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Prognosefaktoren beim Glioblastoma multiforme

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Abkürzungsverzeichnis

DFMO	Difluromethylornithin
EEG	Elektroenzephalogramm
EQD2	Equivalent Dose in 2 Gy Fractions (Äquivalenzdosis)
FSRT	Fractionated Stereotactic Radiation Therapy (fraktionierte stereotaktische Strahlentherapie)
GBM	Glioblastoma multiforme
GTR	Gross Total Resection (komplette Resektion)
HFSRT	Hypofractionated Stereotactic Radiation Therapy (hypofraktionierte stereotaktische Strahlentherapie)
HR	Hazard Ratio
KA	Krampfanfälle.
KPS	Karnofsky Performance Score (Karnofsky-Index)
MGMT	O6-Methylguanin-DNA-Methyl-Transferase
MIB1	Molecular Immunology Borstel 1
MMST	Mini-Mental-Status-Test
RPA	Recursive Partitioning Analysis
SRS	Stereotactic Radiosurgery (stereotaktische Radiochirurgie)
STR	Subtotal Resection (subtotale Resektion)
SURF-ROGG	Seizures During Radiotherapy for High-grade Gliomas
TMZ	Temozolomid
WHO	World Health Organization (Weltgesundheitsorganisation)
ZNS	Zentrales Nervensystem

I Einleitung

Das Glioblastoma multiforme (GBM) macht etwa 35 % der primären Hirntumore bei Erwachsenen aus und ist damit der häufigste primäre Tumor des zentralen Nervensystems (ZNS) in dieser Altersgruppe. Weltweit wird eine Gesamtinzidenz des GBM von etwa 3 pro 100.000 Einwohner angegeben. Die Klassifikation der Weltgesundheitsorganisation (WHO) umfasst vier Grade (°I bis °IV). Patient*innen mit Gliomen des °IV (GBM) haben die schlechteste Prognose mit einer 5-Jahres-Überlebenswahrscheinlichkeit von nur etwa 5 %.

Bessere Ergebnisse können mit einem trimodalen Therapieansatz erzielt werden. Seit der Veröffentlichung der randomisierten Studie von Stupp *et al.* im Jahr 2005 hat sich die Standardbehandlung des GBM geändert und beinhaltet eine maximal mögliche neurochirurgische Resektion gefolgt von einer gleichzeitigen Radiochemotherapie und Erhaltungschemotherapie. Das in der Stupp-Studie verwendete Dosis-Fraktions-Schema (EORTC 26981/22981-NCIC CE3) bestand aus 60 Gy in 30 Fraktionen (2,0 Gy pro Fraktion an fünf aufeinanderfolgenden Tagen pro Woche) in Kombination mit der Gabe von 75 mg/m^2 Temozolomid (TMZ) an sieben Tagen pro Woche. Auf die simultane Radio-Chemotherapie folgten sechs Zyklen TMZ als Monotherapie (150-200 mg/m² an fünf aufeinanderfolgenden Tagen alle vier Wochen). Dieses Schema führte zu einem medianen Überleben von 14,6 Monaten, welches 2,5 Monate länger war als die Resektion mit Strahlentherapie ohne TMZ.

Einige Patient*innen, insbesondere wenn sie älter oder in einem reduzierten Allgemeinzustand sind, können jedoch ein trimodales Therapiekonzept hinsichtlich der Belastung und dem Auftreten möglicher Nebenwirkungen nicht tolerieren; sie könnten von einem individualisierten Behandlungskonzept profitieren.

Im Jahr 2004 wurde in einer randomisierten Studie eine länger andauernde Strahlentherapie mit 60 Gy in 30 Fraktionen über sechs Wochen mit einem kürzeren Regime von 40 Gy in 15 Fraktionen mit je 2,66 Gy über drei Wochen bei älteren Patient*innen verglichen. Das mediane Überleben und das Überleben nach 6 Monaten nach Randomisierung waren in beiden Gruppen ähnlich. In diesem Fall wurde „älter" als ≥60 Jahre definiert. In den letzten Jahrzehnten ist das mediane Alter von Patient*innen mit einem GBM auf 64 Jahre gestiegen.

Somit könnte 40 Gy in 15 Fraktionen für viele Betroffene mit dieser aggressiven Erkrankung eine sinnvolle Option sein, insbesondere bei kurzer oder mittlerer Überlebensprognose. Kürzlich stellten Roa *et al.* eine weitere randomisierte Studie vor, die 40 Gy in 15 Fraktionen über drei Wochen mit einer sehr kurzen Strahlentherapie, von 25 Gy in 5 Fraktionen über eine Woche, bei Patient*innen in höherem Alter (≥65 Jahre) und/oder einem reduzierten Allgemeinzustand (Karnofsky Performance Score (KPS) 50-70 %) verglich. In dieser Studie waren 25 Gy in 5 Fraktionen dem Regime mit 40 Gy in 15 Fraktionen hinsichtlich des Gesamtüberlebens und des progressionsfreien Überlebens nicht unterlegen. Ausgewählte Patient*innen, insbesondere bei Vorliegen einer Methylierung der O6-Methylguanin-DNA-Methyl-Transferase (MGMT), können auch für eine systemische Behandlung mit TMZ als Monotherapie geeignet sein.

Diese Überlegungen zeigen, dass es wichtig ist, die Überlebensprognose der Betroffenen vor Beginn der Therapie abschätzen zu können. Patient*innen mit sehr schlechter Prognose können für eine sehr kurze Strahlentherapie, TMZ-Monotherapie oder Best Supportive Care in Betracht gezogen werden. Bei intermediärer Prognose erscheint eine Strahlentherapie mit 40 Gy in 15 Fraktionen geeignet, die mit TMZ kombiniert werden kann. Patient*innen mit einer günstigeren Prognose sollten das trimodale Therapiekonzept erhalten, welches zu einem verbesserten Überleben führen kann. Da bei günstiger Überlebensprognose auch behandlungsbedingte Spätfolgen von Bedeutung sind, kann eine Strahlentherapie mit 59,4 Gy mit Dosen pro Fraktion von 1,8 Gy gegenüber 60 Gy mit Dosen pro Fraktion von 2,0 Gy vorzuziehen sein. Das Risiko für strahlenbedingte Spätkomplikationen des normalen Gewebes des zentralen Nervensystems (ZNS) steigt sowohl mit der Gesamtdosis als auch mit der Dosis pro Fraktion.

Des Weiteren beträgt die mediane Zeit bis zur Progression des GBM nach trimodalem Therapiekonzept im Durchschnitt nur 6,9 Monate. Die Mehrzahl der GBM-Rezidive tritt in zuvor bestrahlten Hirnregionen auf (In-Field-Rezidive). In Folge des Rezidivs erhalten viele dieser Patient*innen eine erneute Strahlentherapie (Re-Bestrahlung). Die Prognose von Patient*innen, die wegen eines rezidivierenden GBM erneut bestrahlt werden, ist oft schlecht und die Behandlung ist palliativ. In einer systematischen Übersichtsarbeit und Meta-

Analyse lag die 1-Jahres-Überlebensrate nach Re-Bestrahlung bei nur 36 %. Auch hier würden die Betroffenen von einer individualisierten Behandlung profitieren.

GBM sind oft mit signifikanten Symptomen einschließlich Krampfanfällen verbunden. Die Mehrzahl der Gliom-bedingten Anfälle treten vor der Behandlung des Glioms auf. Die Prävalenz der vor der Behandlung auftretenden Anfälle zeigt in der Literatur eine extrem große Bandbreite von 9-87 %. Beim GBM wurden Häufigkeiten zwischen 9 % und 45 % und bei Gliomen niedrigen Grades (WHO °II) zwischen 30 % und 87 % berichtet. Frühere Studien legten nahe, dass Krampfanfälle, die vor der Initiierung einer Behandlung auftraten, mit einer besseren Überlebensprognose verbunden sind. Die Zahlen bezüglich der Prävalenz von Anfällen vor der Behandlung variieren jedoch in der Literatur und liegen zwischen 12 % und 35 %. Auch hier wäre es für die Therapieentscheidung hilfreich, Prognose- bzw. Risikofaktoren für das Auftreten von zerebralen Krampfanfällen zu kennen.

Wesentliche Ziele der Arbeiten im Rahmen dieser kumulativen Dissertation sind die Identifikation von Prognosefaktoren sowie die Entwicklung eines Prognose-Scores, um zur Personalisierung der Behandlung von Patient*innen mit malignen Gliomen beizutragen.

II Prognosefaktoren nach Strahlentherapie beim Glioblastoma multiforme

II.1 Prognosefaktoren für die lokale Kontrolle und das Überleben nach Strahlentherapie beim neu diagnostiziertem Glioblastoma multiforme (Publikation 1)

Die Standardbehandlung des GBM umfasst eine Resektion, eine mehrwöchige Strahlentherapie gefolgt von einer Chemotherapie. Für einige Patient*innen kann dieses multimodale Therapiekonzept hinsichtlich der Verträglichkeit und dem Ausmaß der Nebenwirkungen zu belastend sein. Genau diese Patient*innen können von einem individualisierten Therapiekonzept profitieren.

Diese Studie zielte darauf ab, zur Individualisierung der Therapie beizutragen, indem Prädiktoren für den Therapieerfolg nach einer mehrwöchigen Strahlentherapie identifiziert wurden. Bei 91 Patient*innen wurden die Anzahl, die Lokalisation, der maximale Läsionsdurchmesser, das Antigen Ki-67, die MGMT-Promoter-Methylierung, der KPS, die Symptome, das Geschlecht, das Alter sowie die Resektion hinsichtlich lokaler Kontrolle und Überleben ausgewertet.

Sowohl die lokale Kontrolle des GBM als auch das Überleben wurden ab dem ersten Tag der Strahlentherapie berechnet. Die für die univariaten Analysen der lokalen Kontrolle und des Überlebens verwendeten Methoden umfassten die Kaplan-Meier-Methode und den Log-Rank-Test. p-Werte von <0,05 wurden als signifikant und p-Werte von <0,06 als Hinweis auf einen Trend angesehen. Merkmale, die Signifikanz erreichten, wurden zusätzlich in einer multivariaten Analyse (Cox Proportional Hazards Model) ausgewertet. Die Patient*innen wurden bis zum Tod oder für mindestens 24 Monate nachbeobachtet.

In der univariaten Analyse war eine komplette Tumorresektion signifikant (p=0,029) mit einer besseren lokalen Kontrolle assoziiert. Dies wurde in der multivariaten Analyse bestätigt (Hazard Ratio (HR)=1,64; p=0,025). MGMT-Methylierung (p=0,004), KPS ≥80 % (p=0,022) sowie die Tumorresektion (p<0,001) waren in der univariaten Analyse signifikant mit einem verbesserten Überleben assoziiert (Tabelle I). Für das unifokale GBM (p=0,056) zeigte sich ein Trend. In der multivariaten Analyse waren die MGMT-Methylierung (HR=3,63; p=0,009), der KPS (HR=2,01; p=0,018) sowie das Ausmaß der Tumorresektion (HR=3,29; p<0,001) signifikant.

Tabelle I Überlebensraten 1 und 2 Jahre nach Beginn der Strahlentherapie (unvariate Analysen, n=91)

Faktor		**1 J. (%)**	**2 J. (%)**	**p-Werte**
Anzahl der GBM-Läsionen	Einzelne	70	57	0,056
	Mehrere	33	33	
Hauptlokalisation des GBM	Thalamus	20	20	0,061
	Temporal	76	64	
	Frontal	58	47	
	Parietal	30	20	
	Okzipital	50	50	
	Parieto-okzipital	71	71	
	Fronto-parietal	75	25	
	Temporo-frontal	100	100	
	Temporo-parietal	78	67	
	Andere	80	60	
Maximaler kumulativer Durchmesser der GBM-Läsionen	<40 mm	66	50	0,953
	≥40 mm	52	45	
Ki-67/MIB1 Index	<25 %	65	54	0,149
	≥25 %	52	42	
MGMT-Promoter-Methylierung	Nein	18	9	**0,004**
	Ja	72	61	
KPS	≤70	45	34	**0,022**
	≥80	73	61	
Anzahl der vorbestehenden Symptome	1	55	48	0,615
	≥2	67	51	
Geschlecht	Weiblich	58	47	0,490
	Männlich	68	57	
Alter zu Beginn der Bestrahlung	≤60 Jahre	70	61	0,162
	≥61 Jahre	57	45	
neurochirurgische Resektion	Nein	28	22	**<0,001**
	Ja	73	60	
Ausmaß der Resektion	GTR	81	71	0,077
	STR	69	56	

Hinweis: Hervorgehobene p-Werte waren signifikant.

II.2 Ein neuer Überlebensscore nach einer Strahlentherapie beim neu diagnostiziertem Glioblastoma multiforme (Publikation 2)

In einer früheren Studie, die die Strahlentherapie bei neu diagnostiziertem GBM untersuchte, wurden signifikante sowie tendenziell signifikante Assoziationen mit dem Überleben für den KPS, eine vorherige Resektion, die MGMT-Promotor-Methylierung und das unifokale GBM gefunden. Ziel dieser Studie war es, einen Überlebensscore auf Basis der gefundenen Faktoren zu erstellen.

Tabelle II Univariate Analysen der im Scoring-System enthaltenen Prognosefaktoren: Überlebensraten 6 und 12 Monate nach Beginn der Strahlentherapie beim GBM

Prognosefaktor		**6 Monate (%)**	**12 Monate (%)**	**p-Werte**
Anzahl der GBM-Läsionen	Mehrere (*n*=11)	64	9	**<0,001**
	Einzelne (*n*=70)	86	66	
KPS	≤70 % (*n*=36)	72	47	**0,039**
	≥80 % (*n*=45)	91	67	
Neurochirurgische Resektion	Nein (*n*=22)	55	18	**<0,001**
	Ja (*n*=59)	93	73	
MGMT-Promoter-Methylierung	Nein (*n*=38)	76	42	**0,026**
	Ja (*n*=43)	88	72	

Hinweis: Hervorgehobene p-Werte waren signifikant.

Die meisten der 81 Patient*innen erhielten eine vorherige Resektion des GBM gefolgt von einer Radiochemotherapie (59,4 Gy/33 Fraktionen oder 60 Gy/30 Fraktionen). Die zuvor identifizierten Prädiktoren für das Überleben wurden anschließend erneut ausgewertet. Faktoren, die signifikant mit dem Überleben assoziiert waren, wurden anschließend zur Erstellung des Scores einbezogen.

Die Überlebenszeit wurde ab dem ersten Tag der Strahlentherapie berechnet. Univariate Analysen erfolgten mit der Kaplan-Meier-Methode. Unterschiede zwischen den Kaplan-Meier-Kurven wurden mit dem Wilcoxon-Test berechnet. Faktoren, die signifikant ($p<0,05$) mit dem Überleben assoziiert waren, wurden in das Scoring-System aufgenommen. Es zeigte sich, dass alle Faktoren signifikant mit dem Überleben assoziiert waren (Tabelle II). Für jeden Faktor wurden

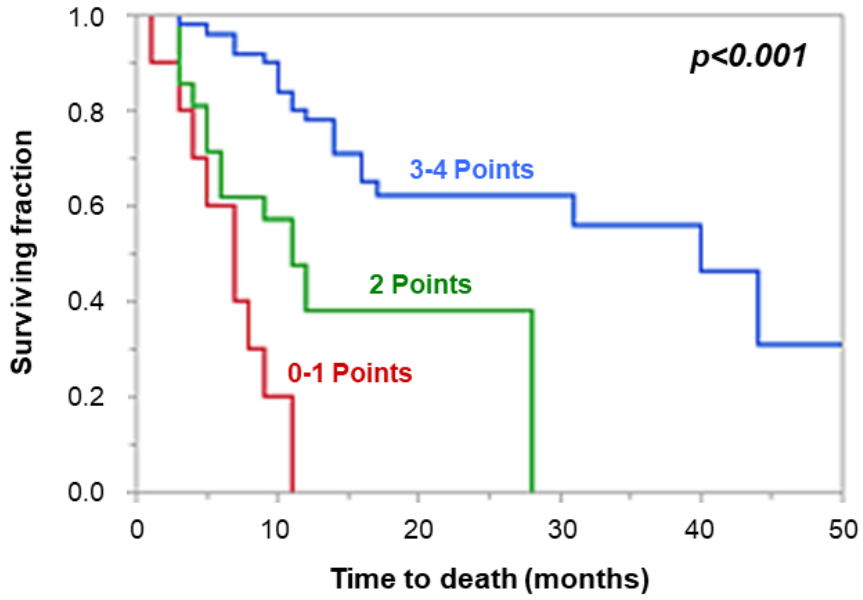
0 Punkte (schlechteres Überleben) oder 1 Punkt (besseres Überleben) vergeben (Tabelle III). Die so entstandenen Werte wurden addiert.

