotherapeutika, auch in Kombination (18). Gleichwohl konnten vergleichbare Survivalraten in der Literatur gefunden werden (19, 23).
Trotz dieser vielversprechenden Ergebnisse gibt es auch Diskussionsbedarf.
Die ausgewertete Kohorte war insgesamt sehr heterogen. So gab es auch Patienten, bei denen initial ein Low grade-Tumor diagnostiziert worden war, und die seit der Erstdiagnose und seit erster Bestrahlung bereits eine langjährige, multimodale Therapie hinter sich gebracht hatten. Erst seit Bevacizumab zur Therapie hinzugezogen wurde, wurden auch diese Patienten einer Re-Bestrahlung zugänglich.
Ein wichtiger Punkt ist auch die Tumorgröße, die in der primären Erkrankungssituation einen prognostischen Faktor darstellt (44). Auch wurden in unserer Kohorte Patienten mit größeren Rezidivtumoren und mit multifokalem Rezidiv re-bestrahlt, anders als bei Combs et al (8). Dass trotzdem die Therapie gut verträglich war, ist möglicherweise damit zu erklären, dass die Hinzunahme von Bevacizumab die Neurotoxizität der Bestrahlung kompensieren kann. So wird Bevacizumab auch zur Therapie einer Radionekrose eingesetzt (32).
In unserer Kohorte waren die Ergebnisse bei alleiniger Re-Bestrahlung schlechter als in der Literatur beschrieben. Auch dies lässt sich möglicherweise durch die großen Tumorvolumina erklären. Gleichzeitig wurde in dem klinikeigenen Kollektiv eine eher konservative Fraktionierung analog Combs et al (6) gewählt. Dies lässt sich auch mit dem großen Sicherheitssaum von 10mm erklären. Da bisher eher Rand- oder distante Rezidive gefunden wurde (55), ist auch weiterhin dieses Vorgehen vertretbar. Eine Definition eines Boostvolumens auf das GTV mit Erhöhung der Gesamtdosis auf einen kleinen Bereich ist zu überlegen und wird inzwischen auch im klinischen Alltag in ausgewählten Fällen unter Berücksichtigung der Vorbelastung der Risikoorgane angewendet.
Der fehlende MGMT-Status bei einigen re-bestrahlten Patienten scheint vernachlässigbar, da sich der MGMT-Methylierungsstatus als kein prognostischer Faktor in der Rezidivsituation erwiesen hatte. Bedauerlicherweise war in Tumormaterial, das auswärtig

gesichert wurde, nicht in allen Fällen der MGMT-Status durchgeführt worden oder nachforderbar.
Bezüglich der Therapie nach erfolgter Re-Radiotherapie konnten keine eindeutigen Ergebnisse gefunden werden. Es zeigte sich kein signifikanter Unterschied zwischen einer direkt adjuvant begonnenen systemischen Therapie und keiner Chemotherapie. Auch konnte kein Unterschied zwischen adjuvanter Therapie und salvage Chemotherapie gefunden werden.
Betrachtet man das Ergebnis des zweiten Papers, so zeigt sich, dass auch Scholtyssek et al. den Heidelberger Score nicht validieren konnten, obwohl in dieser Kohorte keine Low grade-Tumore behandelt wurden (54). Hier zeigte sich ebenfalls, dass das Intervall zwischen erste Bestrahlung und Re-Radiotherapie nicht als prognostischer Faktor verwendet werden konnte.
Zusammenfassend lässt sich zur Re-Bestrahlung mit Bevacizumab sagen, dass Patienten mit dem Rezidiv eines Glioblastoms nach multimodaler Vortherapie von einer kombinierten Therapie wie in unserem Setting profitieren können. Die Toxizität der Therapie ist in einem vertretbaren Rahmen.
Gleichwohl sind weitere, insbesondere auch randomisierte Studien zu diesem Thema notwendig, um einerseits Faktoren zu ermitteln, die es ermöglichen, dass Patienten identifiziert werden können, die tatsächlich von einer Re-Bestrahlung profitieren. Dies wird zum Beispiel mit Datenkonsortien, zum Beispiel der Radplanbio-Datenbank erreicht. So konnte im Rahmen einer multizentrischen DKTK- Kooperation ein neuer Re-Bestrahlungsscore ermittelt werden (66), bei dem initiale Histologie, Karnofsky-Index und Alter zum reRT risk score (RRRS) zusammengefasst werden.
Andererseits können weiterführende Studien auch zur Verbesserung der Zielvolumendefinition beitragen, wodurch auch die Erhöhung der Dosis im Tumor unter weiterhin guter Schonung des gesunden Gewebes sowie des vorbelasteten Gehirngewebes erreicht werden kann.

Summary

Both papers show that re-irradiation with bevacizumab may allow for prolonged survival in selected patient subgroups with glioblastoma relapse. At the same time the combined therapy s feasible with acceptable toxicity. The first paper shows that the toxicity rates are not higher than for a single bevacizumab therapy or for therapies with other chemotherapeutic agents, even in combination (18). Nevertheless comparable survival rates could be found in the literature (19,23).

Despite these promising results there is also a need for discussion.

The evaluated cohort was very heterogeneous overall. There were patients who had initially been diagnosed with a low-grade tumor and who already had a long-term multimodal therapy since the first diagnosis and since the first irradiation. It was not until bevacizumab was used for treatment that these patients became accessible to re-irradiation.

Another important point is the tumor size, which is a prognostic factor in the primary disease situation (44). Also our cohort re-irradiated patients with major recurrent tumors and multifocal relapse unlike Combs et al (8). Nevertheless the therapy was well tolerated. This may be explained by neuroprotective effects of the addition of bevacizumab. Bevacizumab is also used to treat radionecrosis (32).

In our cohort the results on sole re-irradiation were worse than described in the literature. This may also be explained by the large tumor volumes. At the same time a more conservative fractionation was chosen in the clinic's own collective analogous to Combs et al (6). It can also be explained with the large safety margin of 10mm. As marginal or distant recurrences have been found so far (55), this procedure is still acceptable. A definition of a boost volume on the GTV with an increase in the total dose to a small area is to be considered and is now also used in everyday clinical practice in selected cases taking into account the preloading of the organs at risk.

The lack of MGMT status in some re-irradiated patients seems negligible as MGMT methylation status has not been shown to be a prognostic factor in the recurrence situation. Regrettably in tumor material which has been saved externally MGMT status has not been performed or demanded in all cases.

Regarding the therapy after re-radiotherapy no clear results could be found. There was no significant difference between adjuvant systemic therapy and no chemotherapy. Also no difference between adjuvant therapy and salvage chemotherapy could be found.

Looking at the result of the second paper it can be seen that Scholtyssek et al. could not validate the Heidelberg score although no low grade tumors were treated in this cohort (54). The interval between first irradiation and re-radiotherapy showed to be no prognostic factor.

In summary for re-irradiation with bevacizumab patients with recurrence of glioblastoma after multimodal pre-treatment may benefit from combined therapy as in our setting. The toxicity of the therapy is within reasonable limits.

Nevertheless further and in particular randomized studies on this topic are necessary in order to find factors that make it possible to identify patients who actually benefit from re-irradiation. This is achieved with data consortia for example the Radplanbio database. For example, a new re-irradiation score (66) was identified in a multi-center DKTK cooperation, in which initial histology, Karnofsky index and age are combined into the reRT risk score (RRRS).

On the other hand further studies can also contribute to the improvement of the target volume definition whereby the increase in the dose in the tumor can be achieved while continuing to protect the healthy tissue as well as the preloaded brain tissue.