Tabelle III Prognosefaktoren für das Überleben und entsprechende Scoring-Punkte

Prognosefaktor		**Punktevergabe**
Anzahl der GBM-Läsionen	Mehrere	0
	Einzelne	1
KPS	≤70 %	0
	≥80 %	1
Neurochirurgische Resektion	Nein	0
	Ja	1
MGMT-Promoter-Methylierung	Nein	0
	Ja	1

Es wurden drei Gruppen gebildet. 0-1 Punkt (n=10), 2 Punkte (n=21) und 3-4 Punkte (n=50). Die 12-Monats-Überlebensraten waren 0 %, 38 % bzw. 78 % (Abbildung I, p<0,001).

Abbildung I. Kaplan-Meier-Kurven für die drei prognostischen Gruppen: Das Überleben nach Strahlentherapie (aus Publikation 2)



Der neue Überlebensscore kann zur Individualisierung der Behandlung von Patient*innen mit einem GBM, die eine Strahlentherapie erhalten sollen, beitragen.

II.3 Prognosefaktoren für das Überleben nach Re-Bestrahlung bei rezidiviertem Glioblastoma multiforme (Publikation 3)

Patient*innen, die bei einem rezidivierten GBM eine erneute Bestrahlung benötigen, können von einer individualisierten Therapie profitieren. Ziel dieser Studie war es, Prädiktoren für das Überleben zu identifizieren und so zur Individualisierung der Behandlung beizutragen.

Bei 28 Patient*innen mit rezidiviertem GBM wurden neun Faktoren auf Assoziation mit dem Überleben analysiert: Hauptlokalisation und Art des Rezidivs, KPS, Alter, Geschlecht, Intervall zwischen primärer Strahlentherapie und dem Rezidiv, Ausmaß der Resektion, Äquivalenzdosis (EQD2) der Re-Bestrahlung und kumulative EQD2 von primärer Bestrahlung plus Re-Bestrahlung.

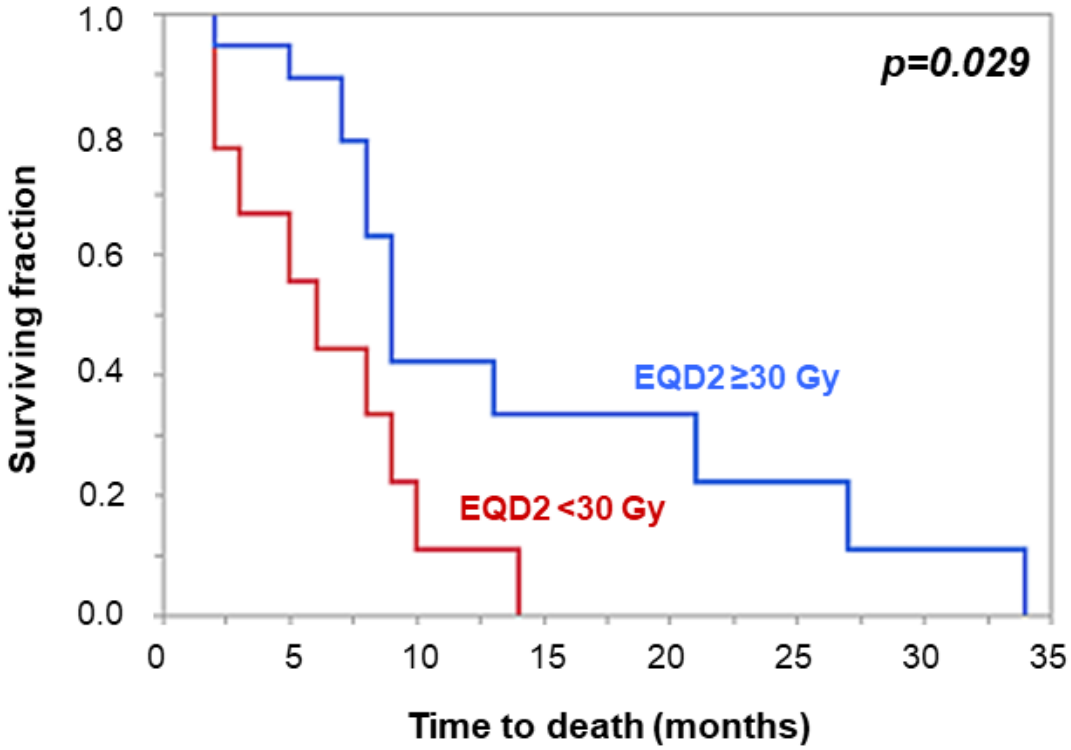
Das Überleben wurde ab dem ersten Tag der Re-Bestrahlung berechnet. Univariate Analysen wurden mit der Kaplan-Meier-Methode und dem Wilcoxon-Test durchgeführt. p-Werte <0,05 wurden als signifikant angesehen, p-Werte <0,12 als Hinweis auf einen Trend. Diese Faktoren wurden anschließend in eine multivariate Analyse (Cox-Regression) eingeschlossen.

In den univariaten Analysen waren eine vollständige Resektion (GTR, p=0,047), eine EQD2 ≥30 Gy (Abbildung II, p=0,029) und eine kumulative EQD2 ≥90 Gy (p=0,023) signifikant mit einem besseren Überleben assoziiert. Eine frontale Lage (p=0,119) sowie ein KPS von 80-100% (p=0,067) zeigten einen Trend.

In der multivariaten Analyse waren eine frontale Lage (p=0,032) sowie eine kumulative EQD2 von ≥90 Gy (p=0,038) signifikant. Ein KPS zwischen 80-100 % (p=0,110) sowie eine EQD2 von ≥30 Gy (p=0,083) zeigten einen Trend.

Zusammenfassend wurden Prädiktoren für das Überleben nach Re-Bestrahlung bei rezidivierendem GBM identifiziert, die bei dem Design individualisierter Behandlungen und zukünftiger klinischer Studien hilfreich sein können. Die Verwendung einer EQD2 der Re-Bestrahlung ≥30 Gy und einer kumulativen EQD2 von Primär- und Re-Bestrahlung von ≥90 Gy schienen niedrigeren Dosen überlegen zu sein und sollten somit angestrebt werden.

Abbildung II Kaplan-Meier-Kurven für das Überleben, Vergleich der Äquivalenzdosen (EQD2) der Re-Bestrahlung (aus Publikation 3)



III Krampfanfälle vor der Strahlentherapie von Gliomen

III.1 Prävalenz und Risikofaktoren (Publikation 4)

Krampfanfälle stellen häufig eine Manifestation von Gliomen dar. Diese Studie evaluiert die Prävalenz von Krampfanfällen vor der Strahlentherapie sowie potentielle Risikofaktoren und eine mögliche Assoziation zwischen dem Auftreten von Krampfanfällen und dem Überleben.

Acht Faktoren wurden bei 222 Patient*innen hinsichtlich möglicher Assoziation mit dem Auftreten von Krampfanfällen analysiert: Anzahl, Größe und Lokalisation der Gliome, Grading (WHO-Klassifikation), Allgemeinzustand (KPS), Geschlecht, Alter sowie vorherige Resektion. Diese Faktoren sowie zusätzlich die Symptome vor der Strahlentherapie und das Auftreten von Krampfanfällen wurden ebenfalls hinsichtlich einer möglichen Assoziation mit dem Überleben untersucht.

Für die statistischen Analysen in Bezug auf die Korrelationen mit dem Auftreten von Anfällen vor der Strahlentherapie verwendeten wir den Chi-Quadrat-Test. p-Werte von <0,05 wurden als signifikant betrachtet und p-Werte von <0,13 als Hinweis auf einen Trend. Die univariaten Analysen für das Überleben wurden mit der Kaplan-Meier-Methode und dem Wilcoxon-Test durchgeführt. Wiederum wurden p-Werte von <0,13 als Hinweis auf einen Trend angesehen. Signifikante ($p<0,05$) Faktoren wurden in eine multivariate Analyse (Cox-Proportional-Hazard-Model) einbezogen (p-Werte <0,05 wurden als signifikant angesehen).

Die Prävalenz der prä-radiotherapeutischen Krampfanfälle betrug 29,3 %; eine signifikante Korrelation wurde für °II Astrozytome ($p=0,002$) gefunden. Trends zeigten sich beim Alter von ≤59 Jahren ($p=0,123$) und bei nicht erfolgter Resektion ($p=0,113$). Darüber hinaus zeigte sich ein Trend für eine Assoziation zwischen dem Auftreten von Krampfanfällen und dem Überleben in der univariaten Analyse ($p=0,075$). In der multivariaten Analyse waren °II Astrozytome ($p=0,002$) und eine erfolgte Resektion ($p=0,004$) signifikant mit einem besseren Überleben assoziiert; für unifokale Gliome zeigte sich ein Trend ($p=0,062$) (Tabelle IV).

Tabelle IV Multivariate Analyse für Risikofaktoren für das Auftreten von Krampfanfällen vor Strahlentherapie (Cox-Proportional-Hazard-Model)

Faktor	Hazard Ratio	95 %-Konfidenzintervall	p-Werte
Anzahl der Läsionen	1.95	0.97–3.72	0,062
WHO-Einstufung	1.96	1.26–3.30	**0,002**
vorherige Resektion	2.54	1.36–4.57	**0,004**

Hinweis: Hervorgehobene p-Werte waren signifikant.

III.2 Re-Evaluation von Prognosefaktoren inklusive prätherapeutischer Krampfanfälle für das Überleben nach Strahlentherapie von Gliomen: Eine ergänzende Analyse (Publikation 5)

In der vorherigen Studie wurden Prädiktoren für das Überleben nach einer Bestrahlung von zerebralen Gliomen des °II bis °IV identifiziert. In dieser ergänzenden Analyse wurde das Überleben nun auf eine geeignetere Weise als in der ursprünglichen Studie berechnet.

Zehn Faktoren wurden hinsichtlich des Überlebens bei den Patient*innen aus der Initialstudie neu bewertet, einschließlich der Krampfanfälle vor Strahlentherapie. In der ursprünglichen Studie wurde das Überleben ab dem Ende der letzten Strahlentherapie, also der letzten verabreichten Fraktion (sowohl der Primär- als auch der Re-Bestrahlung) berechnet. Nach erneuter Überprüfung wurde dieser Ansatz als unangemessen erachtet. Das Überleben hätte immer bei allen Patient*innen ab der letzten Fraktion des ersten Kurses der Bestrahlung berechnet werden sollen, wie in dieser ergänzenden Analyse geschehen.

In der multivariaten Analyse waren WHO-°II Tumore (p=0,006) sowie die vorherige Resektion (p=0,001) mit einem besseren Überleben assoziiert. In den univariaten Analysen zeigte sich unter anderem ein Trend für eine positive Assoziation zwischen dem Überleben und dem Auftreten von Krampfanfällen vor Beginn der Strahlentherapie (p=0,060) (Tabelle V).

Die Ergebnisse dieser ergänzenden Analyse hinsichtlich der Identifikation von prognostischen Faktoren für das Überleben stimmten somit mit den Ergebnissen der initialen Studie überein.

Tabelle V Univariate Analysen für das Überleben nach Ende der initialen Bestrahlungsserie

Faktor		**1 Jahr (%)**	**2 Jahre (%)**	**3 Jahre (%)**	**p-Werte**
Symptome vor der Strahlentherapie	Keine (n=12)	82	72	72	0,30
	Nur KA (n=21)	90	84	70	
	KA+Andere (n=44)	95	68	57	
	Nur Andere (n=145)	79	69	62	
Krampfanfälle vor Strahlentherapie	Nein (n=157)	79	70	64	0,060
	Ja (n=65)	93	74	61	
Anzahl der Läsionen	Unifokal (n=179)	85	74	66	**0,010**
	Multifokal (n=32)	71	52	37	
Hauptort des Glioms	Frontal (n=62)	81	65	52	0,11
	Parietal (n=38)	88	80	80	
	Temporal (n=91)	87	77	69	
	Andere (n=31)	74	56	50	
Kumulative Größe des Glioms	<40 mm (n=90)	83	68	59	0,77
	≥40 mm (n=80)	83	73	63	
WHO-Grad	°II (n=18)	100	94	94	**0,035**
	°III (n=41)	93	76	58	
	°IV (n=163)	79	66	61	
KPS	≤70 % (n=65)	83	64	59	0,28
	≥80 % (n=136)	85	73	64	
Geschlecht	Weiblich (n=92)	82	69	63	0,54
	Männlich (n=136)	84	72	62	
Alter	≤59 Jahre (n=119)	88	77	68	0,057
	≥60 Jahre (n=103)	78	62	54	
vorherige Resektion	Nein (n=44)	65	49	41	**<0,001**
	Ja (n=178)	88	75	67	

Hinweise: Wenn die Zahl der Patient*innen für einen Faktor kleiner als 222 ist, lagen für die fehlenden Patient*innen keine Daten zu diesem Faktor vor. Hervorgehobene p-Werte waren signifikant.

III.3 SURF-ROGG – Eine prospektive Studie zur Bewertung der Anfallsaktivität während einer Strahlentherapie bei hochgradigen Gliomen (Publikation 6)

Aufgrund einer akuten Entzündungsreaktion, die mit einem Ödem im bestrahlten Hirnareal und einer möglichen Erhöhung des intrakraniellen Drucks einhergeht, kann es im Verlauf einer Strahlentherapieserie zum Auftreten oder Progress von klinischen Symptomen wie z.B. Krampfanfällen kommen. Bislang gibt es keine Studien, die sich mit der subakuten Wirkung der Strahlentherapie auf die Anfallsaktivität während einer Behandlung von Gliomen befasst haben. Diese Daten wären wichtig, um Überwachung und antiepileptische Behandlung der Betroffenen zu verbessern. Diese einarmige prospektive Studie untersucht die Anfallsaktivität während der Strahlentherapie von hochgradigen Gliomen.

Eine Progression der Anfallsaktivität im Verlauf der Strahlentherapie im Vergleich zum Ausgangswert ist definiert als Zunahme der Anfallshäufigkeit um mehr als 50 %, Zunahme des Schweregrads der Anfälle (d.h. Zunahme der generalisierten Anfälle um mehr als 50 %), Erhöhung der Dosis der antikonvulsiven Medikation um mindestens 25 % oder Beginn einer antikonvulsiven Medikation. Diese Parameter werden anhand eines Anfallstagebuchs, das von den Patient*innen während des Verlaufs der Strahlentherapie geführt wird, beurteilt. Zusätzlich werden die Anfallshäufigkeit bis zu 6 Wochen nach der Strahlentherapie (Fortführung des Anfallstagebuchs), die Zufriedenheit der Patient*innen mit dem Anfallstagebuch und das Auftreten von epilepsietypischen Potentialen im Elektroenzephalogramm (EEG) ausgewertet.

IV Diskussion

IV.1 Prognosefaktoren bei der Strahlentherapie von malignen Gliomen (Publikationen 1-3)

Ein besseres Überleben war in unserer Studie unabhängig mit einem niedrigeren WHO-Grad und einer vorangehenden Resektion assoziiert. Das unifokale Gliom zeigte einen Trend in der multivariaten Analyse und das Alter von ≤59 Jahre einen Trend in der univariaten Analyse. Diese vier Faktoren haben sich bereits früher als signifikant mit günstigeren Überlebensprognosen assoziiert erwiesen.

In der ergänzend durchgeführten Studie wurde das Überleben ab dem Ende der ersten Strahlentherapie einheitlich festgelegt. Wie in der Initialstudie erwiesen sich WHO °II und die vorangegangene Resektion als unabhängige Prädiktoren für ein besseres Überleben. Für das Auftreten von Krampfanfällen vor der Strahlentherapie und das Alter von ≤59 Jahren zeigten sich in der univariaten Analyse entsprechende Trends, welches mit unserer initialen Studie übereinstimmte. In der univariaten Analyse war das unifokale Gliom in der Initialstudie und auch in der Re-Evaluationsstudie signifikant mit einem besseren Überleben assoziiert. Das unifokale Gliom zeigte in der multivariaten Analyse der Initialstudie einen Trend für ein besseres Überleben (p=0,062), der in der ergänzenden Studie nicht beobachtet wurde (p=0,11).

Die schlechte Prognose von Patient*innen mit einem GBM ist vor allem auch die Folge von intrazerebralen Rezidiven. Wenn ein Rezidiv auftritt, erhalten viele Patient*innen eine erneute Bestrahlung. Für diese Situation muss die optimale Dosis der Re-Bestrahlung weiter geklärt werden. Da für die Re-Bestrahlung verschiedene Dosis-Fraktionierungs-Schemata verwendet werden, werden die Dosen oft als EQD2 angegeben, um die Vergleichbarkeit der verschiedenen Schemata zu gewährleisten. Die EQD2 berücksichtigt sowohl die Gesamtdosis als auch die Dosis pro Fraktion und basiert auf dem linear-quadratischen Modell. Das alpha/beta-Verhältnis stellt die Dosis dar, bei der die Zellvernichtung durch die lineare und die quadratische Komponente gleich ist. Als alpha/beta-Verhältnis für die Zellvernichtung von Tumorzellen wird bei der überwiegenden Mehrheit der malignen Tumore ein Wert von 10 Gy verwendet.

In einer früheren Meta-Analyse wurde kein signifikanter Unterschied hinsichtlich der Ergebnisse nach erneuter Bestrahlung (externe Strahlentherapie) bei einem rezidivierten GBM zwischen EQD2 <36 Gy und ≥36 Gy gefunden. Die Autoren wiesen jedoch darauf hin, dass in mehreren Studien, die in ihre Meta-Analyse eingeschlossen wurden, viele verschiedene Dosis-Fraktions-Schemata verabreicht wurden und die Verwendung der medianen EQD2 möglicherweise nicht die optimale Methode zur Definition einer Dosis-Wirkungs-Beziehung ist. Eine Dosis-Wirkungs-Beziehung wurde in einer retrospektiven Studie bei 20 Patient*innen mit malignen Gliomen (19 mit GBM) gefunden, die eine hypo-fraktionierte stereotaktische Strahlentherapie (HFSRT) bei persistierender oder rezidivierender Erkrankung erhielten. Die Ansprechraten betrugen 0 % nach 24 Gy in 8 Fraktionen (EQD2=26,0 Gy) und 79 % nach 30 Gy bzw. 35 Gy in 10 Fraktionen (EQD2=32,5 Gy bzw. 39,4 Gy). In einer weiteren retrospektiven Studie mit 19 Patient*innen (14 mit GBM, 5 mit anaplastischem Astrozytom), die bei rezidivierender Erkrankung mit HFSRT behandelt wurden, führten absolute Gesamtdosen (nicht EQD2) von ≥30 Gy zu einem grenzwertig signifikant besseren medianen Überleben als Dosen <30 Gy (11,1 vs. 7,4 Monate, p=0,051). Da die Befunde bezüglich der optimalen Dosis der Re-Bestrahlung widersprüchlich sind, würden weitere Studien helfen, die optimale Dosis bei einem rezidivierten GBM besser zu definieren. Außerdem sollten weitere Cut-off-Dosen der EQD2 untersucht werden.

In der vorliegenden Studie wurden EQD2-Dosen von <30 Gy mit ≥30 Gy verglichen. In der univariaten Analyse waren Dosen ≥30 Gy signifikant besser als <30 Gy, welches zu absoluten Unterschieden von 45 % (89 % vs. 44 %) nach 6 Monaten und 31 % (42 % vs. 11 %) nach 12 Monaten führte. In der multivariaten Analyse zeigten die Ergebnisse einen Trend. Darüber hinaus war die kumulative EQD2 der Strahlentherapie des primären GBM und der Re-Bestrahlung des rezidivierten GBM sowohl in der univariaten als auch in der multivariaten Analyse signifikant mit dem Überleben assoziiert. Dosen ≥90 Gy waren signifikant besser als <90 Gy.

Neben der geeigneten Dosis der Re-Bestrahlung zeigten auch andere Faktoren vor der Bestrahlung eine signifikante Assoziation mit dem Überleben oder zumindest einen Trend. Die frontale Lokalisation des rezidivierten GBM war in der

multivariaten Analyse signifikant mit einem besseren Überleben assoziiert. Ein hoher KPS (80-100 %) zeigte einen Trend sowohl in der univariaten als auch in der multivariaten Analyse. Die GTR war in der univariaten Analyse signifikant mit einem besseren Überleben verbunden. Diese prognostischen Faktoren können eine individualisierte Behandlung von Patient*innen mit einem rezidivierten GBM erleichtern. Patient*innen mit einem oder mehreren günstigen Faktoren können von einer normo-fraktionierten Strahlentherapie mit höherer Gesamtdosis profitieren, die mit einer systemischen Behandlung kombiniert werden kann. Bei Patient*innen ohne günstige prognostische Faktoren ist eine alleinige Kurzzeit-Strahlentherapie z. B. mit 5×5 Gy über 1 Woche zu erwägen.

Bei der Betrachtung dieser Vorschläge sollten die Limitationen der Studie berücksichtigt werden. Dazu gehören die begrenzte Fallzahl und das retrospektive Design mit dem Risiko eines Selektionsbias. Die 6- und 12-Monats-Überlebensraten dieser Studie (75 % und 32 %) waren ähnlich wie die der Meta-Analyse von Kazmi *et al.* (73 % und 36 %). Dies zeigt eine gewisse Konsistenz der Daten unserer Studie. Hinzu kommt, dass die drei von uns identifizierten Prognosefaktoren auch in anderen Studien gefunden wurden. Carson *et al.* präsentierten Daten von 333 Patient*innen mit einem rezidivierten Gliom und fanden ein besseres Überleben bei einem KPS von ≥80 % sowie bei Tumoren, die auf den Frontallappen beschränkt waren. Ähnliche Ergebnisse wurden in einer gepoolten Analyse von 300 Patient*innen mit rezidiviertem GBM aus acht Phase-I- oder -II-Studien berichtet. Auch der Stellenwert der Re-Resektion wurde in mehreren Studien gezeigt. In der retrospektiven Studie von Skeie *et al.* betrugen die medianen Überlebenszeiten 9 Monate nach alleiniger Gamma Knife Radiochirurgie (N=32) und 15 Monate nach Gamma Knife Radiochirurgie plus Re-Resektion (N=19). In der retrospektiven Studie von Kim *et al.*, war die Resektion, wenn sie mit stereotaktischer Radiochirurgie oder HFSRT kombiniert wurde, mit einem signifikant verbesserten Überleben assoziiert (p=0,010). Das Ausmaß der Resektion zeigte einen Trend zur positiven Assoziation mit dem Überleben (p=0,071).

In den letzten fast 30 Jahren wurden Überlebens-Scores für Patient*innen, die aufgrund eines GBM bestrahlt wurden, entwickelt. 1993 präsentierten Curran *et al.* eine „Recursive Partitioning Analysis“ (RPA) basierend auf den Daten dreier

Studien mit sechs RPA-Klassen und 12 Untergruppen. Die medianen Überlebenszeiten lagen zwischen 4,3 und 58,6 Monaten. Die Kohorte, die zur Entwicklung dieser Klassifikation verwendet wurde, beinhaltete jedoch unterschiedliche WHO-Grade und berücksichtigte nicht die MGMT-Promotor-Methylierung, die erst mehr als 10 Jahre später als wichtiger Prädiktor für das Überleben entdeckt wurde.

Im Jahr 2004 stellten Lamborn *et al.* eine RPA-Klassifikation speziell für Patient*innen mit GBM vor. Basierend auf Alter, KPS, Ausmaß der Resektion und Lokalisation des GBM bildeten sie vier Risikogruppen. Die medianen Überlebenszeiten dieser Gruppen betrugen 132, 71, 63 bzw. 37 Wochen. Im Gegensatz zur Studie von Curran *et al.* konzentrierte sich die Klassifikation von Lamborn *et al.* speziell auf Patient*innen mit GBM, berücksichtigte aber ebenfalls nicht die MGMT-Promotor-Methylierung.

Nach der Veröffentlichung der Stupp-Studie im Jahr 2005 wurde die Kombination der Strahlentherapie mit TMZ der neue Standard für die Behandlung des GBM. 2006 präsentierten Mirimanoff *et al.* eine Studie, die die RPA-Klassifikation von 1993 in der Kohorte der Stupp-Studie untersuchte und signifikant unterschiedliche Ergebnisse zwischen den RPA-Klassen III, IV und V mit medianen Überlebenszeiten von 17, 15 bzw. 10 Monaten fand. Allerdings wurde auch hier die prognostische Rolle der MGMT-Promotor-Methylierung nicht berücksichtigt. Im Jahr 2008 entwickelten die Autoren der Stupp-Studie anhand der Daten ihrer Studie drei Nomogramme zur Abschätzung der 2-Jahres-Überlebenswahrscheinlichkeit. Obwohl diese Nomogramme prinzipiell bei der Auswahl eines individuellen Behandlungsregimes unterstützen können, erscheinen sie aufgrund ihrer Komplexität für die klinische Routine nur bedingt geeignet. Hinzu kommt, dass die Nomogramme an ausgewählten Patient*innen entwickelt wurden, die die Kriterien für den Einschluss in eine randomisierte Studie erfüllen mussten. Auch wird der MMST-Score in der täglichen Routine bzw. außerhalb klinischer Studien in der Regel nicht erhoben. Der in der vorliegenden Studie entwickelte, einfacher zu handhabende Überlebensscore könnte eine sinnvolle Ergänzung zu den drei bisherigen Nomogrammen sein.

Im Jahr 2012 wurde eine zusätzliche RPA-Klassifikation vorgestellt, die sich auf ältere Patient*innen (≥70 Jahre) mit GBM beschränkte. Die medianen

Überlebenszeiten in den vier RPA-Klassen betrugen 9,3; 6,4; 4,6 bzw. 2,3 Monate. Allerdings wurden Patient*innen, die jünger als 70 Jahre alt waren, und der Status der MGMT-Promotor-Methylierung nicht berücksichtigt. Der jüngste Überlebensscore (Straube *et al.*) für Patient*innen, die wegen eines GBM bestrahlt wurden, war ebenfalls auf ältere Patient*innen (≥65 Jahre) beschränkt. Der Score beinhaltete zwei prognostische Gruppen mit medianen Überlebenszeiten von 2,7 bzw. 7,8 Monaten. Im Gegensatz zu früheren Scores berücksichtigte der Score von Straube *et al.* die MGMT-Promoter-Methylierung, ließ aber Patient*innen unter 65 Jahren unberücksichtigt.

Somit erscheint ein zusätzlicher Überlebensscore sinnvoll, der die MGMT-Promoter-Methylierung berücksichtigt und für Patient*innen jeden Alters in der täglichen Routine verwendet werden kann. Unser neuer Überlebens-Score basierte auf vier prognostischen Faktoren, die in einer früheren Studie von Patient*innen, die eine Strahlentherapie bei einem GBM erhielten, identifiziert wurden. Diese Faktoren waren Anzahl der GBM-Läsionen, KPS, Ausmaß der neurochirurgischen Resektion und MGMT-Promotor-Methylierung. Das mediane Überleben in der vorliegenden Kohorte (16 Monate) war vergleichbar mit der TMZ-Gruppe in der Stupp-Studie (14,6 Monate) und mit Patient*innen einer „gematchten“ (Propensity-Score-Matching) Studie (15 Monate).

Unser neuer Überlebens-Score beinhaltete drei Gruppen, 0-1, 2 bzw. 3-4 Punkte. Die Patient*innen der 0-1-Punkte-Gruppe hatten die schlechteste Prognose. Die mediane Überlebenszeit betrug nur 7 Monate und kein Patient überlebte länger als 10 Monate. Daher sollten diese Patient*innen für eine Behandlung mit einer sehr kurzen Strahlentherapie in Betracht gezogen werden, z.B. mit 25 Gy in fünf Fraktionen über eine Woche. Die Patient*innen der 2-Punkte-Gruppe mit einem medianen Überleben von 11 Monaten und einer 12-Monats-Überlebensrate von 38 % stellten die intermediäre Prognosegruppe dar. Da weniger als die Hälfte dieser Patient*innen 12 Monate oder länger überlebten, könnte für diese eine Kurzzeit-Strahlentherapie mit 40 Gy in 15 Fraktionen über drei Wochen in Betracht gezogen werden. Die Kurzzeit-Strahlentherapie sollte, wenn sinnvoll, durch TMZ ergänzt werden. In einer randomisierten Studie führte die zusätzliche Gabe von TMZ zur Strahlentherapie bei älteren Patient*innen (≥65 Jahre) mit einem GBM zu einem signifikant längeren Überleben als die alleinige Kurzzeit-Strahlentherapie.

Die Patient*innen der 3-4-Punkte-Gruppe hatten die günstigste Prognose mit einer medianen Überlebenszeit von 40 Monaten und einer 12-Monats-Überlebensrate von 78 %. Diese Patient*innen profitieren wahrscheinlich von einer multimodalen Behandlung einschließlich Resektion, normo-fraktionierter Strahlentherapie und TMZ. Die Strahlentherapie kann in diesen Fällen mit 60 Gy in 30 Fraktionen oder 59,4 Gy in 33 Fraktionen erfolgen. Es wird erwartet, dass das letztere Schema zu weniger Spätfolgen führt, da die EQD2 für Spätkomplikationen im ZNS-Gewebe 56,4 Gy beträgt und damit niedriger ist als bei 60 Gy in 30 Fraktionen (EQD2 60,0 Gy). Bei der Interpretation der Ergebnisse dieser Studie müssen wiederum die Limitationen berücksichtigt werden, zu denen unter anderem das retrospektive Studiendesign und die vergleichsweise geringe Fallzahl gehören.

Aus Sicht des Radioonkologen ist eine wichtige Frage die nach dem optimalen Dosis-Fraktions-Schema. Bereits 1979 zeigte eine gepoolte Analyse von Patient*innen mit malignen Gliomen eine Dosis-Wirkungs-Beziehung. Patient*innen, die 60 Gy erhielten, hatten ein signifikant längeres medianes Überleben (42 Wochen) als Patient*innen, die 55 Gy (36 Wochen), 50 Gy (28 Wochen) oder ≤45 Gy (13,5 Wochen) erhielten. Außerdem zeigte eine randomisierte Studie, dass 60 Gy in 30 Fraktionen über 6 Wochen signifikant besser war als 45 Gy in 20 Fraktionen über 4 Wochen (p=0,007). Im Jahr 2001 wurden in einer Phase-III-Studie vier Behandlungsschemata für neu diagnostizierte GBM verglichen. Diese beinhalteten eine akzeleriert-hyperfraktionierte Strahlentherapie (70,4 Gy, 2 x 1,6 Gy/Tag) mit oder ohne Radiosensitizer (Difluromethylornithin=DFMO) und eine normo-fraktionierte Strahlentherapie (59,4 Gy, 1 x 1,8 Gy/Tag) mit oder ohne DFMO. Sowohl die akzeleriert-hyperfraktionierte Strahlentherapie als auch die Zugabe von DFMO führten nicht zu einer Verbesserung des Gesamtüberlebens und des progressionsfreien Überlebens. Somit können Gesamtdosen von 59,4 Gy und 60,0 Gy als optimal für die Behandlung des GBM angesehen werden.

Es wurde jedoch erkannt, dass ältere Patient*innen mit einem schlechten KPS eine ungünstigere Überlebensprognose haben. Außerdem sind diese möglicherweise nicht in einem gesundheitlichen Zustand, der eine intensive trimodale Behandlung zulässt. Im Jahr 2004 wurde in einer randomisierten Studie mit 100 Patient*innen mit GBM im Alter von ≥60 Jahren eine kürzere (40 Gy in

15 Fraktionen über 3 Wochen) mit einer längeren Strahlentherapie (60 Gy in 30 Fraktionen über 6 Wochen) hinsichtlich des Überlebens verglichen. Das mediane Überleben sowie die Überlebensraten nach 6 Monaten waren ähnlich (p=0,57) und die kürzere Strahlentherapie wurde als sinnvolle Option für GBM-Patient*innen ≥60 Jahre angesehen. Eine kürzere Strahlentherapie kann auch bei eingeschränkter Überlebensprognose sinnvoll sein, um zu vermeiden, dass die Betroffenen einen größeren Teil ihrer verbleibenden Lebenszeit mit der Behandlung des GBM verbringen müssen als zwingend erforderlich.

In der vorliegenden Studie wurden die Daten von 91 Patient*innen, die wegen eines GBM bestrahlt wurden, analysiert, um Prognosefaktoren für die lokale Kontrolle und das Überleben zu identifizieren. Eine verbesserte lokale Kontrolle war signifikant mit einer GTR assoziiert. Daher sollte eine GTR angestrebt werden, wann immer dies unter Berücksichtigung der potentiellen Schädigung wichtiger Hirnstrukturen sowie des KPS und Begleiterkrankungen der Patient*innen möglich ist. Ein schlechteres Überleben war sowohl in der univariaten als auch in der multivariaten Analyse signifikant mit dem Fehlen einer MGMT-Promotor-Methylierung, einem schlechteren KPS (≤70) und nicht erfolgter vorangehender Resektion assoziiert. Zusätzlich zeigte das multifokale GBM in der univariaten Analyse einen Trend für ein schlechteres Überleben. Unter Berücksichtigung der randomisierten Studie von Roa *et al.* können Patient*innen mit einem oder mehreren dieser negativen prognostischen Faktoren für eine kürzere Bestrahlung mit 40 Gy in 15 Fraktionen über 3 Wochen anstelle einer längeren Bestrahlung über 6 Wochen in Betracht gezogen werden. Nach der randomisierten Studie von Perry *et al.* führte die Kombination einer verkürzten Strahlentherapie mit TMZ zu einem verbesserten Überleben bei älteren Patient*innen (≥65 Jahre) und kann auch bei Vorliegen von negativen prognostischen Faktoren in Betracht gezogen werden. Ausgewählte Patient*innen können auch für TMZ als Monotherapie (ohne Bestrahlung) geeignet sein. Im Gegensatz dazu konnte in einer retrospektiven Studie mit 112 Patient*innen im Alter von ≥60 Jahren kein signifikanter Vorteil für den Zusatz von TMZ zu einer kürzer dauernden Strahlentherapie gefunden werden. Insbesondere Patient*innen ohne MGMT-Promotor-Methylierung profitieren möglicherweise nicht von TMZ.