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CLINICAL STUDY

Re-irradiation and bevacizumab in recurrent high-grade glioma: an effective treatment option

Maya Flieger · Ute Ganswindt · Silke Birgit Schwarz · Friedrich-Wilhelm Kreth · Jörg-Christian Tonn · Christian la Fougère · Lorenz Ertl · Jennifer Linn · Ulrich Herrlinger · Claus Belka · Maximilian Niyazi

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Abstract Re-irradiation has been shown to be a meaningful option for recurrent high-grade glioma (HGG) patients. Furthermore, bevacizumab exerts certain activity in combination with chemotherapy/as monotherapy and was safely tested in combination with radiotherapy in several previous studies. To our knowledge, this is the largest cohort of patients treated with both re-irradiation and bevacizumab to date. After receiving standard radiotherapy (with or without TMZ) patients with recurrent HGG were treated with bevacizumab (10 mg/kg intravenously at d1 and d15) during re-irradiation. Median prescribed radiation dose during re-treatment was 36 Gy, conventionally fractionated. Datasets of 71 re-irradiated patients were retrospectively analyzed. Patients either received bevacizumab ($N = 57$) or not ($N = 14$; other substances ($N = 4$) and sole radiation ($N = 10$)). In patients receiving bevacizumab, both post-recurrence survival (PRS) (median 8.6 vs. 5.7 months; $p = 0.003$, log-rank test) and post-recurrence progression-free survival (PR-PFS, 5.6 vs. 2.5 months; $p = 0.005$, log-rank test; PFS-6 42.1 % for the bevacizumab group) were significantly increased which was confirmed by multivariate analysis. KPS, re-surgery, MGMT methylation status, sex, WHO grade, tumor volume and age were no significant predictors for neither PR-PFS nor PRS (univariate analysis). Re-irradiation with bevacizumab remains a feasible and highly effective treatment schedule. Studies on further salvage strategies and timing of sequential treatment options versus observation are warranted.

Keywords Bevacizumab · Re-irradiation · Radiotherapy · Glioma · Glioblastoma

Introduction

In patients with high-grade glioma (HGG) a high rate of local failures has been observed after multimodal therapy

All authors except UH are members of the CCC Neuro-Oncology, University of Munich.

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M. Flieger · U. Ganswindt · S. B. Schwarz · C. Belka · M. Niyazi (✉)
Department of Radiation Oncology, University of Munich, Marchioninistr. 15, 81377 Munich, Germany
e-mail: Maximilian.Niyazi@med.uni-muenchen.de

C. Belka
e-mail: claus.belka@med.uni-muenchen.de

F.-W. Kreth · J.-C. Tonn
Department of Neurosurgery, University of Munich, Marchioninistr. 15, 81377 Munich, Germany

C. la Fougère
Department of Nuclear Medicine, University of Munich, Marchioninistr. 15, 81377 Munich, Germany

L. Ertl · J. Linn
Department of Neuroradiology, University of Munich, Marchioninistr. 15, 81377 Munich, Germany

U. Herrlinger
Division of Clinical Neurooncology, Department of Neurology, University of Bonn Medical Center, Sigmund-Freud-Straße 25, 53127 Bonn, Germany

[1]. The addition of temozolomide (TMZ) increased local control and survival whereas the 2-year survival rate remained 27.2 % [2].

In selected patients, a second course of radiotherapy (RT) seems to be a reasonable treatment option [3–5]. Contrarily, conventional cytotoxic approaches were found to be not adequately effective [6] so that molecularly targeted drugs either alone or in combination with cytotoxic agents are currently undergoing clinical testing.

Various groups have investigated the use of bevacizumab—a humanised monoclonal antibody against VEGF-A with an already established role in metastatic colon, breast, and lung cancer [7]—for patients with recurrent HGG [8] and several trials have documented its efficacy [9–13] which may be due to the presence of pronounced hypoxia as well as high levels of tumor driven angiogenesis in HGG [14].

In glioma patients it has been proven beneficial by improving clinical symptoms reducing the extent of tumor edema. Glioma cell regression can occur independently from vascular regression, suggesting that high doses of bevacizumab have indirect anticancer cell properties in vivo [15]. VEGF-A has also been postulated to be involved in glioma tumor cell migration [16]. Bevacizumab was also tested in combination with radiotherapy and TMZ as up-front treatment of malignant glioma [17–19]. A recent prospective phase III trial (AVAglio) was designed to prove the efficacy of TMZ based radiochemotherapy with bevacizumab as first-line therapy [20].

Since the efficacy of radiation-based re-treatment is limited, it is reasonable to test in how far the addition of a radiation response modulator would impact on the efficacy of re-treatment. In this regard, one group tested the sequential use of radiosurgery and bevacizumab with favorable outcome [21]. Alternatively, Gutin et al. [22] determined the safety and activity of RT and concomitant bevacizumab—for the GBM cohort, PFS-6 was 65 %. In a previous retrospective study on 30 patients, 20 being treated with bevacizumab and 10 without bevacizumab we could show that PFS-6 within the bevacizumab-treated cohort was 72 % and survival was significantly enhanced [23].

After the publication of latter initial results we extended the use in clinical practice. During the first period, safety and feasibility were the most relevant issues—going forward with this treatment option, efficacy became a more relevant topic. Thus, the value of this approach was determined retrospectively by comparing the outcomes of patients having received a bevacizumab based re-irradiation treatment with those being re-treated without bevacizumab with a higher case number and substantially longer follow-up.

Materials and methods

Patient selection

Only patients with histologically and/or FET-PET/MRI proven recurrence and macroscopic tumor (maximum diameter 5 cm with few exceptions, multifocality per se was no contraindication) were admitted to re-irradiation, the interval between first radiotherapy and re-irradiation had to be 6 months at minimum. Another precondition was the absence of meaningful alternative treatment options, e.g. complete resection by re-surgery, interstitial brachytherapy or systemic chemotherapy. In our hands, TMZ in combination with radiation in re-treatment settings has only been employed whenever initial TMZ use was limited. Historically, few patients did not receive any additional systemic therapy concurrently with the re-irradiation course.

Treatment schedule and follow-up

Before treatment, a gadolinium-enhanced brain MRI with gradient echo sequence and perfusion and/or a [^{18}F]FET-PET. Patients treated with bevacizumab received 10 mg/kg at days 1 and 15 during radiotherapy. If applied in patients who had no previous progression after TMZ pre-treatment a dosage of 75 mg/m^2 daily was chosen.

Treatment outcome was evaluated on a regular basis (every 3 months) by brain MRI [24] and/or FET-PET.

All MRI datasets were independently assessed by two experienced neuroradiologists (LE, JL) with regard to progressive disease (PD) or potential pseudoprogression according to the radiographic aspects of imaging criteria in the AVAglio protocol [25].

Adjuvant chemotherapy was prescribed on an individual base as no standard has been defined yet but was not defined as mandatory.

Radiotherapy

By analogy with Combs et al. [26]. patients received a total dose of 36 Gy in 18 fractions (2 Gy single doses) employing 3D conformal radiotherapy or IMRT if adjacent critical structures were present. Planning target volume (PTV) was defined as gross tumor volume (GTV) plus 10 mm margin at maximum. GTV included the contrast enhancing lesion in T1w + Gd MRI. To ensure reproducibility patients were immobilized with a thermoplastic mask system. Treatment planning was performed using the Oncentra® treatment planning system (OTP MasterPlan®, Nucletron, Solingen, Germany).

Toxicity evaluation

Adverse events and toxicity were determined retrospectively using the National Cancer Institute's Common Toxicity Criteria, version 4.0 as reported before [23, 27]. Concerning adverse events of radiotherapy, focus was set on radiation necrosis as well as generalized leukoencephalopathy.

Statistics

Outcome measures of this retrospective analysis were overall survival for the total cohort from initial treatment, safety of bevacizumab given in combination with RT for recurrent HGG as well as post-recurrence and progression-free survival (PRS & PR-PFS) in patients treated with or without bevacizumab. Comparisons between groups were carried out using Fisher's exact test or the Mann–Whitney U test. Survival analyses were based on Kaplan–Meier estimates, uni- and multivariate modelling was performed using a Cox proportional hazards analysis. For all patients, overall survival was measured from initial diagnosis, PRS from the first day of re-irradiation until death or last follow-up and progression-free survival until progressive disease or death (otherwise censored). A two-tailed $p \leq 0.05$ was considered significant.

Results

Patient characteristics

Using the department's database, 71 patients with recurrent HGG treated at our department from 5/2004 to 3/2012 were identified and retrospectively analyzed. All patient characteristics are shown in Table 1.

8.5 % of patients had a WHO grade II glioma at initial diagnosis, progressing to a secondary HGG at relapse, median age was 53 years (range 18–68 years) and median KPS was 80 (range 40–100). Thirty-four patients had a histologically proven relapse.

Before initial irradiation, 81.7 % of the patients received total or subtotal resection and 12.7 % upfront to re-irradiation (subtotal only). 78.9 % of patients were treated with TMZ during adjuvant/primary RT.

Because MGMT promoter methylation status was not systematically analyzed before 2006, it is only available in 61 out of 71 patients; a retrospective determination was not possible as no pathologic material was provided by external departments.

57 patients (14 WHO grade III, 43 WHO grade IV) received bevacizumab in addition to re-irradiation, 14 patients (5 WHO grade III, 9 WHO grade IV) were re-irradiated without bevacizumab.

Table 1 Patient characteristics, $N = 71$

Characteristic	Patients
Sex	
Male	46 (64.8 %)
Female	25 (35.2 %)
Median age (year)	53.0 (18–68)
Median KPS	80 (40–100)
KPS < 70	16 (22.5 %)
KPS ≥ 70	54 (76.1 %)
Unknown	1 (1.4 %)
Median dose of primary radiotherapy	60 Gy
Median dose of re-irradiation	36 Gy
Median GTV size (ml)	34.88 (1.95–157.94)
Bevacizumab during re-irradiation	
Yes (WHO grade III/IV)	57 (14/43) (80.3 %)
No (WHO grade III/IV)	14 (5/9) (19.7 %)
MGMT methylation status	
Methylated	30 (43.7 %)
Not methylated	31 (42.2 %)
Unknown	10 (14.1 %)
Initial WHO grade	
II	6 (8.5 %)
III	16 (22.5 %)
IV	49 (69.0 %)
WHO grade at relapse	
III	19 (26.8 %)
IV	52 (73.2 %)
Resection before re-irradiation	
Yes	9 (12.7 %)
No	62 (87.3 %)
Concomitant TMZ treatment during first RT	
Yes	56 (78.9 %)
No	15 (21.1 %)
Adjuvant/salvage chemotherapy	
No chemotherapy	38
Bevacizumab + X	18 (X = nil (7), procarbazine (3), TMZ (2), irinotecan (6))
TMZ + X	11 (X = nil (10), sunitinib (1))
TMZ intensified + X	4 (X = nil (3), carmustine (1))

Median follow-up for all patients from the start of re-irradiation was 18 months (95 % CI 10–26 months).

Survival and toxicity data

Median overall survival (mOS) of the patient cohort was 32.5 months (95 % CI 26.7–38.3 months). As expected, patients with lower WHO grade had a longer survival history, median survival for WHO grade II patients was

Table 2 Safety profile of bevacizumab ($N = 57$), according to CTCAE v 4.0

Toxicity	No. of patients (%) and grade
Fatigue	1 (1.8) grade 2
CNS hemorrhage	0 (0)
Hypertension	1 (1.8) grade 2
Wound-healing complication	1 (1.8) grade 4
Deep vein thrombosis	1 (1.8) grade 3
Thrombocytopenia	1 (1.8) grade 2, 1 (1.8) grade 4
Colonic perforation	1 (1.8) grade 5

196.1 months (95 % CI 53.3–338.9 months), for grade III 35.0 months (95 % CI 25.7–44.2 months; $p = 0.003$ compared to WHO grade II) and 27.5 months for grade IV (95 % CI 23.4–31.6 months; $p = 0.16$ compared to WHO grade III).

Considering now the course after re-irradiation, median post-recurrence progression-free survival (PR-PFS) was 4.9 months (95 % CI 4.0–5.8 months) and median post-recurrence survival 7.8 months, (95 % CI 6.0–9.5 months) for the entire patient population.

Re-irradiation with bevacizumab was generally well tolerated (three grade 2 toxicities, one grade 3, two grade 4 toxicity and one grade 5 toxicity) (Table 2).

Concerning the grade 5 toxicity, this patient suffered a perforation of the sigmoid colon the day after completed radiotherapy due to an existing diverticulosis with concomitant high-dose intake of steroids. Despite immediate surgical treatment, the patient died 4 days later.

Furthermore, imaging and histo-pathology revealed at maximum three cases with changes compatible with radiation necroses (see an example in Fig. 1).

Furthermore, three cases of grade 1 leukoencephalopathy, five cases of grade 2 and one case of grade 3 leukoencephalopathy were observed.

Comparison between re-irradiation with and without bevacizumab

When comparing both therapeutic subgroups (bevacizumab vs. no bevacizumab during re-irradiation), no statistically significant differences could be observed concerning WHO grade ($p = 0.502$), MGMT methylation status ($p = 0.081$), age ($p = 0.131$), sex ($p = 0.223$), tumor volume ($p = 0.930$), KPS ($p = 0.128$), re-surgery ($p = 0.068$) or adjuvant/salvage chemotherapy ($p = 1.000$)—so no relevant bias was present towards one of the subgroups (see Supplementary Table).

The results of this analysis show an association between increased PRS and PR-PFS rates and the combined treatment of re-irradiation and bevacizumab.

Median PR-PFS was 2.5 months in the group treated with radiotherapy alone compared to 5.6 months with re-irradiation plus bevacizumab ($p = 0.005$). PFS-6 was 42.1 % for re-irradiation and bevacizumab compared to re-irradiation alone with 14.3 % (Fig. 2). Median PRS after re-irradiation alone was 5.7 months, whereas median PRS after re-irradiation with additional bevacizumab increased to 8.6 months. This result was statistically significant ($p = 0.003$, Fig. 2).

Additionally performed early adjuvant (<8 weeks after the end of re-irradiation)/salvage systemic chemotherapy slightly increased median PRS (9.1 months with adjuvant therapy vs. 7.1 months without/with salvage therapy), however the difference between both groups was not significant ($p = 0.274$, log-rank test). Considering the subgroup of patients who received bevacizumab this difference seemed to be slightly more pronounced—median PRS 9.8 versus 7.5 months ($p = 0.20$, log-rank test).

When comparing PR-PFS for patients who did not receive adjuvant chemotherapy versus patients with adjuvant chemotherapy, no significant improvement in PR-PFS could be observed (median PR-PFS 4.2 vs. 4.4 months, $p = 0.19$); patients who received salvage chemotherapy had a trend towards longer PR-PFS before their relapse (median 7.9 vs. 4.2 months, $p = 0.06$).

Univariate and multivariate analyses

In order to define prognostic and/or predictive factors for PRS and PR-PFS univariate and multivariate testing were performed whereas for the latter significance/trend within univariate analysis and WHO grade were employed. The results are shown in Table 3.

Bevacizumab, chemotherapy post re-irradiation (adjuvant or as salvage treatment) and a total re-irradiation dose ≥36 Gy were the variables with statistically significant impact on survival in univariate testing ($p = 0.003$, $p = 0.017$ and $p = 0.022$, respectively). Concerning PR-PFS, only bevacizumab use remained significant ($p = 0.005$) whereas there was a trend for chemotherapy ($p = 0.064$).

Interestingly, WHO grade at relapse was non-significant regarding survival in the univariate analysis ($p = 0.195$), median PRS in patients with WHO IV was 9.1 months compared to 7.1 months in patients with WHO III.

Volume of the GTV (median 34.88 ml) showed a trend towards improved PRS and PR-PFS in case of a smaller volume (as continuous variable: $p = 0.099$, HR 0.62); patients with a volume smaller than the median volume (categorical variable) had a median PRS of 9.1 months versus 6.3 months (larger volumes), $p = 0.096$ whereas PR-PFS was 5.1 versus 3.8 months, $p = 0.152$.