IV.2 Krampfanfälle vor und während einer Strahlentherapie (Publikationen 4-6)

Die im Rahmen der ersten Studie festgestellte Prävalenz der Krampfanfälle bei Gliomen der WHO °II-°IV vor der Strahlentherapie betrug 29,3 %. Dies korreliert mit dem in der Literatur beschriebenen Bereich von 9-87 %. Beim GBM betrug die Prävalenz 21,5 %, welche ebenfalls mit den zuvor berichteten Daten von 9-45 % übereinstimmte. Auch die Prävalenz beim °II Tumor lag mit 55,6 % im Bereich der in der Literatur berichteten Daten von 30-87 %. Für Anfälle vor der Radiatio beim WHO °III Gliomen liegen weniger Daten vor. In einer systematischen Übersicht wurden jedoch Anfallsraten von 29-67 % für diese Patient*innen berichtet. Die in unserer Studie gefundene Prävalenz von 48,8 % lag innerhalb dieses Bereichs.

Gemäß den Ergebnissen der vorliegenden Studie war der WHO-Grad signifikant mit dem Auftreten von Krampfanfällen vor der Strahlentherapie assoziiert. Die höchste Prävalenz von Krampfanfällen wurde bei geringgradigen Gliomen gefunden. In einer retrospektiven Studie mit 492 Patient*innen sowohl mit primären als auch metastatischen Hirntumoren – darunter 334 mit einem Gliom – war das Auftreten von präoperativen Krampfanfällen signifikant mit Gliomen des °I und °II (im Vergleich zu °III und °IV) assoziiert (Odds Ratio=4,0; p<0,001). In einer weiteren retrospektiven Studie von 190 Patient*innen mit astrozytären Tumoren lag die Rate der präoperativen Anfälle bei Patient*innen mit Tumoren der Grade II, III und IV bei 34 %, 29 % bzw. 18 %. Im Übersichtsartikel von Fan *et al.* hatten
30-87 % der Patient*innen mit einem niedriggradigen Gliom und 21-33 % der GBM-Patient*innen bei der Erstvorstellung bereits Anfälle. In einer größeren retrospektiven Studie (N=1.028) betrug die Prävalenz von Krampfanfällen während des gesamten Krankheitsverlaufs 85 % (322/379) bei niedriggradigen Gliomen, 69 % (95/137) bei anaplastischen Gliomen und 49 % (251/512) beim GBM.

Zusätzlich zum WHO-Grad wurden Trends für die Korrelationen von Krampfanfällen vor der Strahlentherapie für ein jüngeres Alter (≤59 Jahre) und nicht erfolgter Resektion gefunden. Das jüngere Alter wurde bereits früher als Risikofaktor für Krampfanfälle vor der Behandlung beschrieben. In der Studie von Hwang *et al.* hatten Patient*innen im Alter von <40 Jahren ein höheres Risiko für präoperative Anfälle als ältere Patient*innen (Odds Ratio=3,08; p=0,013). In der

Studie von Kaloshi *et al.*, die 62 Patient*innen mit supratentoriellen niedriggradigen Gliomen im Alter von ≥60 Jahren mit 704 jüngeren Patient*innen verglich, wurden in 85 % bzw. 47 % der Fälle Krampfanfälle als Erstsymptom eines Glioms identifiziert (p<0,001). In der Studie von Skardelly *et al.*, die auch Patient*innen mit Hirnmetastasen einschloss, hatten ebenfalls Patient*innen von ≤60 Jahre ein höheres Risiko für präoperative (Odds Ratio=1,66; p=0,020) Krampfanfälle. Auch Lote *et al.* berichteten eine inverse Korrelation zwischen dem Auftreten von Krampfanfällen vor Behandlung und dem Alter beim GBM (p<0,01).

Der Zusammenhang zwischen Krampfanfällen vor der Strahlentherapie und nicht erfolgter vorheriger Resektion lässt sich dadurch erklären, dass die Resektion zu einer signifikanten Reduktion der Anfälle führt. Darüber hinaus haben einige Autoren die Tumorlokalisation als Risikofaktor für Gliom-bedingte Krampfanfälle angegeben, obwohl die Berichte nicht einheitlich bezüglich der Lokalisation waren. In den Übersichtsartikeln von Kerkhof & Vecht sowie Englot *et al.* war eine temporal gelegene Lokalisation mit der höchsten Prävalenz von Krampfanfällen assoziiert, während in der Studie von Skardelly *et al.* die höchste Anfallsrate für frontale Lokalisationen gefunden wurde. In der vorliegenden Studie wurde kein signifikanter Zusammenhang zwischen den Krampfanfällen vor der Strahlentherapie und der Lokalisation des Glioms festgestellt, ähnlich wie in mehreren anderen Studien.

In unserer Studie zeigten die Anfälle vor der Strahlentherapie einen Trend für eine Assoziation mit dem Überleben. Ein signifikanter Zusammenhang für Patient*innen mit hochgradigen Gliomen, nicht aber für Patient*innen mit niedriggradigen Gliomen wurde zuvor bereits in einer großen Studie (N=1.028) mit Gliompatient*innen beschrieben. Andere Studien haben allerdings signifikante Assoziationen zwischen Krampfanfällen und verbessertem Überleben auch bei niedriggradigen Gliomen gefunden.

Im Verlauf einer Strahlentherapie von Gliomen können ebenfalls erstmals zerebrale Krampfanfälle auftreten oder die Häufigkeit vorbestehender Anfälle zunehmen, da die Strahlentherapie zu einer akuten Entzündungsreaktion führt, die mit Ödemen und erhöhtem intrakraniellen Druck einhergehen kann. Im Jahr 2004 berichteten Bhansali *et al.* über 11 Patient*innen mit strahleninduzierten

Hirnstörungen. Vier dieser Patient*innen (36 %) hatten generalisierte Krampfanfälle entwickelt. In einem 2007 veröffentlichten Übersichtsartikel wurde berichtet, dass Krampfanfälle sowohl Symptome einer akuten radiogenen Enzephalopathie als auch einer späten strahlenbedingten Nekrose sind. Allerdings gibt es bisher keine Studie, die den Einfluss einer cerebralen Bestrahlung auf die Anfallsaktivität im Verlauf einer Therapieserie bei Patient*innen mit hochgradigen Gliomen untersucht hat. Jedoch wären diese Daten sehr wichtig, um die Überwachung und ggf. die antikonvulsive Behandlung dieser Patient*innen zu verbessern. Daher wurde die SURF-ROGG-Studie konzipiert, die die Anfallshäufigkeit während einer Strahlentherapie bei hochgradigen (°III oder °IV) Gliomen prospektiv untersucht. Patient*innen mit niedriggradigen (°I oder °II) Gliomen werden nicht eingeschlossen, da sich deren Behandlung inklusive der Fraktionierung der Strahlentherapie fast immer von der Behandlung hochgradiger Gliome unterscheidet.

V Zusammenfassung und Ausblick

Ziele der Arbeiten im Rahmen dieser kumulativen Dissertation sind die Identifikation von Prognosefaktoren und die Entwicklung von Prognose-Scores, um zur Personalisierung der Behandlung von Patient*innen mit einem malignen Gliom beizutragen. Die Datenerhebung erfolgte retrospektiv und schloss Patient*innen ein, die zwischen 2005 und 2019 aufgrund eines malignen Glioms (WHO-Klasse II-IV) bestrahlt wurden.

Zusammenfassend konnte auf Basis der im Rahmen dieser Arbeiten erhobenen Daten eine Vielzahl von Erkenntnissen geschaffen werden. Zum einen konnte bestehendes Wissen untermauert, zum anderen neues Wissen bei der Therapie von Gliomen generiert werden. Die Prävalenz von Krampfanfällen vor der Strahlentherapie in unseren Arbeiten stimmt mit den Literaturangaben überein; neue Risikofaktoren für das Auftreten von Krampfanfällen wurden identifiziert. Hinsichtlich des Überlebens von Patient*innen mit malignen Gliomen in verschiedenen Situationen (Primär- oder Rezidiv-Situation) wurden diverse Prognosefaktoren identifiziert, die eine personalisierte Behandlung erleichtern und zur Stratifizierung bei zukünftigen randomisierten Studien herangezogen werden können. Dies gilt insbesondere für einen neu entwickelten Überlebensscore, der die MGMT-Promotor-Methylierung berücksichtigt und für Patient*innen jeden Alters verwendbar ist. Bei Patient*innen mit malignen Gliomen und deutlich eingeschränkter Überlebensprognose ist es wichtig, die Behandlung so kurz und schonend wie möglich zu gestalten, um die verbleibende Lebenszeit nicht mit nebenwirkungsreichen Therapien zu beeinträchtigen.

Zusätzlich zu den retrospektiven Studien wurde eine prospektive Studie (SURF-ROGG) auf den Weg gebracht, die die Anfallsaktivität im Verlauf einer Strahlentherapie bei hochgradigen Gliomen untersucht. Sollte diese Studie eine Zunahme der Aktivität zeigen, könnten deren Ergebnisse den Weg für eine größere prospektive Studie ebnen. Auch werden die Ergebnisse wahrscheinlich zu einer intensiveren Überwachung der Patient*innen sowie zu einer Verbesserung der antiepileptischen Behandlung beitragen.

VI Anhang

VI.1 Voten der Ethikkommission

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Herrn
Prof. Dr. med. Dirk Rades
Klinik für Strahlentherapie

im Hause

Ethik-Kommission

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Herr Prof. Dr. med. Alexander Katalinic
Stellv. Vorsitzender:
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Tel.: +49 451 3101 1008
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ethikkommission@uni-luebeck.de

Aktenzeichen: 15-355A
Datum: 16. September 2016

Untersuchung möglicher Prognosefaktoren bei Patienten und Patientinnen, die aufgrund eines eines Glioblastoma multiforme (GBM) eine Strahlentherapie oder eine Radio-Chemotherapie erhalten haben
Ihr Schreiben vom 13. September 2016

Sehr geehrter Herr Prof. Rades,

mit Ihrem o.g. Schreiben informieren Sie die Ethik-Kommission über Ihr geplantes Vorhaben.

Es werden ausschließlich anonymisierte Daten verarbeitet und kein Biomaterial einbezogen.

Die Ethik-Kommission nimmt das von Ihnen in Ihrem Anschreiben beschriebene Vorhaben zur Kenntnis. Eine Behandlung im normalen Antragsverfahren wird nicht für notwendig erachtet.

Mit freundlichen Grüßen

Mit freundlichen Grüßen

i.V.

Prof. Dr. med. Alexander Katalinic
Vorsitzender

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Aktenzeichen: 15-355A
Datum: 19. August 2020

Untersuchung möglicher Prognosefaktoren bei Patienten und Patientinnen, die aufgrund eines eines Glioblastoma multiforme (GBM) eine Strahlentherapie oder eine Radio-Chemotherapie erhalten haben
Ihre E-Mail vom 17. August 2020

Sehr geehrter Herr Prof. Rades,

mit Ihrer o.g. E-Mail informieren Sie die Ethik-Kommission über folgende Änderung:

Die Analyse wird auf Gliome WHO-Grad II-III erweitert.
Der Behandlungszeitraum wird aktualisiert auf 2009 bis 2019.

Mit freundlichen Grüßen

Prof. Dr. med. Alexander Katalinic
Vorsitzender

UNIVERSITÄT ZU LÜBECK

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Aktenzeichen: 20-120A
Datum: 03. April 2020

Häufigkeit, Risikofaktoren und prognostische Bedeutung von zerebralen Krampfanfällen vor Beginn einer Strahlentherapie bei PatientInnen mit Hirnmetastasen oder hirneigenen Tumoren

Sehr geehrter Herr Prof. Rades,

die Ethik-Kommission bewertet das o.g. Vorhaben im verkürzten Verfahren zustimmend.

Folgende Unterlagen wurden vorgelegt:

- Ihr Anschreiben vom 02. April 2020
- Studienprotokoll in der Version 1.0 vom 31. März 2020.

Eine Vorlage im Normalverfahren wird als nicht erforderlich betrachtet.

Mit freundlichen Grüßen

Prof. Dr. med. Alexander Katalinic
Vorsitzender

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Aktenzeichen: 20-311
Datum: 15. September 2020

Votum der Ethik-Kommission
Antragssteller: Herr Prof. Dr. Rades
Titel: SeizURe Frequency during a Radiotherapy cOurse for high-Grade Gliomas - SURF-ROGG

Sehr geehrter Herr Prof. Rades,

vielen Dank für Ihre E-Mail vom 11. September 2020 in der Sie den Hinweisen aus unserem Votum vom 10. September 2020 nachkommen.
Folgende Unterlagen lagen vor:

- Geändertes Basisformular
- Geändertes Studienprotokoll Version 1.0 vom 10 August 2020

Die Kommission hat gegen die Durchführung der Studie nunmehr keine Bedenken.

Bei Änderung des Studiendesigns sollte der Antrag erneut vorgelegt werden.
Über alle schwerwiegenden oder unerwarteten und unerwünschten Ereignisse, die während der Studie auftreten, ist die Kommission umgehend zu benachrichtigen.
Die Deklaration von Helsinki in der aktuellen Fassung fordert in § 35 dazu auf, jedes medizinische Forschungsvorhaben mit Menschen zu registrieren. Daher empfiehlt die Kommission grundsätzlich die Studienregistrierung in einem öffentlichen Register (z.B. unter www.drks.de).
Die ärztliche und juristische Verantwortung des Studienleiters und der an der Studie teilnehmenden Ärzte bleibt entsprechend der Beratungsfunktion der Ethikkommission durch unsere Stellungnahme unberührt.
Datenschutzrechtliche Aspekte von Forschungsvorhaben werden durch die Ethikkommission grundsätzlich nur kursorisch geprüft. Dieses Votum / diese Bewertung ersetzt mithin nicht die Konsultation des zuständigen Datenschutzbeauftragten.

Mit freundlichem Gruß

Prof. Dr. med. Alexander Katalinic
Vorsitzender

VI.2 Danksagung

Mein herzlicher Dank gilt Herrn Prof. Dr. med. Dirk Rades für die Überlassung des Themas, die hervorragende Betreuung und die sehr gute Zusammenarbeit.

Auch möchte ich Herrn Prof. Dr. med. Steven E. Schild für die Unterstützung bei der statistischen Auswertung meinen Dank aussprechen.

Nicht zuletzt danke ich allen Mitarbeitern unserer Klinik.

Mein besonderer Dank gilt meinen Eltern, meiner Schwester und meinen Großeltern sowie meiner Ehefrau, die mich in allem unterstützen und in jeglicher Hinsicht die Grundsteine für meinen Weg gelegt haben.