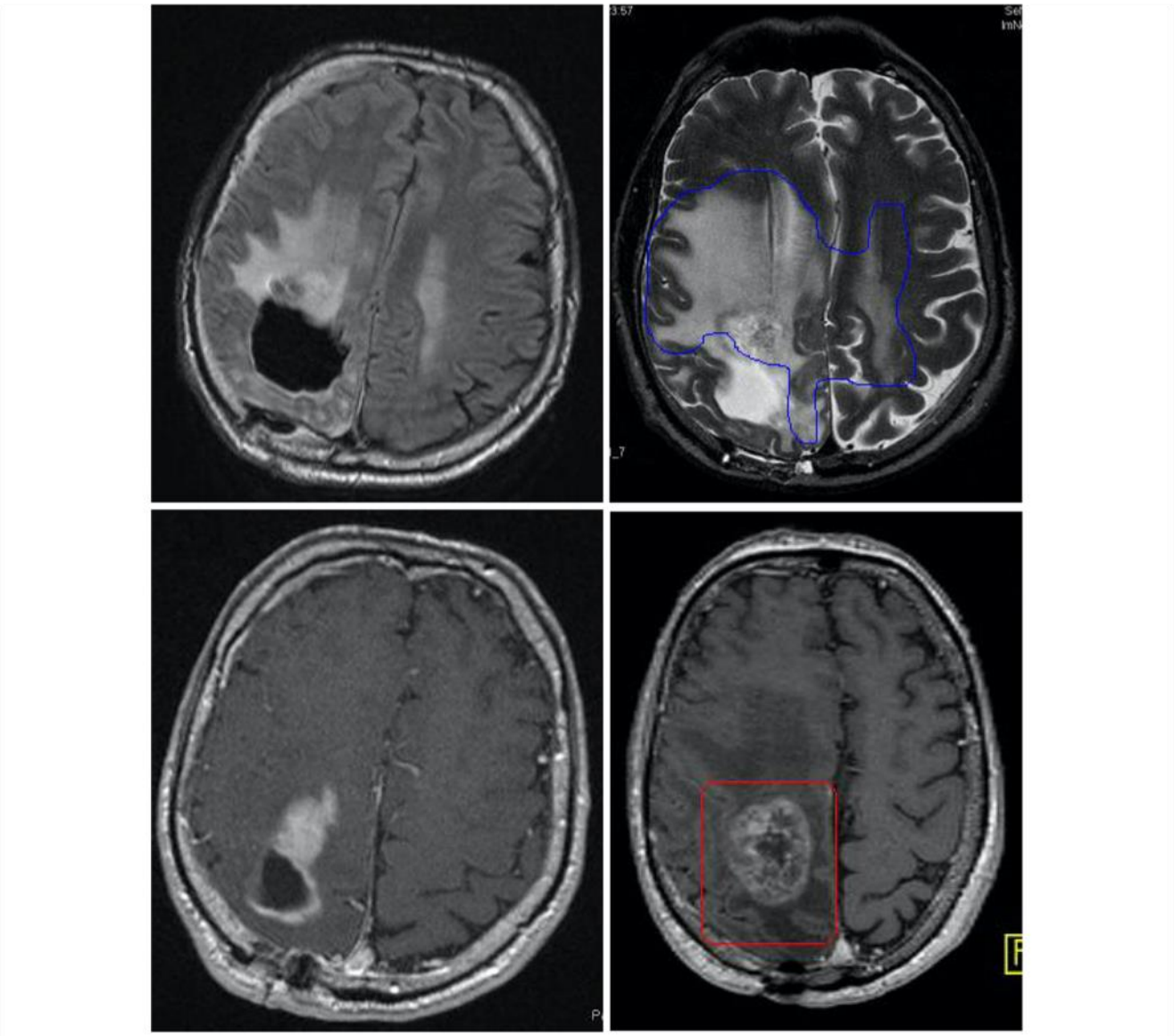

Fig. 1 One sample patient with a mass suspicious for radiation necrosis. On the *left side* MRI before re-irradiation (contrast-enhanced T1, T2 FLAIR) and 4 months after re-irradiation (contrast-enhanced T1, T2)

Age, sex, MGMT methylation status, time interval between first percutaneous irradiation and re-irradiation as well as surgery before re-irradiation were found to be non-significant variables within the univariate analysis (p values see Table 3).

KPS was not statistically significant neither for PRS ($p = 0.132$), nor for PR-PFS ($p = 0.104$).

Concerning PRS and PR-PFS, the only factor that turned out to be a significant variable within the full multivariate Cox model as well in the univariate analysis was treatment with bevacizumab (PRS: $p = 0.004$, hazard ratio (HR) 3.27 (95 % CI 1.45–7.36; PR-PFS: $p = 0.002$, HR 3.56 (95 % CI 1.62–7.83).

Categorial GTV size turned out to be significant within multivariate analysis though being univariately not significant (PRS: $p = 0.030$, HR 0.49 (95 % CI 0.26–0.93); PR-PFS: $p = 0.048$, HR 0.56 (95 % CI 0.32–0.99)).

Applying chemotherapy in general (adjuvant/salvage) after re-irradiation showed a marginal influence in the multivariate analysis on PRS ($p = 0.065$), HR 1.77 (95 % CI 0.97–3.23) and KPS had significant influence on PR-PFS ($p = 0.049$, HR 1.96 (95 % CI 1.00–3.82), the remaining factors WHO grade at relapse, re-irradiation dose were non-significant according to PRS and PR-PFS, see hazard ratios in Table 3.

Subgroup analyses

The results for the entire patient cohort are shown together in Fig. 2 differentiated by subgroups including WHO grade

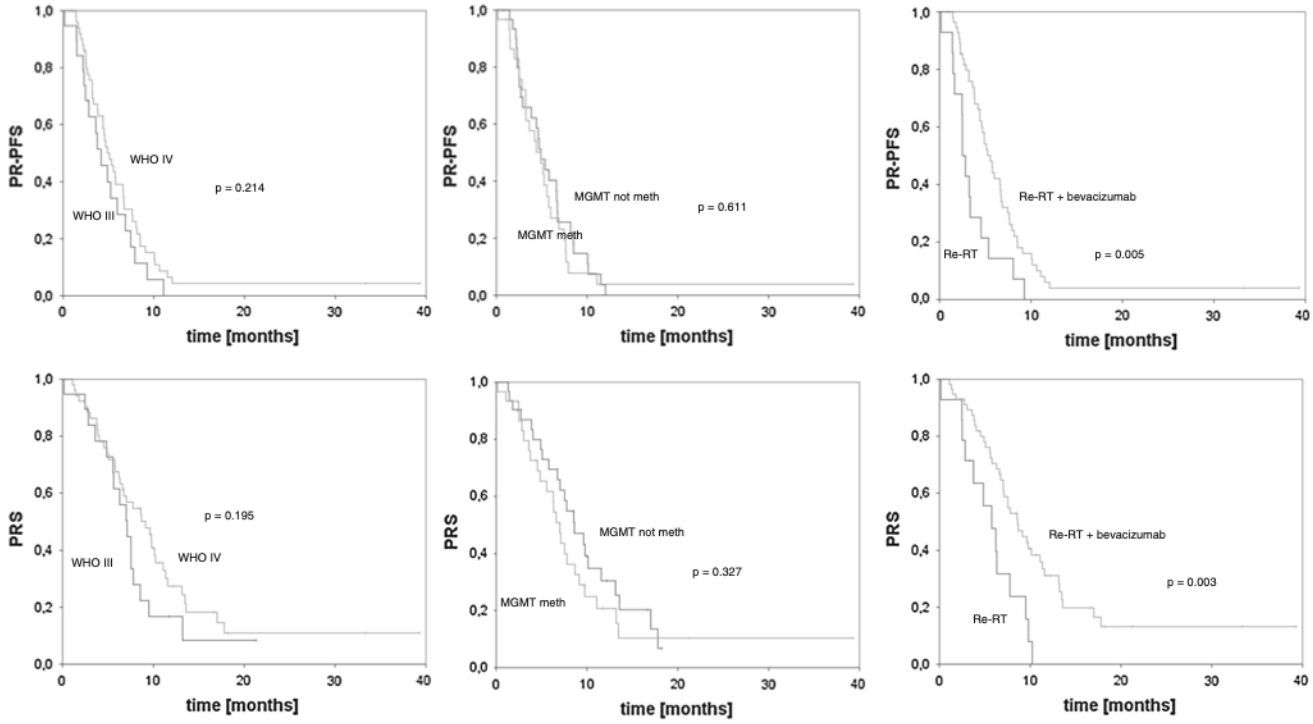

Fig. 2 Kaplan–Meier PR-PFS and PRS curves for the entire patient cohort depending on different subgroups. From *left* to *right* grouped by WHO grade at relapse, MGMT methylation status and the application of bevacizumab. *P* values derived from log-rank test