VI.3 Lebenslauf

Persönliche Daten

Name:	Jaspar Witteler
Geburtsdatum:	22.01.1991
Geburtsort:	Paderborn

Berufliche Laufbahn

Seit Februar 2019	Arzt in Weiterbildung am Universitätsklinikum Schleswig-Holstein (Campus Lübeck); Abteilung Strahlentherapie

Akademische Laufbahn

Dezember 2018	Approbation als Arzt
Dezember 2018	Drittes Staatsexamen der Humanmedizin
Oktober 2017	Zweites Staatsexamen der Humanmedizin
ab November 2015	Dissertation zum Thema „Prognosefaktoren beim Glioblastoma multiforme“
September 2014	Erstes Staatsexamen der Humanmedizin
Oktober 2011	Studium der Humanmedizin an der Universität zu Lübeck

Berufs- und Schulausbildung

August 2010 - Juli 2011	Fachoberschule Klasse 13 Erwerb der „Allgemeinen Hochschulreife“
August 2007 – Juli 2010	Fachschule für Biologisch-Technische Assistenten am Berufskolleg Olsberg Berufsabschluss zum „Staatlich geprüften Biologisch-Technischen Assistenten“ mit Allgemeiner Fachhochschulreife

Veröffentlichte Publikationen

Apr. 2021 A prospective interventional study evaluating seizure activity during a radiotherapy course for high-grade gliomas (SURF-ROGG)
Dirk Rades[1], Jaspar Witteler[1], Denise Olbrich[2], Peter Trillenberg[3], Steven E. Schild[4], Soeren Tvilsted[5] and Troels W. Kjaer[6]
BMC Cancer 21(1) DOI:10.1186/s12885-021-08121-y

Jan. 2021 Palliative Radiotherapy of Primary Glioblastoma
Jaspar Witteler[1], *Steven E. Schild[2]* and *Dirk Rades[1]*
In vivo (Athens, Greece) 35(1):483-487 DOI:10.21873/invivo.12282

Jan. 2021 A New Survival Score for Patients Receiving Radiotherapy for Newly Diagnosed Glioblastoma Multiforme
Dirk Rades[1], Jaspar Witteler[1], Steven E. Schild[2], Peter Trillenberg[3], Matteo M. Bonsanto[4] and Jan Leppert[4]
Anticancer Research 41(1):379-384 DOI:10.21873/anticanres.14786

Dez. 2020 Re-Irradiation for Recurrent Glioblastoma Multiforme
Jaspar Witteler[1], Troels W. Kjaer[2], Soeren Tvilsted[3], Steven E. Schild[4] and Dirk Rades[1]
Anticancer Research40(12):7077-7081
DOI:10.21873/anticanres.14735

Dez. 2020 Prognostic Factors of Local Control and Survival in Patients Irradiated for Glioblastoma Multiforme (GBM)
Jaspar Witteler[1], Steven E. Schild[2] and Dirk Rades[1]
Anticancer Research40(12):7025-7030
DOI:10.21873/anticanres.14728

Nov. 2020 Re-Evaluation of Prognostic Factors for Survival After Radiotherapy of Cerebral Gliomas: A Supplementary Analysis to a Previous Study
Jaspar Witteler[1], Troels W. Kjaer[2], Soeren Tvilsted[3], Steven E. Schild[4] and Dirk Rades[1]
Anticancer Research40(11):6513-6515
DOI:10.21873/anticanres.14674

Nov. 2020 Clinical Prognostic Factors for Local Control and Survival After Irradiation of Grade II Gliomas
Dirk Rades[1], Jaspar Witteler[1], Liesa Dziggel[1], Troels W. Kjaer[2], Soeren Tvilsted[3] and Steven E. Schild[4]
In vivo (Athens, Greece) 34(6):3719-3722
DOI:10.21873/invivo.12220

Nov. 2020 Radiotherapy of Grade III Gliomas: Identification of Clinical Prognostic Factors for Local Tumor Control and Survival
Dirk Rades[1], Jaspar Witteler[1]and Steven E. Schild[2]
In vivo (Athens, Greece) 34(6):3627-3630
DOI:10.21873/invivo.12208

Sep. 2020 Pre-Treatment Seizures in Patients With 1-3 Cerebral Metastases Receiving Local Therapies Plus Whole-brain Radiotherapy
Jaspar Witteler[1], Troels W. Kjaer[2], Soeren Tvilsted[3], Steven E. Schild[4] and Dirk Rades[1]
In vivo (Athens, Greece) 34(5):2727-2731
DOI:10.21873/invivo.12094

Sep. 2020 Pre-operative Seizures in Patients With Single Brain Metastasis Treated With Resection Plus Whole-Brain Irradiation and a Boost
Dirk Rades[1], *Jaspar Witteler[1]*, *Troels W. Kjaer[2]*, *Soeren Tvilsted[3]* and *Steven E. Schild[4]*
In vivo (Athens, Greece) 34(5):2705-2709
DOI:10.21873/invivo.12091

Jul. 2020 Seizures Prior to Radiotherapy of Gliomas: Prevalence, Risk Factors and Survival Prognosis
Jaspar Witteler[1], Troels W. Kjaer[2], Soeren Tvilsted[3], Steven E. Schild[4] and Dirk Rades[1]
Anticancer Research 40(7):3961-3965
DOI:10.21873/anticanres.14388

Jun. 2020 Seizures Prior to Whole-brain Irradiation for Metastatic Disease: Prevalence, Risk Factors and Association With Survival
Dirk Rades[1], Jaspar Witteler[1], Liesa Dziggel[1], Troels W. Kjaer[2], Soeren Tvilsted[3] and Steven E. Schild[4]
Anticancer Research 40(6):3429-3434
DOI:10.21873/anticanres.14328

Jun. 2020 Occurrence of Seizures Prior to Single-fraction Radiosurgery or Multi-fraction Stereotactic Radiotherapy in Patients With Very Few Brain Metastases
Dirk Rades[1], Jaspar Witteler[1], Troels W. Kjaer[2], Soeren Tvilsted[3] and Steven E. Schild[4]
Anticancer Research 40(6):3499-3504,
DOI:10.21873/anticanres.14337

VI.4 Verzeichnis der verwendeten Publikationen

1. Witteler J, Rades D, Schild S E: Prognostic Factors of Local Control and Survival in Patients Irradiated for Glioblastoma Multiforme (GBM).
   Anticancer Research December 2020, 40 (12) 7025-7030 [IF = 2,480]
2. Rades D, Witteler J, Schild S E, Trillenberg P, Bonsanto M M, Leppert J: A New Survival Score for Patients Receiving Radiotherapy for Newly Diagnosed Glioblastoma Multiforme.
   Anticancer Research January 2021, 41 (1) 379-384 [IF = 2,480]
3. Rades D, Witteler J, Leppert J, Schild S E: Re-Irradiation for Recurrent Glioblastoma Multiforme.
   Anticancer Research December 2020, 40 (12) 7077-7081 [IF = 2,480]
4. Witteler J, Kjaer T W, Tvilsted S, Schild S E, Rades D: Seizures Prior to Radiotherapy of Gliomas: Prevalence, Risk Factors and Survival Prognosis.
   Anticancer Research July 2020, 40 (7) 3961-3965 [IF = 2,480]
5. Witteler J, Kjaer T W, Tvilsted S, Schild S E, Rades D: Re-Evaluation of Prognostic Factors for Survival after Radiotherapy of Cerebral Gliomas: A Supplementary Analysis to a Previous Study.
   Anticancer Research November 2020, 40 (11) 6513-6515 [IF = 2,480]
6. Rades D, Witteler J, Olbrich D, Trillenberg P, Schild S E, Tvilsted S, Kjaer T W: A prospective interventional study evaluating seizure acitivity during a radiotherapy course for high-grade gliomas (SURF-ROGG).
   BMC Cancer (2021) 21:386 [IF = 4,430]

ANTICANCER RESEARCH *40*: 7025-7030 (2020)
doi:10.21873/anticanres.14728

Prognostic Factors of Local Control and Survival in Patients Irradiated for Glioblastoma Multiforme (GBM)

JASPAR WITTELER[1], STEVEN E. SCHILD[2] and DIRK RADES[1]

[1]*Department of Radiation Oncology, University of Lübeck, Lübeck, Germany;*
[2]*Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, U.S.A.*

Abstract. *Background/Aim: Standard treatment of glioblastoma multiforme (GBM) includes resection, longer-course radiotherapy and chemotherapy. Some patients cannot tolerate these regimens and may benefit from personalized treatments. This study aims to contribute to treatment personalization by identifying predictors of outcomes after longer-course radiotherapy. Patients and Methods: In 91 patients, number/site/diameter of lesions, Ki-67, MGMT promoter methylation, Karnofsky performance score (KPS), symptoms, gender, age and resection were evaluated for local control and survival. Results: On univariate analyses, gross resection (p=0.029) was significantly associated with improved local control. It maintained significance in the multivariate analysis [hazard ratio (HR)=1.64, p=0.025]. MGMT-methylation (p=0.004), KPS ≥80 (p=0.022) and resection (p<0.001) were significantly associated with improved survival on univariate analyses, unifocal GBM (p=0.056) showed a trend. In the multivariate analyses, MGMT-methylation (HR=3.63, p=0.009), KPS (HR=2.01, p=0.018) and resection (HR=3.29, p<0.001) were significant. Conclusion: Predictors of local control and survival were identified that may guide physicians when tailoring treatments to patients with GBM.*

Glioblastoma multiforme (GBM) accounts for about 35% of primary brain tumors in adults (1, 2). In the United States, the overall incidence of GBM was reported to be 4.40 per 100,000 inhabitants (3). The prognoses of patients with GBM are generally poor with a 5-year survival probability of only about 5% (2, 4). Better outcomes can be achieved with a tri-modality treatment approach that is quite intensive and includes neurosurgical resection followed by longer-course radiotherapy plus concurrent and adjuvant chemotherapy (5-7). However, some patients, particularly if they are elderly or frail, may not be able to tolerate a tri-modality treatment regimen and could benefit from a personalized treatment approach (8). Personalized treatments need to consider the patient's individual situation, personal needs and preferences. Moreover, the patient's survival prognosis and the potential benefit from an intensive treatment program should be considered to avoid over- or undertreatment. Patients with favorable survival prognoses and good chances to benefit from an intensive treatment regimen in terms of improved local control and survival should receive the standard tri-modality treatment (5, 6). In contrast, patients with short survival times and little expected benefits from an intensive treatment appear better treated with less aggressive regimens (8). Such regimens may include shorter-course radiotherapy (lasting 3 instead of 6 weeks) with or without systemic treatment and omit extensive neurosurgical resection (8-10).

Tailoring a treatment regimen to a patient's individual situation can be facilitated by applying prognostic factors that allow estimating the probability of local control of the GBM and the patient's remaining survival time. This study aimed to identify predictors of both local control and survival in patients treated with longer-course radiotherapy with or without additional treatment (upfront neurosurgical resection, systemic treatment).

Patients and Methods

The data of 91 patients irradiated for histologically confirmed GBM between 2005 and 2019 were retrospectively evaluated with respect to local control and survival. The study was approved by the Ethics Committee of the University of Lübeck (15-355A).

The majority of the patients received longer-course radiotherapy with 60.0 Gy in 30 fractions of 2.0 Gy given over 6 weeks (n=54) or 59.4 Gy in 33 fractions of 1.8 Gy given over 6.5 weeks (n=19). In those 18 patients receiving less than 59.4 Gy, total doses were given as planned in 11 patients (range=54.0 to 58.0 Gy). In seven patients, the administered dose was less than initially planned; five of these patients received less than 54.0 Gy. Radiotherapy was performed as 3D-

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Key Words: Glioblastoma multiforme, longer-course radiotherapy, local control, survival, prognostic factors.

conformal radiotherapy (n=53) or as volumetric modulated arc therapy (n=38). In all but three patients, radiotherapy was supplemented by systemic treatment with temozolomide. In the entire cohort, 69 patients (81%) received upfront neurosurgical resection of the GBM, which was a gross total resection (GTR) in 18 patients (26%) and a subtotal resection (STR) in 44 patients (64%). Extent of resection was not specified in seven patients (10%).

A total of 11 characteristics were evaluated for potential associations with local control (defined as freedom from progression or recurrence of the treated GBM lesions and freedom from new GBM lesions) and survival. These characteristics included number of GBM lesions (single *vs.* multiple), main site of GBM (thalamus *vs.* temporal *vs.* frontal *vs.* parietal *vs.* occipital *vs.* parieto-occipital *vs.* fronto-parietal *vs.* temporo-frontal *vs.* temporo-parietal *vs.* other sites), maximum cumulative diameter of GBM lesions (<40 mm *vs.* ≥40 mm, median=40 mm), Ki-67/molecular immunology Borstel (MIB)1 labeling index (<25% *vs.* ≥25%, median=25%), O6-methylguanine-DNA methyl-transferase (MGMT) promoter methylation (MGMT-methylation) (no *vs.* yes), Karnofsky performance score (≤70 *vs.* ≥80, median=80), number of pre-treatment symptoms (1 *vs.* ≥2), gender (female *vs.* male), age at the start of irradiation (≤60 *vs.* ≥61 years, median=61 years), neurosurgical resection (no *vs.* yes) and extent of resection (GTR *vs.* STR). Distributions of these characteristics are shown in Table I.

Both local control of GBM and survival were referenced from the first day of radiotherapy. The methods used for the univariate analyses of local control and survival included the Kaplan-Meier method and the log-rank test. *p*-Values of <0.05 were considered significant and *p*-values of <0.06 were considered indicating a trend. Characteristics achieving significance were additionally evaluated in a multivariate analysis (Cox proportional hazards model). Characteristics that were significant in the multivariate analysis ($p<0.05$) were considered independent predictors of post-treatment outcomes. Patients were followed until death or for at least 24 months after the start of radiotherapy.

Table I. *Characteristics that were analyzed with respect to local control and survival.*

Factor	Number of patients (%) for analyses of local control	Number of patients (%) for analyses of survival
Number of GBM lesions		
Single	72 (85)	76 (84)
Multiple	13 (15)	15 (16)
Main site of GBM		
Thalamus	4 (5)	5 (6)
Temporal	23 (27)	25 (27)
Frontal	19 (22)	19 (21)
Parietal	9 (11)	10 (11)
Occipital	4 (5)	4 (4)
Parieto-occipital	7 (8)	7 (8)
Fronto-parietal	3 (4)	4 (4)
Temporo-frontal	3 (4)	3 (3)
Temporo-parietal	8 (9)	9 (10)
Other sites	5 (6)	5 (6)
Maximum cumulative diameter		
<40 mm	35 (41)	38 (42)
≥40 mm	39 (46)	42 (46)
Unknown	11 (13)	11 (12)
Ki-67/MIB 1 labeling index		
<25%	34 (40)	37 (41)
≥25%	28 (33)	31 (34)
Unknown	23 (27)	23 (25)
MGMT promoter methylation		
No	7 (8)	11 (12)
Yes	16 (19)	18 (20)
Unknown	62 (73)	62 (68)
Karnofsky performance score		
≤70	25 (29)	29 (32)
≥80	60 (71)	62 (68)
Number of pre-treatment symptoms		
1	25 (29)	29 (32)
≥2	49 (58)	51 (56)
Unknown	11 (13)	11 (12)
Gender		
Female	36 (42)	38 (42)
Male	49 (58)	53 (58)
Age at radiotherapy		
≤60 Years	41 (48)	44 (48)
≥61 Years	44 (52)	47 (52)
Neurosurgical resection		
No	16 (19)	18 (20)
Yes	69 (81)	73 (80)
Extent of resection		
GTR	18 (26)	21 (29)
STR	44 (64)	45 (62)
Not specified	7 (10)	7 (10)

GBM: Glioblastoma multiforme, MIB1: molecular immunology Borstel 1, MGMT: O^6-methylguanine-DNA methyl-transferase, GTR: gross total resection, STR: subtotal resection.

Results

Median follow-up times were 24 months (range=1-128 months) in the entire cohort and 35.5 months (range=24-128 months) in patients alive at the last contact.

Data regarding local control were available for 85 patients (93%). Of these patients, 33 (39%) experienced a local failure. In the entire cohort, the local control rates at 1 and 2 years were 91% and 70%, respectively. On univariate analyses (Table II), improved local control was significantly associated with GTR ($p=0.029$). In the subsequent multivariate analysis, extent of resection remained significant [hazard ratio (HR)=1.64, 95% confidence interval (CI)=1.06-2.75, $p=0.025$].

In 53 patients of the entire cohort (58%), death was recorded during the period of follow-up. Survival rates at 1 and 2 years were 64% and 53%, respectively. On univariate analyses (Table III), improved survival was significantly associated with MGMT promoter methylation ($p=0.004$), a KPS ≥80 ($p=0.022$) and upfront neurosurgical resection ($p<0.001$). In addition, a trend was observed for unifocal GBM ($p=0.056$). In the multivariate analyses, MGMT promoter methylation (HR=3.63, 95% CI=1.39-9.80, $p=0.009$), KPS ≥80 (HR=2.01, 95% CI=1.13-3.50, $p=0.018$) and upfront resection (HR=3.29, 95% CI=1.75-5.95, $p<0.001$) maintained significance.

Table II. *Local control rates at 1 and 2 years after the start of radiotherapy (n=85).*

Factor	1 Year (%)	2 Years (%)	*p*-Value
Number of GBM lesions			
Single	90	71	0.573
Multiple	100	60	
Main site of GBM			
Thalamus	100	100	0.761
Temporal	85	69	
Frontal	83	73	
Parietal	100	100	
Occipital	100	100	
Parieto-occipital	100	40	
Fronto-parietal	100	100	
Temporo-frontal	100	67	
Temporo-parietal	100	57	
Other sites	80	80	
Maximum cumulative diameter			
<40 mm	90	61	0.738
≥40 mm	92	78	
Ki-67/MIB 1 labeling index			
<25%	89	72	0.752
≥25%	95	81	
MGMT promoter methylation			
No	80	40	0.103
Yes	92	67	
Karnofsky performance score			
≤70	86	77	0.656
≥80	92	67	
Number of pre-treatment symptoms			
1	89	83	0.166
≥2	95	64	
Gender			
Female	92	73	0.230
Male	90	68	
Age at radiotherapy			
≤60 Years	88	75	0.886
≥61 Years	93	63	
Neurosurgical resection			
No	100	100	0.764
Yes	90	67	
Extent of resection			
GTR	94	74	**0.029**
STR	89	64	

GBM: Glioblastoma multiforme, MIB: molecular immunology Borstel 1, MGMT: O^6-methylguanine-DNA methyl-transferase, GTR: gross total resection, STR: subtotal resection. Bold *p*-values were significant.

Table III. *Survival rates at 1 and 2 years after the start of radiotherapy (n=91).*

Factor	1 Year (%)	2 Years (%)	*p*-Value
Number of GBM lesions			
Single	70	57	0.056
Multiple	33	33	
Main site of GBM			
Thalamus	20	20	0.061
Temporal	76	64	
Frontal	58	47	
Parietal	30	20	
Occipital	50	50	
Parieto-occipital	71	71	
Fronto-parietal	75	25	
Temporo-frontal	100	100	
Temporo-parietal	78	67	
Other sites	80	60	
Maximum cumulative diameter			
<40 mm	66	50	0.953
≥40 mm	52	45	
Ki-67/MIB 1 labeling index			
<25%	65	54	0.149
≥25%	52	42	
MGMT promoter methylation			
No	18	9	**0.004**
Yes	72	61	
Karnofsky performance score			
≤70	45	34	**0.022**
≥80	73	61	
Number of pre-treatment symptoms			
1	55	48	0.615
≥2	67	51	
Gender			
Female	58	47	0.490
Male	68	57	
Age at radiotherapy			
≤60 Years	70	61	0.162
≥61 Years	57	45	
Neurosurgical resection			
No	28	22	**<0.001**
Yes	73	60	
Extent of resection			
GTR	81	71	0.077
STR	69	56	

GBM: Glioblastoma multiforme, MIB: molecular immunology Borstel 1, MGMT: O^6-methylguanine-DNA methyl-transferase, GTR: gross total resection, STR: subtotal resection. Bold *p*-values were significant.

Discussion

The treatment generally considered standard for GBM includes maximum neurosurgical resection followed by concurrent radiochemotherapy (60 Gy in 30 fractions plus temozolomide) and six courses of temozolomide alone (5-7). In a randomized trial, this regimen led to a median survival time of 14.6 months and 2-year, 3-year and 5-year survival rates of 27.2%, 16.0% and 9.8%, respectively (5, 6). When looking at these low survival rates, it becomes obvious that the outcomes of patients with GBM require further improvement. Many pre-clinical and clinical studies were performed to contribute to better understanding and improved treatment of this malignant disease (11-14).

From the radiation oncologist's perspective, an important question is related to the optimal dose-fractionation schedule. Already in 1979, a pooled analysis was presented including data of patients with malignant gliomas treated with surgery plus irradiation in several studies of the Brain Tumor Study Group (15). This analysis demonstrated a dose-effect relationship. Patients receiving 60 Gy had a significantly longer median survival (42 weeks) than patients receiving 55 Gy (36 weeks), 50 Gy (28 weeks) and ≤45 Gy (13.5 weeks). Moreover, a randomized trial demonstrated that 60 Gy in 30 fractions over 6 weeks was significantly superior to 45 Gy in 20 fractions over 4 weeks (p=0.007) (16). In 2001, a phase III trial compared four treatment regimens for newly diagnosed GBM (17). Treatment regimens included accelerated-hyperfractionated radiotherapy (70.4 Gy, 2×1.6 Gy/day) with or without a radiosensitizer (difluromethylornithine=DFMO) and normofractionated radiotherapy (59.4 Gy, 1×1.8 Gy/day) with or without DFMO. The four groups were balanced for age, KPS and extent of resection. Both accelerated-hyperfractionated radiotherapy and addition of DFMO did not lead to improved overall survival and progression-free survival (17). Thus, total doses of 59.4 Gy and 60.0 Gy are considered optimal for the treatment of GBM.

However, it has been recognized that elderly patients and patients with a poor performance status have less favorable survival prognoses (4, 18). Moreover, these patients may not be able to withstand an intensive tri-modality treatment (5, 6). In 2004, a randomized trial of 100 patients with GBM aged ≥60 years compared shorter-course radiotherapy (40 Gy in 15 fractions over 3 weeks) to longer-course radiotherapy (60 Gy in 30 fractions over 6 weeks for survival (9). Median survival and survival rates at 6 months were similar (p=0.57), and shorter-course radiotherapy was considered a reasonable option for GBM patients ≥60 years of age.

Shorter-course radiotherapy may also be reasonable for patients with limited survival prognoses to avoid that they have to spend more than necessary of their remaining lifespan receiving treatment for GBM. It would be important to be able to judge a patient's survival prognosis prior to assigning a treatment regimen. Prognostic factors of survival can guide the physicians during this process. Moreover, prognostic factors of local control of the GBM are important for selecting the optimal individual treatment, particularly because GBM does not metastasize outside the brain.

In the present study, the data of 91 patients irradiated for GBM were analyzed to identify predictors of both local control and survival. The aim to facilitate the estimation of the survival of patients with GBM has been previously pursued (18). In 2004, a recursive partitioning analysis was presented, which was based on the three prognostic factors age, KPS and extent of resection. The groups with the highest risk of death included all patients >65 years of age and patients 40-65 years of age with either KPS <80 or biopsy only (18). In contrast to our present study, local control of GBM was not investigated. Moreover, since 2004 the treatment of GBM has changed considerably, particularly after publication of the randomized trial of Stupp *et al.* in 2005 (5).

In this study, improved local control of GBM was significantly associated with GTR. Thus, GTR should be aimed at whenever reasonably possible considering potential damage to important brain structures as well as the patient's performance score and comorbidity index. Worse survival was significantly associated in both univariate and multivariate analyses with absence of MGMT promoter methylation, worse KPS (≤70) and no upfront resection. In addition, multifocal GBM showed a trend for worse survival on univariate analysis. Considering the randomized trial of Roa *et al.*, patients with one or more of these negative prognostic factors may be considered for shorter-course with 40 Gy in 15 fractions over 3 weeks instead of longer-course radiotherapy over 6 weeks (9). According to the randomized trial of Perry *et al.*, the addition of temozolomide to shorter-course radiotherapy resulted in improved survival in elderly patients (≥65 years) and may be considered for also for patients with negative prognostic factors identified in this study who likely will tolerate the combined treatment (10). Selected patients may even be candidates for temozolomide alone (19, 20). In contrast, a retrospective study of 112 patients aged ≥60 years did not find a significant benefit for the addition of temozolomide to shorter-course radiotherapy (21). Particularly patients without MGMT promoter methylation may not significantly benefit from temozolomide (5-7, 19, 20).

MGMT promoter methylation (5-7, 10, 19, 20), a better performance score (4, 18, 22, 23), a greater extent of resection (4, 18, 22, 23) and unifocal GBM (24-26) were previously reported as predictors of improved survival of patients with GBM, consistent with the results of the present study. Therefore, these results will likely contribute to the personalization of the treatment of patients with GBM. However, when interpreting the results of this study, one should be aware of its limitations including the retrospective design, which might have led to hidden selection biases. Although patients alive at the last contact must have had a follow up of at least 24 months, some deaths might have been missed due to the retrospective nature of the data. Moreover, the patients were treated during a comparably long time period of 15 years during which treatment concepts for recurrence of GBM have changed. This likely had an impact on the patients' survival.

In summary, in patients receiving longer-course radiotherapy for GBM, better local control was associated with GTR and better survival with MGMT promoter methylation, KPS ≥80, upfront resection and unifocal GBM. These predictors of treatment outcomes may guide physicians when designing personalized treatment programs for patients with GBM.

Conflicts of Interest

The Authors report no conflicts of interest related to the present study.

Authors' Contributions

The study was designed by all Authors. J.W. collected the data that were analyzed by all Authors. The draft of the article was written and finally approved by J.W., S.E.S. and D.R.

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A New Survival Score for Patients Receiving Radiotherapy for Newly Diagnosed Glioblastoma Multiforme

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Abstract. *Background/Aim: In a previous study investigating radiotherapy for newly diagnosed glioblastoma multiforme (GBM), significant or almost significant associations with survival were found for performance status, upfront resection, O^6-methylguanine-DNA methyl-transferase (MGMT) promoter methylation and unifocal GBM. This study aimed to create a survival score based on these factors. Patients and Methods: Most of the 81 patients included received resection of GBM followed by radiochemotherapy (59.4 Gy/33 or 60 Gy/30 fractions). The previously identified predictors of survival were re-evaluated. Factors significantly associated with survival were used for the score. Results: All factors were significantly associated with survival. For each factor, 0 points (less favorable survival) or 1 point (more favorable survival) were assigned and added for each patient. Three groups were designed, 0-1 (n=10), 2 (n=21) and 3-4 points (n=50); 12-month survival rates were 0%, 38% and 78% (p<0.001). Conclusion: A new survival score was created for patients requiring radiotherapy for GBM that can improve treatment personalization.*

Gliomas are the most common primary tumors of the central nervous system (CNS) in adults (1, 2). The classification of the World Health Organization includes four grades (I to IV). Patients with grade IV gliomas (glioblastoma multiforme, GBM) have the worst survival prognoses (3). Since publication of the randomized trial of Stupp *et al.* in 2005, the standard treatment for GBM has changed and includes maximum possible neurosurgical resection followed by concurrent radiochemotherapy and maintenance chemotherapy (4). The dose-fractionation regimen used in the Stupp trial (EORTC 26981/22981-NCIC CE3) consisted of 60 Gy in 30 fractions (2.0 Gy per fraction on five consecutive days per week) combined with administration of 75 mg/m^2 of temozolomide (TMZ) on seven days per week (4). Concurrent radiochemotherapy was followed by six cycles of TMZ alone (150-200 mg/m^2 on five consecutive days every four weeks). This regimen resulted in a median survival of 14.6 months, which was 2.5 months longer than resection plus radiotherapy without TMZ (4). However, such a multi-modality treatment can be difficult for patients. In 2004, a randomized trial compared longer-course radiotherapy with 60 Gy in 30 fractions over six weeks to a shorter-course program, namely 40 Gy in 15 fractions of 2.66 Gy over three weeks in elderly patients (5). Median survival and survival at 6 months after randomization were similar in both groups. In this case, "elderly" was defined as ≥60 years. During the last decades, the median age of patients with GBM has increased to 64 years. Thus, 40 Gy in 15 fractions could be a reasonable option for many patients with this aggressive disease, particularly for patients with short or intermediate survival prognoses (1). More recently, Roa *et al.* presented another randomized trial that compared 40 Gy in 15 fractions over three weeks to a very short course of radiotherapy, 25 Gy in 5 fractions of 5 Gy over one week, in elderly (≥65 years) and/or frail [Karnofsky performance score (KPS) 50-70%] patients (6). They found that 25 Gy in five fractions was not inferior to 40 Gy in 15 fractions with respect to overall survival and progression-free survival. Selected patients, particularly in case of methylation of the O^6-methylguanine-DNA methyl-transferase (MGMT), may be suitable for systemic treatment with TMZ alone (7, 8).

These considerations demonstrate that it is important to be able to estimate a patient's survival prognosis prior to designing an individual treatment program. Patients with very poor prognoses may be considered for a very short

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course of radiotherapy, TMZ alone or best supportive care. Patients with intermediate prognoses appear suitable for radiotherapy with 40 Gy in 15 fractions that can be combined with TMZ (9). Patients with more favorable prognoses should receive multi-modality treatment that can lead to improved survival (4, 10). Since in patients with favorable survival prognoses late treatment-related sequelae are also important, radiotherapy with 59.4 Gy with doses per fraction of 1.8 Gy may be preferable to 60 Gy with doses per fraction of 2.0 Gy. The risk of radiation-related late complications of the normal CNS tissue increases with both total dose and dose per fraction (11, 12).

The present study aimed to develop a survival score for patients with newly diagnosed GBM who are considered candidates for radiotherapy, in order to support physicians during the process of designing a personalized treatment regimen. This new score should be based on four prognostic factors identified in a previous study, namely KPS, upfront neurosurgical resection, *MGMT* promoter methylation and number of GBM lesions (13). It is the first survival score including *MGMT* promoter methylation that does not particularly focus on elderly patients with GBM.

Patients and Methods

In a previous study of patients irradiated for newly diagnosed GBM, a significant association with improved survival was found for KPS ≥80 (*vs.* ≤70%), upfront neurosurgical resection of GBM (*vs.* no resection) and *MGMT* promoter methylation (*vs.* no methylation); borderline significance was observed for a single lesion (*vs.* multiple lesions) of GBM (13). The present study was performed to create a survival score for patients requiring radiotherapy for newly diagnosed GBM based on these four factors. The new score should particularly help estimate the survival probability at 12 months after the start of radiotherapy. The study received approval from the local Ethics Committee (University of Lübeck, *ref.* 15-355A).

This study included 81 patients irradiated between 06/2010 and 02/2020, in whom data regarding the four prognostic factors stated above were available. Twenty-eight patients (35%) were included in the previous study (13). Of the 81 patients of the present study, 30 (37%) were female and 51 (63%) were male. The median age was 59 years (range=21-81 years). The two most common sites of GBM were the temporal lobe (*n*=34) and frontal lobe (*n*=19). In 78 patients (96%), radiotherapy was combined with concurrent and adjuvant chemotherapy, which consisted of temozolomide. Fifty-nine patients (73%) received an upfront neurosurgical resection of the GBM, which was a gross total resection (GTR) in 27 patients and a subtotal resection (STR) in 30 patients.

Radiotherapy was performed as 3D-conformal radiotherapy in 5 patients (6%) and as volumetric modulated arc therapy in 76 patients (94%). Dose-fractionation regimens included 59.4 Gy in 33 fractions of 1.8 Gy over 6.5 weeks in 56 patients and 60 Gy in 30 fractions of 2.0 Gy over 6 weeks in 19 patients. In the other 6 patients, radiotherapy was given as planned in 5 patients. Four patients received 55.8 Gy in 31 fractions of 1.8 Gy and one patient 54 Gy in 30 fractions of 1.8 Gy. In one patient, radiotherapy was stopped after 57.6 Gy of the planned 59.4 Gy.

Table I. *Univariate analyses of the four prognostic factors included in the scoring system: Survival rates at 6 and 12 months after the start of radiotherapy for glioblastoma.*

Prognostic factor	6 Months (%)	12 Months (%)	*p*-Value
Number of GBM lesions			
Multiple (n=11)	64	9	**<0.001**
Single (n=70)	86	66	
Karnofsky performance score			
≤70% (n=36)	72	47	**0.039**
≥80% (n=45)	91	67	
Neurosurgical resection			
No (n=22)	55	18	**<0.001**
Yes (n=59)	93	73	
MGMT promoter methylation			
No (n=38)	76	42	**0.026**
Yes (n=43)	88	72	

GBM: Glioblastoma multiforme; MGMT: O^6-methylguanine-DNA methyl-transferase; bold *p*-values were significant.

Table II. *Prognostic factors and corresponding scoring points.*

Prognostic factor	Scoring points
Number of GBM lesions	
Multiple	0
Single	1
Karnofsky performance score	
≤70%	0
≥80%	1
Neurosurgical resection	
No	0
Yes	1
MGMT promoter methylation	
No	0
Yes	1

GBM: Glioblastoma multiforme; MGMT: O^6-methylguanine-DNA methyl-transferase.

Survival time was calculated from the first day of radiotherapy. Univariate analyses were performed with the Kaplan–Meier method. Differences between the corresponding Kaplan–Meier curves were calculated with the Wilcoxon test. *p*-Values <0.05 were considered significant and *p*-values <0.10 indicated a trend. Those factors that were significantly associated with survival were included in the scoring system.

Results

The patients were followed until death or for at least 12 months after the start of radiotherapy. The median survival time was 16 months, and the survival rates at 6 months and at 12 months were 83% and 58%, respectively. On univariate

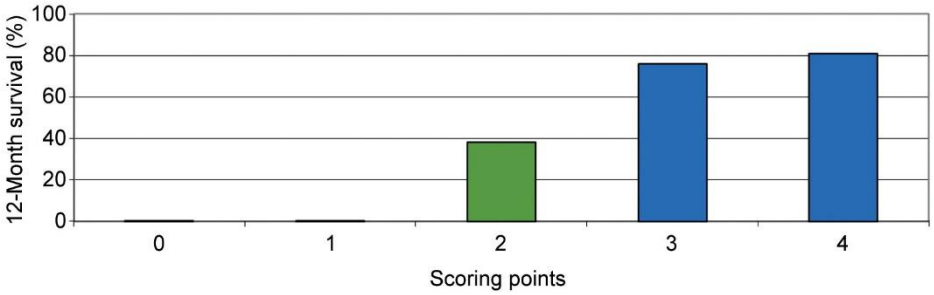

Figure 1. *The 12-month survival rates related to the scoring points calculated for each patient (patient scores).*

analyses (Table I), significant associations with better survival were found for a single lesion of GBM ($p<0.001$), upfront resection ($p<0.001$), *MGMT* promoter methylation ($p=0.026$) and KPS ≥80% ($p=0.039$).