at relapse, MGMT methylation status and the use of bevacizumab during re-irradiation. When performing a stratified subgroup analysis, especially patients with an MGMT promoter methylation had advanced PR-PRS and PRS rates (median PR-PFS 5.6 (bevacizumab) vs. 2.5 months (no bevacizumab); median PRS 7.8 vs. 2.8 months, $p < 0.001$ in both cases), for patients without MGMT methylation the difference was not significant whereas the case number was small. PRS was improved by bevacizumab in both WHO grade III and IV patients and again ($p = 0.045$, $p = 0.039$), the differences were non-significant for PR-PFS due to a small case number.

Another interesting aspect was stratification upon bevacizumab concerning tumor volume—taking the GTV cutoff of median 34.88 ml there was a strong significant difference in PRS in the relatively small group of patients without bevacizumab (7.8 vs. 2.5 months, $p = 0.001$) whereas this difference was not significant in patients treated with bevacizumab (9.6 vs. 7.7 months, $p = 0.186$). The same was true for PR-PFS: 3.3 versus 2.5 months (no bevacizumab, $p = 0.027$) and 5.6 versus 4.9 months (bevacizumab, $p = 0.205$).

Concerning the issue of patients with initial WHO II glioma (low-grade gliomas), an evaluation was performed where patients who did not have a stage III/IV histology at initial irradiation were excluded ($N = 4$). Results were comparable, especially bevacizumab remained a significant prognostic variable for improved PR-PFS (median 5.1 vs. 2.8 months, $p = 0.011$) and PRS (median 8.5 vs. 6.2 months, $p = 0.012$).

When focusing on GBM patients who had been treated according to the EORTC/NCIC regimen during their primary therapy ($N = 45$, 38 patients treated with bevacizumab additionally to re-irradiation), median PR-PFS was 5.1 months (bevacizumab) versus 3.4 months (no bevacizumab), $p = 0.06$. Median PRS was 9.3 months (bevacizumab) compared to 6.1 months (no bevacizumab), $p = 0.27$, so in principle comparable results were derived whereas significance was failed due to only seven patients in the arm without bevacizumab. When comparing the cohort ($N = 30$) which was examined in a previous evaluation of our group [23], there were no significant differences in patient characteristics concerning age, sex, tumor volume, time interval between previous and re-irradiation or histology but patients had a significantly better KPS (87.5 vs. 63.3 % $\geq$70, $p = 0.02$) and there was a trend towards a more frequent use of bevacizumab (87.8 vs. 70.0 %, $p = 0.08$). Nevertheless, PRS and PR-PFS were not significantly different (PRS: median 8.6 vs. 7.0 months, $p = 0.75$; PR-PFS: median 5.7 vs. 4.2 months, $p = 0.52$).

Discussion

For certain subgroups of recurrent HGG patients re-irradiation may be a strategy to prolong survival with

Table 3 Univariate analysis (log-rank test/Cox regression), influence on post-recurrence survival (PRS) and post-recurrence progression-free survival (PR-PFS) as well as multivariate Cox proportional hazards analysis (model parameters)

Variable	Univariate p value PRS/PR-PFS	Multivariate p value PRS/PR-PFS	HR–PRS/PR-PFS
Age (<60, ≥60 years)	ns ($p = 0.986$)/ns ($p = 0.381$)	–/–	–/–
KPS (<70, ≥70)	ns ($p = 0.132$)/ns ($p = 0.104$)	ns ($p = 0.124$)/$p = 0.049$	1.73/1.96
surgery (yes/no)	ns ($p = 0.207$)/ns ($p = 0.696$)	–/–	–/–
MGMT (meth/not meth)	ns ($p = 0.327$)/ns ($p = 0.611$)	–/–	–/–
GTV (<34.88, ≥34.88 ml)	ns ($p = 0.096$)/ns ($p = 0.152$)	$p = 0.030$/$p = 0.048$	0.45/0.56
WHO grade at relapse (III/IV)	ns ($p = 0.195$)/ns ($p = 0.214$)	ns ($p = 0.462$)/ns ($p = 0.219$)	1.30/1.515
Bevacizumab (no/yes)	$p = 0.003$/$p = 0.005$	$p = 0.004$/$p = 0.002$	3.27/3.56
Adjuvant/salvage chemotherapy (no/yes)	$p = 0.017$/ns ($p = 0.064$)	ns ($p = 0.065$)/ns ($p = 0.205$)	1.77/1.44
Re-irradiation dose (<36, ≥36 Gy)	$p = 0.022$/ns ($p = 0.223$)	ns ($p = 0.273$)/ns ($p = 0.808$)	1.46/0.92
Sex (male/female)	ns ($p = 0.359$)/ns ($p = 0.599$)	–/–	–/–
Time interval between first and re-RT	ns ($p = 0.593$)/ns ($p = 0.517$)	–/–	–/–

$N = 71$, *ns* not significant, *meth* MGMT methylated, *HR* hazard ratio

acceptable toxicity. The aim of this study was to analyze whether the improvement caused by the use of concomitant bevacizumab in our previous analysis was still present within a larger patient cohort and with longer follow-up keeping in mind that this is the largest cohort to our knowledge uniformly treated with re-irradiation and bevacizumab in one center.

In this regard, the outcome of our trial compares nicely with data presented by Gutin and colleagues or those of Hundsberger et al. [28]. The results of Gutin et al. combining bevacizumab with radiation were superior than those of a matched cohort of patients who received re-irradiation only which is in line with our results [22]. But in contrast to Gutin, our updated study was monocentric and is to date the only one directly comparing survival rates of re-irradiated patients with or without bevacizumab; thus it may be regarded being less biased concerning institutional differences. A further difference was the fact that bevacizumab was applied until disease progression which was not regularly the case in our cohort. The survival rate of the combined treatment is promising and PFS-6 compares favorably with data found in the literature [3, 4, 29].

The combined treatment approach was well tolerated. Overall toxicity in our study was not higher than in the use of sole re-irradiation and bevacizumab alone or in combination with other agents in patients with HGG [30, 31].

Since all of the approaches in recurrent HGGs have a limited activity and are associated with relevant and sometimes severe toxicity we consider re-irradiation with bevacizumab to be a very effective and safe approach for those patients in whom a second course of radiotherapy is feasible. The survival data obtained for re-irradiation and bevacizumab are very promising and even in this retrospective unselected cohort, a long-term survival plateau of 13.2 %, a median PRS of 8.6 months and a 1y-PRS of 31.1 % could be achieved which is quite favorable compared to historical data of bevacizumab mono [32–34] or re-irradiation alone [29].

Nevertheless, we have to discuss several shortcomings and interesting aspects of this analysis.

Firstly, the patient cohort is very heterogeneous with a potential timing bias as some patients with initially low-grade tumors have been multimodally treated many years before re-irradiation—due to the introduction of bevacizumab and initial positive results this option became more frequently used so that results could be obtained for a more realistic patient cohort without selection bias. This explains why the historical group of patients who have only been re-irradiated is comparatively small. Though this control group was small, the power is adequate and the type II error negligible.