Therefore, all four investigated factors were used for creating the scoring system. For each factor, either 0 points (less favorable survival) or 1 point (more favorable survival) were assigned (Table II). The points of the four factors were added for each patient to receive the individual scoring points (patient scores). The resulting patient scores ranged between 0 and 4 points. The corresponding 12-month survival rates were 0% (0 points), 0% (1 point), 38% (2 points), 76% (3 points) and 81% (4 points), respectively ($p<0.001$, Figure 1). Based on these survival rates, three prognostic groups were designed, namely 0-1 points ($n=10$), 2 points ($n=21$) and 3-4 points ($n=50$). Twelve-month survival rates of these groups were 0%, 38% and 78%, respectively, and median survival times were 7, 11 and 40 months, respectively ($p<0.001$, Figure 2).

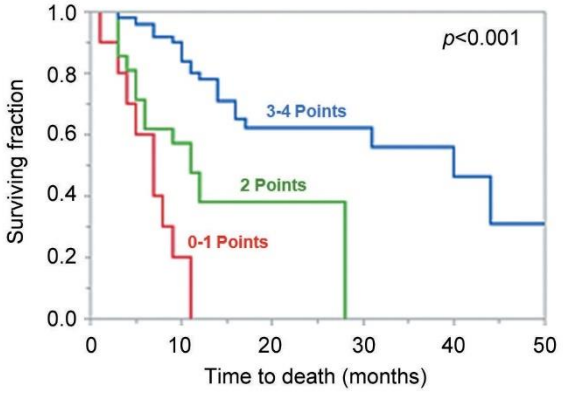

Figure 2. *Kaplan–Meier curves of the three prognostic groups 0-1 points, 2 points and 3-4 points. The p-value was calculated with the log-rank test.*

Discussion

Although considerable research has been performed during the last decade, the outcomes of the majority of patients with GBM are still poor with the 5-year survival probability of less than 10% requiring further improvement (14-19). This may be achieved with aggressive multi-modality treatment. On the other hand, if patients have a very short remaining survival time, their treatment should be as short and convenient as possible. Thus, patients with GBM will likely benefit from personalized treatments that consider their individual situation including treatment preferences, age, co-morbidities, social environment and remaining lifespan.

For almost 30 years, scoring systems have been created that aimed to predict the survival of patients irradiated for GBM. In 1993, Curran *et al*. presented a recursive partitioning analysis (RPA) of prognostic factors using data of patients with malignant gliomas from three Radiation Therapy Oncology Group trials (20). Six RPA classes and 12 subgroups (terminal nodes) were designed based on prognostic factors including performance status, age, changes in mental status, resection, total radiation dose and histology (WHO grade). Median survival times ranged between 4.3 and 58.6 months (20). However, the cohort of patients used to develop this RPA classification included different WHO grades and did not consider *MGMT* promoter methylation that was discovered to be an important predictor of survival more than 10 years later (21). In 2004, Lamborn *et al*. presented an RPA classification particularly for patients with GBM (22). Based on age, KPS, extent of resection and location of GBM, they classified patients into four risk groups, two lower risk groups (age <40 years; lowest risk with involvement of the frontal lobe only), one intermediate risk group (KPS ≥80%, resection, age 40-65 years) and one higher risk group (age >65 years, or age 40-65 years plus KPS ≤70% and/or biopsy only). Median survival times of the four groups were 132, 71, 63 and 37 weeks, respectively (22). In contrast to the previous study of Curran

et al., the classification of Lamborn *et al*. focused specifically on GBM but also did not consider the *MGMT* promoter methylation (20, 22).

After publication of the Stupp trial in 2005, the addition of TMZ to radiotherapy has become very popular for the treatment of GBM (4). In 2006, Mirimanoff *et al*. presented a study that investigated the RPA classification from 1993 (20) in the cohort of the Stupp trial (4) and found significantly different survival outcomes between RPA classes III, IV and V with median survival times of 17, 15 and 10 months, respectively (23). However, again the prognostic role of the *MGMT* promoter methylation was not investigated. In 2008, authors of the Stupp trial used the data of their trial to develop three nomograms for estimating the 2-year survival probability of patients with GBM (24). One nomogram was based on assignment to treatment (radiotherapy plus temozolomide *vs*. radiotherapy alone), age, extent of neurosurgical resection, mini-mental state examination (MMSE) score and corticosteroids at randomization. The other two nomograms were based on age, performance status and MMSE score and on *MGMT* promoter methylation, performance status and MMSE score, respectively (24). Although these nomograms can support physicians when designing an individual treatment program, they appear relatively complex. Moreover, one has to be aware that the nomograms were developed from selected patients meeting the criteria for inclusion in a randomized trial. The results obtained from these patients may likely not be generalized to other patients, who make up a considerable proportion of patients with GBM during daily routine. Furthermore, the MMSE score is generally not assessed during daily routine outside clinical trials. The easier-to-use survival score developed in the present study may be a reasonable supplement to the three previous nomograms (24).

In 2012, an additional RPA classification was presented that was limited to elderly patients (≥70 years) with GBM (24). Four RPA classes were designed: age <75.5 years and resection (class I), age ≥75.5 years and resection (class II), KPS 70-100% and biopsy only (class III), KPS<70% and biopsy only (class IV). Median survival times were 9.3, 6.4, 4.6 and 2.3 months, respectively (25). However, patients younger than 70 years and *MGMT* promoter methylation were not considered.

The most recent survival score for patients irradiated for GBM was also limited to elderly patients (≥65 years) (26). The score considered three independent predictors of survival, namely age, KPS and *MGMT* promoter methylation. It included two prognostic groups, namely 4-8 and 9-14 points, with median survival times of 2.7 and 7.8 months, respectively. In contrast to previous scores, the score of Straube *et al*. considered *MGMT* promoter methylation but was not made for patients younger than 65 years (26).

We felt that an additional survival score might be useful for patients irradiated for newly diagnosed GBM, a score that considers *MGMT* promoter methylation and can be used for unselected patients of all ages during daily routine. The new score was based on four prognostic factors identified in a previous study of patients receiving radiotherapy for GBM (13). These factors were number of GBM lesions, KPS, neurosurgical resection and *MGMT* promoter methylation. Median survival in the present cohort (16 months) was similar to the TMZ-group in the Stupp trial (14.6 months) and to patients treated after 2005 in a propensity score weighted population-base analysis (15 months) (27). Moreover, the 12-month survival rate of the present study was very similar to the rate found in the propensity score weighted population-base analysis (58% *vs*. 59%). These similarities demonstrate consistency of the data of the present study.

The four previously identified prognostic factors (13) were re-evaluated in the present study. Since they showed significant associations with survival, all four factors were considered eligible for inclusion in the survival score. Based on these factors, three groups were designed. Patients of the 0-1 points group had the worst survival outcomes. The median survival time was only 7 months, and no patient survived longer than 10 months. Therefore, these patients should be considered for treatment with a very short course of radiotherapy such as 25 Gy in five fractions over one week (6). Patients of the 2 points group with a median survival of 11 months and a 12-month survival probability of 38% represented the intermediate risk group. Since less than half of these patients lived for 12 months or longer, they might be considered for short-course radiotherapy with 40 Gy in 15 fractions over three weeks (5). Short-course radiotherapy should be supplemented by TMZ if reasonable. In a randomized trial, the addition of TMZ to radiotherapy resulted in significantly longer survival than short-course radiotherapy alone in elderly patients (≥65 years) with GBM (28). However, in a retrospective study of 112 patients aged ≥60 years a significant benefit of the addition of TMZ to shorter-course radiotherapy was not observed (29). This might be a result of the absence of the *MGMT* promoter methylation in a certain number of patients, which was not investigated in that study (29). *MGMT* promoter methylation was shown to be positively associated with outcomes after treatment with TMZ in patients with GBM (7, 8, 21).

Patients of the 3-4 points group had the most favorable survival prognoses with a median survival of 40 months and a 12-month survival rate of 78%. These patients likely benefited from multi-modality treatment including resection, longer-course radiotherapy and TMZ. Longer-course radiotherapy may be given with 60 Gy in 30 fractions of 2.0 Gy or 59.4 Gy in 33 fractions of 1.8 Gy. The latter regimen is expected to result in less late sequelae, since the equivalent doses in 2 Gy fractions (EQD2) for late complications of normal CNS tissue are 60.0 Gy for 60 Gy/30 fractions and 56.4 Gy for 59.4 Gy/33 fractions, respectively (11, 12). The EQD2 for 57.6 Gy/32 fractions and 55.8 Gy/31 fractions are 54.7 Gy and 53.0 Gy, respectively. According the quantitative analyses of normal

tissue effects in the clinic (QUANTEC), a maximum dose to the brain of <60 Gy is associated with a probability of symptomatic necrosis <3% (30, 31). Regarding the brain stem, a volume of 1-10 ml should not receive more than 59 Gy and the maximum dose should be <54 Gy to keep the risk of late complications <5% (30, 31). Regarding the optic chiasm, doses of 55-60 Gy are associated with a risk of 3-7% of optic neuropathy, and doses <55 Gy with a risk of <3%.

During the interpretation of the results of the present study, its limitations need to be considered that include the retrospective study design (risk of hidden biases) and the comparably small sample size. Moreover, the extent of resection was previously reported to be significantly associated with survival in patients with GBM (32, 33). Since our previous study showed only a trend for such an association, this factor was not included in the present score (13). A potential reason for the lack of significance in the previous study might have been the relatively small sample size. The impact of the extent of resection on survival should be re-evaluated in a larger prospective cohort of patients.

In conclusion, a survival score that considers *MGMT* promoter methylation and can be used for patients of any age was created for patients with newly diagnosed GBM requiring radiotherapy. This new score includes three prognostic groups with significantly different median survival times and 12-month survival rates. It can contribute to treatment personalization for this group and may help designing subsequent clinical studies including randomized trials.

Conflicts of Interest

The Authors report no conflicts of interest related to the present study.

Authors' Contributions

The study was designed by all Authors. Data were collected by J.W. and analyzed by D.R. and S.E.S. The manuscript was drafted by D.R. and S.E.S. and finally approved by all Authors.

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Re-Irradiation for Recurrent Glioblastoma Multiforme

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Abstract. Background/Aim: Patients requiring re-irradiation for recurrent glioblastoma multiforme (GBM) may benefit from individualized therapy. This study aimed to identify predictors of survival and contribute to treatment personalization. Patients and Methods: In 28 patients with recurrent GBM, nine factors were analyzed for associations with survival: Main location and type of recurrence, Karnofsky performance score (KPS), age, gender, interval between primary radiotherapy and recurrence, gross total resection (GTR), equivalent dose in 2-Gy fractions (EQD2) of re-irradiation and cumulative EQD2 of primary and re-irradiation. Results: On univariate analyses, GTR (p=0.047), EQD2 ≥30 Gy (p=0.029) and cumulative EQD2 ≥90 Gy (p=0.023) were significantly associated with better survival; frontal location (p=0.119) and KPS 80-100% (p=0.067) showed trends. In multivariate analyses, frontal location (p=0.032) and cumulative EQD2 ≥90 Gy (p=0.038) were significant; KPS 80-100% (p=0.110) and EQD2 ≥30 Gy (p=0.083) showed trends. Conclusion: Predictors of survival after re-irradiation for recurrent GBM were identified that can help when designing personalized treatments. Use of irradiation with EQD2 ≥30 Gy appeared superior to lower doses.

Of all primary brain tumors in adults, glioblastoma multiforme (GBM) is the most common, with an incidence of approximately three patients per 100,000 inhabitants worldwide (1, 2). The prognoses of most patients with GBM are poor (3). In a randomized trial investigating a tri-modality treatment approach including maximum possible resection of the GBM followed by radio-chemotherapy over 6 weeks with concurrent temozolomide and additional cycles of temozolomide, median survival and 5-year survival were less than 15 months and less than 10%, respectively (4, 5). Moreover, the median time to progression of GBM was only 6.9 months (4). The majority of recurrences of GBM occur in previously irradiated areas of the brain (in-field recurrences) and many patients receive a second course of radiotherapy (re-irradiation) (2).

The prognoses of patients re-irradiated for recurrent GBM are often poor, and treatment is palliative. In a systematic review and meta-analysis, the 1-year survival rate was only 36% after re-irradiation (2). However, selected patients may benefit from more aggressive treatment programs including resection of the recurrent GBM and systemic treatment (6-11). Thus, patients with recurrent GBM would likely benefit from individualized treatment taking into account various factors associated with the patient's survival prognosis in order to avoid too aggressive treatment for those with a very short expected survival and a too limited one for longer-term survivors. In general, patients with an estimated short survival time should receive a short and minimally burdensome treatment such as short-course radiotherapy (12), whereas patients with more favorable prognoses could be candidates for a more aggressive approach including re-resection and administration of systemic therapies (6-11).

The present study aimed to identify predictors of survival in a cohort of patients receiving re-irradiation for recurrent GBM and contribute to treatment personalization for this particular group of patients. Moreover, it aimed to contribute to the definition of the optimal dose of re-irradiation

Patients and Methods

Twenty-six patients irradiated for recurrent GBM (re-irradiation) between 2005 and 2018 were included in this retrospective study, which was approved by the local Ethics Committee (University of Lübeck, reference number 15-355A). Total doses ranged between 15.0 and 60.0 Gy (median=30.0 Gy). Doses per fraction were 1.2-1.5 Gy (twice daily) or 1.8-7.0 Gy (once daily). Radiation techniques included volumetric-modulated arc therapy in 12, fractionated stereotactic radiotherapy in 10 and 3D-conformal radiotherapy in 6 patients. All patients received additional systemic treatment prior to,

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Key Words: Recurrent glioblastoma, re-irradiation, survival, prognostic factors.

Table I. *Characteristics included in the analyses of survival after a second course of radiotherapy (RT) for recurrent glioblastoma (re-irradiation).*

Factor	No. of patients (%)
Main site of recurrent GBM	
Frontal	6 (21.4)
Temporal	11 (39.3)
Parietal/occipital	7 (25.0)
Central	4 (14.3)
Type of recurrence	
In-field only	21 (75.0)
Out-field with/without in-field	7 (25.0)
Karnofsky performance score	
50-70%	15 (53.6)
80-100%	13 (46.4)
Gender	
Female	11 (39.3)
Male	17 (60.7)
Age at RT of recurrence	
≤60 Years	15 (53.6)
>60 Years	13 (46.4)
Interval between primary RT and recurrence	
≤12 Months	15 (53.6)
>12 Months	13 (46.4)
Gross total resection	
No	22 (78.6)
Yes	6 (21.4)
EQD2 of re-irradiation (re-RT)	
≤30 Gy	9 (32.1)
>30 Gy	19 (67.9)
Cumulative EQD2 of primary RT plus re-RT	
≤90 Gy	12 (42.9)
>90 Gy	16 (57.1)

GBM: Glioblastoma multiforme; EQD2: equivalent dose in 2-Gy fractions.

Table II. *Survival rates (univariate analyses) at 6 and 12 months after start of radiotherapy (RT) for recurrent glioblastoma (re-irradiation).*

Factor	6 Months (%)	12 Months (%)	*p*-Value
Main site of recurrent GBM			
Frontal	83	83	0.119
Temporal	82	18	
Parietal/occipital	86	29	
Central	25	0	
Type of recurrence			
In-field only	76	33	>0.99
Out-field with/without in-field	71	29	
Karnofsky performance score			
50-70%	67	13	0.067
80-100%	85	54	
Gender			
Female	91	27	0.62
Male	65	35	
Age at RT of recurrence			
≤60 Years	80	46	0.16
>60 Years	69	15	
Interval between primary RT and recurrence			
≤12 Months	60	27	0.30
>12 Months	92	38	
Gross total resection			
No	68	22	**0.047**
Yes	100	67	
EQD2 of re-irradiation (re-RT)			
<30 Gy	44	11	**0.029**
≥30 Gy	89	42	
Cumulative EQD2 of primary RT plus re-RT			
<90 Gy	50	8	**0.023**
≥90 Gy	94	50	
Entire cohort	75	32	

GBM: Glioblastoma multiforme; EQD2: equivalent dose in 2-Gy fractions. Statistically significant *p*-values are shown in bold.

during and/or following re-irradiation with temozolomide alone in 16, temozolomide and procarbazine/lomustine (PC) or carmustine in six, temozolomide and bevacizumab in two, procarbazine/lomustine alone in two, bevacizumab alone in one and procarbazine/lomustine PC plus bevacizumab in one patient. Resection of recurrent GBM was performed in eight patients (28.6%); in six of these, gross total resection (GTR) was achieved.