Secondly, our results from patients with sole re-irradiation are nominally inferior to other series employing stereotactic fractionated radiotherapy or radiosurgery. This might be due to a slightly more conservative fractionation caused by in average larger tumors and our in-house policy.

Thirdly, one further shortcoming was the fact that in ten cases the MGMT promoter methylation status was not known; in these cases no histopathologic material was available in our university and external departments did not provide relevant material. Though being one of the most important prognostic outcome markers in the primary setting, the influence of the MGMT status in re-treatment settings has not been validated and not in all cases a new status was obtained.

There does not seem to be a necessity to start adjuvant chemotherapy immediately after re-irradiation—there was no significant difference in PFS comparing patients with adjuvant chemotherapy and patients without chemotherapy—altogether adjuvant chemotherapy did not improve

survival when compared to patients without maintenance chemotherapy and those who received salvage chemotherapy (to exclude the bias of salvage patients who lived long enough in order to receive salvage treatment).

Another interesting aspect was the relevance of tumor size—depending on the application of bevacizumab, this well-known prognostic factor lost its significance which leaves the speculation that potential neurotoxicity is compensated by bevacizumab.

Concerning our fractionation schedule, a more conservative approach was chosen. This is historically related to the seminal paper by Mayer and Sminia [35] who derived a cumulative NTD threshold of 100 Gy, but compared to other fractionation schedules [22, 36] 2/36 Gy is far more cautious—ex post one has to state that large tumor volumes were included (up to 158 ml) and margins were not too tight with up to 10 mm. Hypofractionation could have yielded a higher rate of radiation necroses than actually observed in our study and the high rate of marginal/distant recurrences during hypofractionated re-irradiation [37] might be a further reason not to shrink the PTV margin. A simultaneous integrated boost to the GTV would probably be most appropriate for further investigations.

In how far our approach is superior to other approaches is currently difficult to assess since randomized trials comparing different re-treatment options are lacking. At present, bevacizumab based systemic approaches resulted in PFS-6 rates from 29 % to 50.3 % [34, 38, 39]. The result of our series (42.1 %) is in this range.

In conclusion, the results of the randomized controlled trials on the use of bevacizumab concomitantly to irradiation are expected—treatment will probably become more diverse; especially in those patients who were treated with a temozolomide-based radiochemotherapy. Re-irradiation with bevacizumab may be an effective salvage option—many interesting questions on further salvage strategies have to be solved and studies are needed to find prognostic markers to identify those patients who would profit most from re-irradiation [40–42] or to optimize target volume delineation [43].

Conflict of interest The authors declare that conflicts of interest do not exist.

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Validation of the prognostic Heidelberg re-irradiation score in an independent mono-institutional patient cohort

Maximilian Niyazi[1], Maya Flieger[1], Ute Ganswindt[1], Stephanie E Combs[2,3†] and Claus Belka[1*†]

Abstract

Purpose: Re-irradiation has been shown to be a valid option with proven efficacy for recurrent high-grade glioma patients. Overall, up to now it is unclear which patients might be optimal candidates for a second course of irradiation. A recently reported prognostic score developed by Combs et al. may guide treatment decisions and thus, our mono-institutional cohort served as validation set to test its relevance for clinical practice.

Patients and methods: The prognostic score is built upon histology, age (< 50 vs. ≥ 50 years) and the time between initial radiotherapy and re-irradiation (≤ 12 vs. > 12 months). This score was initially introduced to distinguish patients with excellent (0 points), good (1 point), moderate (2 points) and poor (3–4 points) post-recurrence survival (PRS) after re-irradiation. Median prescribed radiation dose during re-treatment of recurrent malignant glioma was 36 Gy in 2 Gy single fractions. A substantial part of the patients was additionally treated with bevacizumab (10 mg/kg intravenously at d1 and d15 during re-irradiation).

Results: 88 patients (initially 61 WHO IV, 20 WHO III, 7 WHO II) re-irradiated in a single institution were retrospectively analyzed. Median follow-up was 30 months and median PRS of the entire patient cohort 7 months. Seventy-one patients (80.7%) received bevacizumab. PRS was significantly increased in patients receiving bevacizumab (8 vs. 6 months, p = 0.027, log-rank test). KPS, age, MGMT methylation status, sex, WHO grade and the Heidelberg score showed no statistically significant influence on neither PR-PFS nor PRS.

Conclusion: In our cohort which was mainly treated with bevacizumab the usefulness of the Heidelberg score could not be confirmed probably due to treatment heterogeneity; it can be speculated that larger multicentric data collections are needed to derive a more reliable score.

Keywords: Bevacizumab, Re-irradiation, Radiotherapy, Glioma, Glioblastoma, Heidelberg score, Prognostic

Introduction

In patients with high-grade glioma (HGG) a substantial rate of local failures has been observed after multimodal therapy [1]. The addition of temozolomide (TMZ) increased local control and survival, whereas the 2-year survival rate remained 27.2% [2].

In selected patients, a second course of radiotherapy (RT) was shown to be a reasonable treatment option [3-5]. One highly important question is which patients should be candidates for a second course of irradiation as not all patients seem to profit from such a second course. Concerning e. g. re-surgery, such a score was derived by Park and colleagues including KPS, tumor volume and the MSM score, which could be validated in an independent patient dataset and was therefore even predictive for patients undergoing re-surgery [6]. Thus, Combs and colleagues developed a prognostic score in order to estimate the survival benefit of patients who are planned to be irradiated [7], whereas no validation was performed by this group.

Therefore, we aimed at a validation in our independent patient cohort. One major difference between the initial and our cohort was the additional application of bevacizumab in a substantial part of the cases.

* Correspondence: Claus.Belka@med.uni-muenchen.de
†Equal contributors
[1]Department of Radiation Oncology, University of Munich, Marchioninistr. 15, 81377 Munich, Germany
Full list of author information is available at the end of the article

Various groups have already investigated the use of bevacizumab – a humanised monoclonal antibody against VEGF-A with an already established role in metastatic colon, breast, and lung cancer [8] – for patients with recurrent HGG [9] and several trials have documented its efficacy [10-14], which may be due to the presence of pronounced hypoxia as well as high levels of tumor driven angiogenesis in HGG [15,16].

Since the efficacy of radiation-based re-treatment is limited, it is reasonable to test in how far the addition of a radiation response modulator would impact on the efficacy of re-treatment. In this regard, Gutin and co-workers determined the safety and activity of RT and concomitant bevacizumab – for the GBM cohort, PFS-6 was 65% [17]. In a previous retrospective study on 30 patients, 20 being treated with bevacizumab we could show that PFS-6 within the bevacizumab-treated cohort was 72% and survival was significantly enhanced [18]. After the publication of latter initial results we extended the use in clinical practice. Thus, the value of this approach was determined retrospectively by comparing the outcomes of patients having received a bevacizumab based re-irradiation treatment with those being re-treated without bevacizumab with a higher case number and substantially longer follow-up [19]. The advantage of adding bevacizumab was still present in this updated analysis.

The aim of this study is to present the results after retrospective determination of the Heidelberg score compared to outcome data and to test its prognostic significance.

Patients and methods

Patient selection

Only patients with histologically and/or FET-PET/MRI proven recurrence and macroscopic tumor (maximum diameter 5 cm with few exceptions, multifocality per se was no contraindication) were admitted to re-irradiation, the interval between first radiotherapy and re-irradiation had to be 6 months at minimum. Patients that received alternative treatment modalities, e. g. complete resection by re-surgery, interstitial brachytherapy or systemic chemotherapy were excluded from the analysis.

Treatment schedule and follow-up

Before treatment, a gadolinium-enhanced brain MRI with gradient echo sequence and perfusion and/or a [^{18}F]FET-PET were performed. Patients treated with bevacizumab received 10 mg/kg at days 1 and 15 during radiotherapy. If applied in patients who had no previous progression after TMZ pre-treatment a dosage of 75 mg/m^2 daily was chosen.

Treatment outcome was evaluated on a regular basis (every three months) by brain MRI [20] and/or FET-PET. Adjuvant chemotherapy was prescribed on an individual base as no standard has been defined yet but was not set as mandatory.

Radiotherapy

By analogy with Combs et al. [21] patients received a total dose of 36 Gy in 18 fractions (2 Gy single doses) employing 3D conformal radiotherapy or IMRT if adjacent critical structures were present. Planning target volume (PTV) was defined as gross tumor volume (GTV) plus 10 mm margin at maximum. GTV included the contrast enhancing lesion in T1w + Gd MRI. To ensure reproducibility patients were immobilized with a thermoplastic mask system. Treatment planning was performed using the Oncentra® treatment planning system (OTP MasterPlan®, Nucletron, Solingen, Germany).

Toxicity evaluation

Adverse events and toxicity were determined retrospectively using the National Cancer Institute's Common Toxicity Criteria, version 4.0 as reported before [18,22]. Concerning adverse events of radiotherapy, focus was set on radiation necrosis as well as generalized leukoencephalopathy.

Statistics

Outcome measures of this retrospective analysis were overall survival for the entire cohort from initial treatment, safety of bevacizumab given in combination with RT for recurrent HGG as well as post-recurrence and progression-free survival (PRS & PR-PFS) in patients treated with or without bevacizumab. Survival analyses were based on Kaplan-Meier estimates, univariate modelling was based on the logrank-test. For all patients, PRS was measured from the first day of re-irradiation until death or last follow-up and progression-free survival until progressive disease or death (otherwise censored). The Heidelberg score was determined as described elsewhere [7]. A two-tailed p-value ≤ 0.05 was considered significant.

Results

Patient characteristics

Using the department's database, 88 patients with recurrent HGG treated at our department from 5/2004 to 9/2013 were identified and retrospectively analyzed. All patient characteristics are shown in Table 1.

8.0% of patients had a WHO grade II glioma at initial diagnosis, progressing to a secondary HGG at relapse, median age was 51 years (range, 18–73 years, 44.3% <50 years) and median KPS was 80 (range, 40–100). 77.3% of patients were treated with TMZ during adjuvant/primary RT.

Because MGMT promoter methylation status was not systematically analyzed before 2006, it is only available in 78 out of 88 patients; retrospective evaluation of

Table 1 Patient characteristics, N = 88

Characteristic	Patients
Sex	
• Male	57 (64.8%)
• Female	31 (35.2%)
Median Age [y]	51.0 (18 – 73)
• < 50	39 (44.3%)
• ≥ 50	49 (55.7%)
Median KPS	80 (40 – 100)
• KPS < 70	18 (20.5%)
• KPS ≥ 70	65 (73.9%)
• Unknown	5 (5.7%)
Median dose of primary radiotherapy	60 Gy
Median dose of re-irradiation	36 Gy
Time interval ≤ 12 months	29 (33%)
Time interval > 12 months	59 (67%)
Bevacizumab during re-irradiation	
• Yes	71 (80.7%)
• No	17 (19.3%)
MGMT methylation status	
• Methylated	42 (47.7%)
• not methylated	36 (40.9%)
• unknown	10 (11.4%)
Initial WHO grade	
• II	7 (8.0%)
• III	20 (22.7%)
• IV	61 (69.3%)
WHO grade at relapse	
• III	23 (26.1%)
• IV	65 (73.9%)
Concomitant TMZ treatment during first RT	
• Yes	68 (77.3%)
• No	20 (22.7%)
Chemotherapy	
• No adjuvant chemotherapy	36 (40.9%)
• Adjuvant therapy	45 (51.1%)
• Unknown	7 (8.0%)

MGMT-promoter methylation status was not a focus of the present manuscript.

Seventy-one patients received bevacizumab in addition to re-irradiation, 17 patients were re-irradiated without bevacizumab. Median follow-up for all patients from the start of re-irradiation was 30 months (95% CI, 12.6-47.3 months) and in 33% of all cases the interval between the end of primary irradiation and re-irradiation was ≤ 12 months.

Survival data

Considering the course after re-irradiation, median post-recurrence progression-free survival (PR-PFS) was 4 months (95% CI, 3–5 months) and median PRS 7 months, (95% CI, 5 – 8 months) for the entire patient population.

Re-irradiation with bevacizumab was generally well tolerated (three grade 2 toxicities (3%), one grade 3 (1%), two grade 4 toxicities (2%) and one grade 5 toxicity (1%)).

When comparing both therapeutic subgroups (bevacizumab vs. no bevacizumab during re-irradiation), no statistically significant differences could be observed concerning WHO grade, age category, sex, KPS or adjuvant chemotherapy – so no bias was present towards one of the subgroups.

The results of this analysis show an association between increased PRS and PR-PFS rates and the combined treatment of re-irradiation and bevacizumab.

Median PR-PFS was 3 months in the group treated with radiotherapy alone compared to 5 months with re-irradiation plus bevacizumab (p = 0.396). PFS-6 was 29.9% for re-irradiation and bevacizumab compared to re-irradiation alone with 25.1% (Figure 1). Median PRS after re-irradiation alone was 6 months, whereas median PRS after re-irradiation with additional bevacizumab increased to 8 months. This result was statistically significant (p = 0.027, Figure 1).

Univariate analysis & prognostic score

In order to define prognostic and/or predictive factors for PRS and PR-PFS univariate testing was performed and results are shown in Table 2.

Age, KPS, MGMT methylation status, initial WHO grade, sex and the time interval between the end of percutaneous primary irradiation and re-irradiation were found to be non-significant variables within the univariate analysis for both PRS and PR-PFS (p-values see Table 2).

Bevacizumab was the only variable with statistically significant impact on survival according to univariate testing (p = 0.027). Concerning PR-PFS, no significant impact of bevacizumab could be derived (p = 0.396). Another factor with a trend towards improved PR-PFS was adjuvant/salvage chemotherapy (p = 0.054), for PRS this result was less pronounced (p = 0.108), see Table 2 and Figure 1. Median PRS was 9 (with) vs. 6 months (without chemotherapy), median PR-PFS was 5 (with) vs. 3 months.

For the Heidelberg score, there was no significant influence on either PRS or PR-PFS (p = 0.664, see Table 3). As shown, the survival is relatively homogeneous among the different subgroups (PRS: median 7 (excellent) vs. 7 (good) vs. 9 (moderate) vs. 7 (poor) months). According to the subgroups stratified by bevacizumab a similar result is observed, whereas the case number for patients without bevacizumab is quite small and therefore categories such as

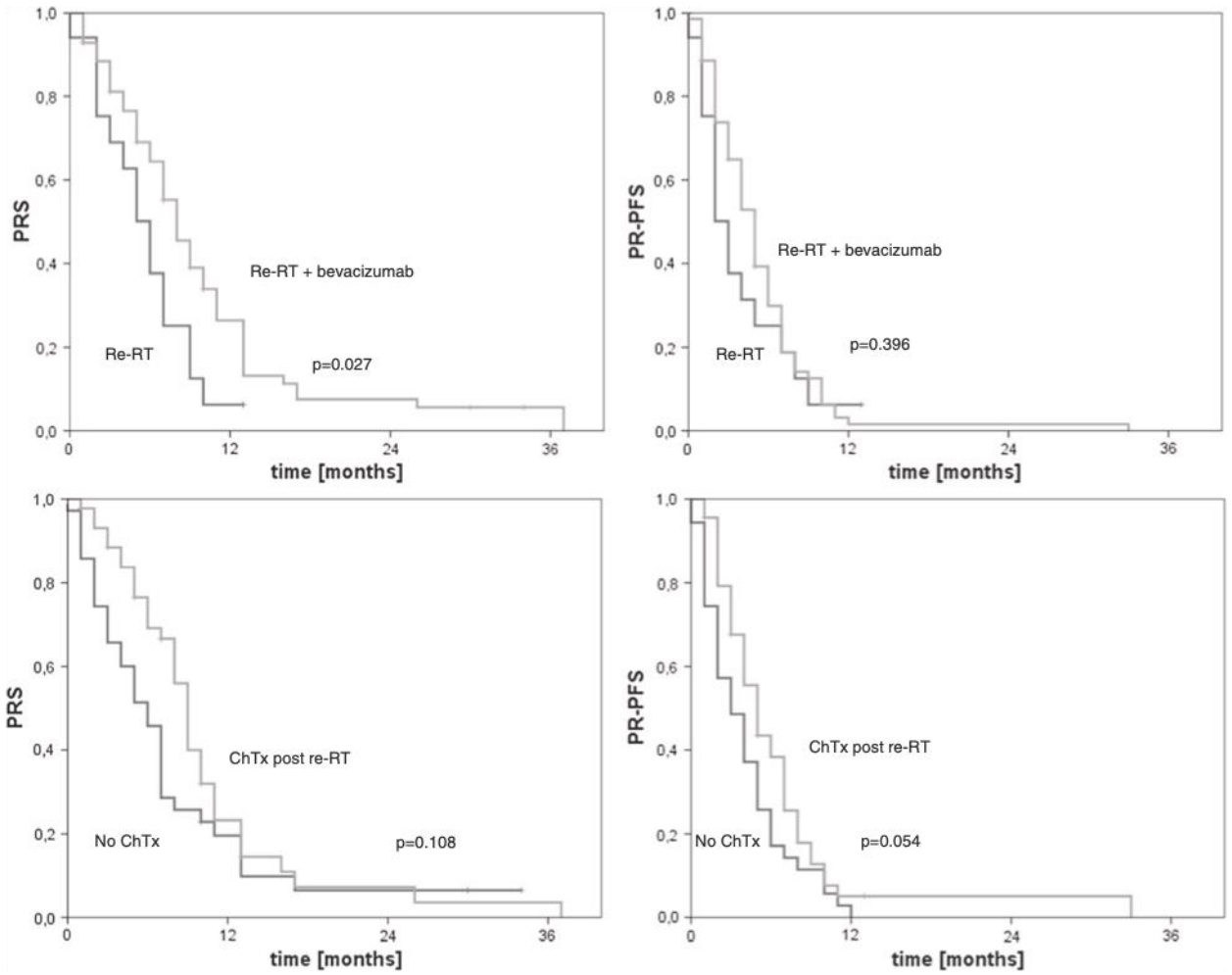

Figure 1 Kaplan-Meier curves for subgroups stratified by chemotherapy and application of concomitant bevacizumab, according to PRS and PR-PFS.

Table 2 Univariate analysis (log-rank test/Cox regression), influence on post-recurrence survival (PRS) and post-recurrence progression-free survival (PR-PFS)

Variable	Univariate p-value PRS/PR-PFS
Age (< 50 y, ≥ 50 y)	ns (p = 0.717)/ns (p = 0.854)
KPS (< 70, ≥ 70)	ns (p = 0.156)/ns (p = 0.095)
MGMT (meth/not meth)	ns (p = 0.897)/ns (p = 0.711)
Initial WHO grade (II/III/IV)	ns (p = 0.996)/ns (p = 0.922)
Bevacizumab (no/yes)	p = 0.027/ns (p = 0.396)
Adjuvant/Salvage chemotherapy (no/yes)	ns (p = 0.108)/ns (p = 0.054)
Sex (male/female)	ns (p = 0.410)/ns (p = 0.304)
Time interval (≤ 12 y, > 12 y)	ns (p = 0.672)/ns (p = 0.349)

N = 88, ns – not significant, meth – MGMT methylated.

"excellent" and "moderate" are missing. If the score values are considered, again no significant results can be observed.

Discussion

For certain subgroups of recurrent high-grade glioma patients re-irradiation may be a strategy to prolong

Table 3 Outcome data concerning PRS stratified by the Heidelberg score; subgroups with and without bevacizumab are shown

Heidelberg score/group	Entire cohort, PRS [months]	Bevacizumab, PRS [months]	No bevacizumab, PRS [months]
Excellent	7	7	–
Good	7	8	2
Moderate	9	9	–
Poor	7	8	6
P-value	ns (p = 0.664)	ns (p = 508)	ns (p = 0.316)

A "poor" score consists of patients with score values of 3 or 4.

survival with acceptable toxicity. The aim of this study was to analyze whether the score derived by the Heidelberg group [7] could be validated in our own mono-institutional patient cohort. We failed to validate the Heidelberg score in our mono-institutional patient cohort. Several reasons could be responsible for this finding.

One specific difference between both groups represents the application of bevacizumab in the majority of cases. In this regard, the outcome of our patient cohort compares nicely with data from other groups presented by Gutin and colleagues [17] or those of Hundsberger et al. [23]. Furthermore, the survival rate of the combined treatment is promising and PFS-6 compares favorably with data found in the literature mostly ranging from 30-50% [3,4,24]. The combined treatment approach was relatively well tolerated. Overall toxicity in our study was not higher than in the use of bevacizumab alone or in combination with other agents in patients with HGG [10,25].

As shown, the stratification by bevacizumab failed to detect subgroups where the score had prognostic meaning.

Another difference compared to the score derived by Combs et al. was the inclusion of larger tumors (up to 5 – 6 cm diameter) and multifocal disease but as shown before there was no prognostic value for larger tumors [26].

Our patient cohort seems to be very heterogeneous with a potential timing bias as some patients with initially low-grade tumors have been multimodally treated many years before re-irradiation – due to the introduction of bevacizumab and initial positive results this option became more frequently used so that results could be obtained for a more realistic patient cohort without selection bias. This explains why the historical group of patients who have only been re-irradiated is comparatively small.

Concerning heterogeneity, further aspects have to be mentioned - our cohort is substantially different to the initial cohort examined by the Heidelberg group concerning previous and maintenance therapies - namely the use of brachytherapy, re-surgery and certain chemotherapy combinations, which makes it even more difficult to derive a prognostic meaning from the time interval between both RT sessions.

Similarly to our findings, Scholtyssek and colleagues also failed to validate the Heidelberg score in their dataset [27]. Their cohort included 64 patients, no initial WHO grade II patients were present and the time interval between primary and re-irradiation had no significant impact on outcome.

Altogether, summarizing both these studies, even within the univariate analysis the factors included in the Heidelberg score were not (this work) or just in part (Scholtyssek et al.) statistically significant; therefore, the inability of validating the Heidelberg score is most likely due to the heterogeneity of the different treatment cohorts.

In conclusion, further studies and consortial data collections such as the Radplanbio database are needed to find prognostic markers in order to identify those patients who would profit most from re-irradiation and to allow for a final judgment of the Heidelberg score [28-30].

Consent

This retrospective study was exempt from requiring ethics approval. Bavarian state law (Bayrisches Krankenhausgesetz/ Bavarian Hospital Law §27 Absatz 4 Datenschutz (Data-protection)) allows the use of patient data for research, provided that any person's related data are kept anonymous. German radiation protection laws request a regular analysis of outcomes in the sense of quality control and assurance, thus in the case of purely retrospective studies no additional ethical approval is needed under German law.

Competing interests

The authors declare that conflicts of interest do not exist.

Authors' contributions

MN & SEC planned, coordinated and performed the study. MF collected and MN analyzed the data. MN, UG, SEC & CB prepared the manuscript. All authors read and approved the final manuscript.

Authors' information

All authors except SEC are members of the CCC Neuro-Oncology, University of Munich.

Author details

[1]Department of Radiation Oncology, University of Munich, Marchioninistr. 15, 81377 Munich, Germany. [2]Department of Radiation Oncology, University of Heidelberg, Im Neuenheimer Feld 672, 69120 Heidelberg, Germany. [3]Department of Radiation Oncology, Klinikum rechts der Isar der TU München, Ismaninger Str. 22, 81675 Munich, Germany.

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