Nine potential prognostic factors were analyzed with respect to survival. These factors were: i) Main site of the recurrent GBM (frontal *vs.* temporal *vs.* parietal and/or occipital *vs.* central), ii) type of recurrence (in-field only *vs.* out-field with/without in-field), iii) Karnofsky performance score (KPS) at the time of re-irradiation (50-70% *vs.* 80-100%, median=70%), iv) gender, v) age at re-irradiation (≤60 *vs.* >60 years, median=60 years), vi) interval between end of primary radiotherapy of GBM and recurrence (≤12 *vs.* >12 months, median interval=12 months), vii) GTR of recurrent GBM (no *vs.* yes), viii) equivalent dose in 2-Gy fractions (EQD2) of re-irradiation (<30 Gy *vs.* ≥30 Gy), ix) and cumulative EQD2 of the primary radiotherapy and re-irradiation (<90 Gy *vs.* ≥90 Gy) (13, 14). Distributions of the factors are summarized in Table I.

Survival was calculated from the first day of re-irradiation. Univariate analyses were performed applying the Kaplan–Meier method and the Wilcoxon test. *p*-Values less than 0.05 were regarded as significant, and *p*-values <0.12 as indicating a trend. The significant factors were subsequently included in a multivariate analysis (Cox regression model).

Results

Median follow-up for the entire cohort was 9 months (range=2-34 months). Twenty-four patients (85.7%) died during the follow-up after median of 9 months. Median follow-up for the remaining four patients was 11 months (range=9-15 months). For the entire cohort, the survival rates at 6 months and 12 months were 75% and 32%, respectively. On univariate analyses (Table II), GTR (p=0.047), an EQD2 of re-irradiation ≥30 Gy (p=0.029, Figure 1) and a cumulative EQD2 of primary and re-irradiation ≥90 Gy (p=0.023, Figure

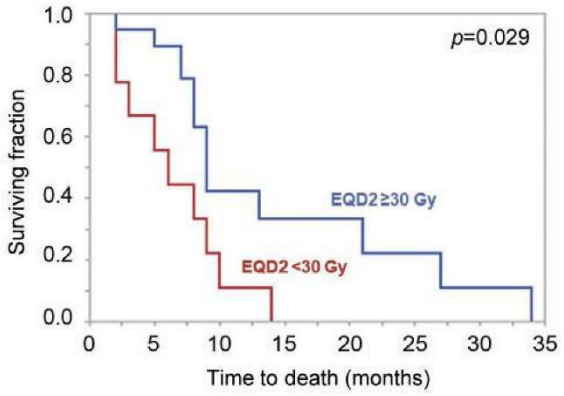

Figure 1. *Kaplan–Meier curves (univariate analysis) for the survival of patients receiving re-irradiation with an equivalent dose in 2-Gy fractions (EQD2) of ≥30 Gy vs. <30 Gy).*

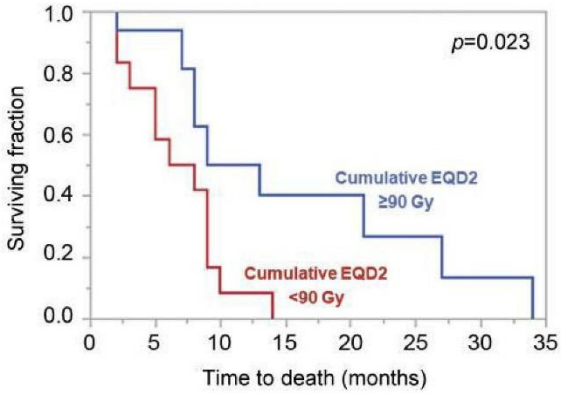

Figure 2. *Kaplan–Meier curves (univariate analysis) for the survival of patients receiving a cumulative equivalent dose in 2-Gy fractions (EQD2) of primary radiotherapy and re-irradiation of ≥90 Gy vs. <90 Gy.*

2) were significantly associated with more favorable survival. In addition, trends were found for frontal location of GBM (p=0.119) and a KPS of 80-100% (p=0.067).

In the subsequent multivariate analyses, frontal location [risk ratio (RR)=1.65, 95% confidence interval (CI)=1.04-2.68, p=0.032] and cumulative EQD2 ≥90 Gy (RR=2.57, 95% CI=1.05-6.49, p=0.038) were significantly associated with more favorable survival. KPS of 80-100% (RR=2.24, 95% CI=0.84-6.21, p=0.110) and EQD2 ≥30 Gy (RR=2.27, 95% CI=0.89-5.52, p=0.083) showed trends, and GTR (RR=2.17, 95% CI=0.66-9.71, p=0.21) was not significant.

Discussion

GBM is the most common primary brain tumor in adults and is often associated with a poor prognosis (1-3). Despite the introduction of multi-modality treatment approaches and considerable pre-clinical and clinical research, the prognoses of patients with GBM need to be improved (4, 5, 15-17). The poor prognoses are mainly the consequence of intracerebral recurrences. In the trial of Stupp *et al.*, median progression-free survival was less than 7 months after tri-modality treatment with neurosurgical resection followed by concurrent radiochemotherapy (60 Gy in 30 fractions over 6 weeks plus temozolomide) and maintenance treatment with temozolomide alone (4, 5).

When experiencing a recurrence of GBM, many patients receive re-irradiation. For this situation, the optimal dose of re-irradiation needs further clarification. Since many different dose-fractionation regimens are used for re-irradiation of recurrent GBM, the doses are often given as EQD2 in order to ensure comparability of different regimens (13, 14). The EQD2 considers both the total dose and dose per fraction and is based on the linear-quadratic model. The alpha/beta ratio represents the dose, where cell killing from the linear and the quadratic components are equal. The alpha/beta ratio for tumor cell kill is considered to be 10 Gy for the vast majority of malignant tumors. In a previous meta-analysis, no significant difference regarding outcomes after re-irradiation (external beam radiation therapy) of recurrent GBM were found between EQD2 <36 Gy and ≥36 Gy (2). However, the authors stated that in several studies included in their meta-analysis, many different dose-fractionation regimens were administered and that using the median EQD2 may not be the optimal method for defining a dose–effect relationship (2). A dose–effect relationship was found in a retrospective study of 20 patients with malignant gliomas (19 with GBM) receiving hypo-fractionated stereotactic radiotherapy (HFSRT) for persistent or recurrent disease (18). Response rates were 0% after 24 Gy in eight fractions (EQD2=26.0 Gy) and 79% after 30 Gy or 35 Gy in 10 fractions (EQD2=32.5 Gy or 39.4 Gy), respectively. In another retrospective study of 19 patients (14 with GBM, five with anaplastic astrocytoma) treated with HFSRT for recurrent disease, absolute total doses (not EQD2) of ≥30 Gy resulted in a borderline significantly better median survival than doses <30 Gy (11.1 *vs.* 7.4 months, p=0.051) (19). Since findings regarding the optimal dose of re-irradiation conflict, additional studies would help better define the optimal dose for recurrent GBM. Moreover, additional cut-off doses of the EQD2 should be investigated.

The present study compared EQD2 doses of <30 Gy to ≥30 Gy. On univariate analysis, doses ≥30 Gy were significantly superior to <30 Gy, resulting in an absolute difference of 45% points (89% *vs.* 44%) at 6 months and 31% points (42% *vs.* 11%) at 12 months. In the multivariate analysis, the results showed at least a trend. In addition, the cumulative EQD2 of

the radiotherapy of the primary GBM and re-irradiation of the recurrent GBM was significantly associated with survival in both univariate and multivariate analyses; doses ≥90 Gy were significantly superior to <90 Gy.

In addition to the appropriate dose of re-irradiation, other pre-radiotherapy factors showed a significant association with survival or at least a trend. Frontal location of recurrent GBM was significantly associated with better survival in the multivariate analysis, demonstrating the main site of GBM to be an independent predictor of survival. A better performance status (KPS of 80-100%) showed a trend for being associated with better survival in both univariate and multivariate analyses, and GTR was significantly associated with improved survival on univariate analysis. These prognostic factors can be used to support physicians who aim to select a personalized treatment for a patient with recurrent GBM. Patients with one or more of these favorable prognostic factors may benefit from longer-course radiotherapy with higher doses that may be combined with systemic treatment (6). Patients without favorable prognostic factors appear more appropriately treated with short-course radiotherapy alone such as 5×5 Gy given over 1 week (12).

When considering these suggestions, one should keep in mind the limitations of the present study. These include the limited size and retrospective nature of the data always bearing the risk of a hidden selection bias. However, the 6-and 12-month survival rates of this study (75% and 32%) were similar to those reported in the meta-analysis of Kazmi *et al.* (73% and 36%) and within the 95% confidence intervals (69-77% and 32-40%) of that meta-analysis (2). This demonstrates consistency of the data of our present study. The consistency is further supported by the fact that the three pre-radiotherapy predictors of survival were found in other studies. In 2007, Carson *et al.* presented data of 333 patients with recurrent glioma and found positive associations of survival with KPS ≥80% and with tumors confined to the frontal lobe (20). Similar results were reported in a pooled analysis of 300 patients with recurrent GBM from eight phase I or II trials (21). KPS ≥80% was significantly associated with improved survival in two studies and a pooled analysis from Germany including patients with recurrent gliomas of any grade (22-24). The value of re-resection has been shown in several studies (7-11). Two of these studies performed comparisons of re-irradiation with *vs.* without re-resection (8, 11). In the retrospective study of Skeie *et al.*, median survival times were 9 months after Gamma Knife radiosurgery alone (n=32) and 15 months after Gamma Knife radiosurgery plus re-resection (n=19) (11). In the retrospective study of Kim *et al.* that included 36 patients with recurrent GBM, surgical resection when added to stereotactic radiosurgery or HFSRT was associated with significantly improved survival (p=0.010), and the extent of resection showed a trend for being positively associated with survival (p=0.071) (8).

In summary, predictors of survival after re-irradiation for recurrent GBM were identified that can help when designing personalized treatments and future clinical trials. Use of an EQD2 of re-irradiation ≥30 Gy and a cumulative EQD2 of primary and re-irradiation ≥90 Gy appeared superior to lower doses and should be administered.

Conflicts of Interest

The Authors report no conflicts of interest related to the present study.

Authors' Contributions

The study was designed by all Authors. The data were collected by J.W. and analyzed by D.R. and S.E.S. The article was drafted by D.R. and S.E.S. and finally approved by all Authors.

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Seizures Prior to Radiotherapy of Gliomas: Prevalence, Risk Factors and Survival Prognosis

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Abstract. *Background/Aim: Seizures represent a common manifestation of gliomas. This study evaluated the prevalence of pre-radiotherapy seizures, potential risk factors and associations with survival. Patients and Methods: Eight factors were analyzed in 222 patients for associations with seizures including number, size and location of glioma, World Health Organization (WHO) grade, performance score, gender, age and upfront resection. These factors plus pre-radiotherapy symptoms and seizures were assessed for survival. Results: Prevalence of pre-radiotherapy seizures was 29.3%. A significant correlation was found for grade II (p=0.002), trends for age ≤59 years (p=0.123) and lack of upfront resection (p=0.113). Unifocal gliomas (p<0.001), grade II (p=0.045) and upfront resection (p<0.001) showed significant associations with survival (univariate analyses). A trend was found for seizures (p=0.075) and age ≤59 years (p=0.091). In the multivariate analysis, grade II (p=0.002) and upfront resection (p=0.004) maintained significance; unifocal gliomas showed a trend (p=0.062). Conclusion: Pre-radiotherapy seizures appeared to be correlated with WHO grade, age and lack of upfront resection, and with better survival.*

Gliomas represent the most common type of primary tumor in the brain (1-3). These tumors are often associated with significant symptoms including seizures (2-7). The majority of glioma-related seizures occur prior to the treatment of the glioma (8). The prevalence of pre-treatment seizures in the literature shows an extremely wide range of 9-87% (3, 9-15). For patients with glioblastomas [grade IV according to the classification of the World Health Organization (WHO)], frequencies between 9% and 45% have been reported, and for low grade gliomas (WHO grade II) frequencies between 30% and 87% (9-13). More studies are required to properly define the prevalence of pre-treatment seizures in glioma patients. Moreover, further clarification is needed with respect to potential risk factors regarding this situation (8, 9, 11, 12, 15). Risk factors may guide physicians during the phases of diagnosis and treatment, for example when considering the prophylactic use of anti-epileptic agents. Furthermore, a potential association of pre-treatment seizures in glioma patients with their survival prognoses is an important issue. The knowledge of prognostic factors for survival facilitates the development of individualized treatment protocols. This study addressed all three issues regarding pre-treatment seizures, *i.e.* prevalence, risk factors and association with survival, in a cohort of glioma patients receiving post-operative radiotherapy or radiotherapy alone.

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Key Words: Glioma, seizures, radiation therapy, prevalence, risk factors, survival.

Patients and Methods

This retrospective study included 222 patients who were irradiated for WHO grade II-IV gliomas between 2008 and 2019 (16, 17). It received approval from ethics committee at the University of Lübeck (20-120A). Radiotherapy was performed with a modern linear accelerator (Varian Medical Systems, Palo Alto, CA, USA). Median total dose was 59.4 Gy (range=50.0-60.0 Gy), and median dose per fraction was 2.0 Gy (range=1.8-2.0 Gy). Median total doses were 54 Gy for WHO grade II gliomas, 59.4 Gy for grade III gliomas and 60.0 Gy for grade IV gliomas, respectively. Two-hundred-and-four patients (91.9%) received chemotherapy, generally with temozolomide, in addition to radiotherapy (18).

In the whole series of 222 patients, the prevalence of seizures prior to radiotherapy, potential risk factors for pre-radiotherapy seizures and a potential association between such seizures and survival were assessed. For a potential association with pre-radiotherapy seizures, eight factors were analyzed including the number of glioma sites (unifocal *vs.* multifocal), main location of the glioma (frontal *vs.* parietal *vs.* temporal *vs.* other locations), cumulative size of the glioma (<40 mm *vs.* ≥40 mm), WHO grade (II *vs.* III *vs.* IV), Karnofsky performance score (≤70 *vs.* ≥80),

Table I. *Summary of the potential prognostic factors analyzed in this study.*

Factor	Number of patients (%)
Symptoms prior to radiotherapy	
No symptoms	21 (9.5)
Seizures only	12 (5.4)
Seizures+other symptoms	44 (19.8)
Other symptoms only	145 (65.3)
Seizures prior to radiotherapy	
No	157 (70.7)
Yes	65 (29.3)
Number of glioma sites	
Unifocal	179 (80.6)
Mutifocal	32 (19.4)
Unknown	11 (5.0)
Main location of glioma	
Frontal	91 (41.0)
Parietal	62 (27.9)
Temporal	38 (17.1)
Other locations	31 (14.0)
Cumulative size of glioma	
<40 mm	90 (40.5)
≥40 mm	80 (36.0)
Unknown	52 (23.4)
WHO grade	
Grade II	18 (8.1)
Grade III	41 (18.5)
Grade IV	163 (73.4)
Karnofsky performance score	
≤70	65 (29.3)
≥80	136 (61.3)
Unknown	21 (9.5)
Gender	
Female	92 (41.4)
Male	130 (58.6)
Age	
≤59 Years	119 (53.6)
≥60 Years	103 (46.4)
Upfront resection	
No	44 (19.8)
Yes	178 (80.2)

WHO: World Health Organization.

gender, age at the time of radiotherapy (≤59 *vs.* ≥60 years, median=59 years), and upfront resection of glioma (no *vs.* yes). In addition, these eight factors plus symptoms prior to radiotherapy (no symptoms *vs.* seizures only *vs.* seizures + other symptoms *vs.* other symptoms only) and pre-radiotherapy seizures (no *vs.* yes) were assessed for correlations with survival. A summary of all ten factors is given in Table I.

For statistical analyses with respect to correlations with the occurrence of pre-radiotherapy seizures, we used the Chi-square test. *p*-Values of <0.05 were considered significant, and *p*-values of <0.13 were considered indicating a trend. The univariate analyses of survival were conducted using the Kaplan-Meier method and the Wilcoxon test. Again, *p*-values of <0.13 were considered indicating a trend. Significant ($p<0.05$) factors were also included in a multivariate Cox proportional hazard model (*p*-values of <0.05= significant *p*-values).

Table II. *Associations between patient characteristics and pre-treatment seizures.*

Factor	Patients with seizures	*p*-Value
Number of glioma sites		
Unifocal (n=179)	53 (29.6%)	0.888
Mutifocal (n=32)	10 (31.3%)	
Main location of glioma		
Frontal (n=62)	16 (25.8%)	0.715
Parietal (n=38)	12 (31.6%)	
Temporal (n=91)	25 (27.5%)	
Other locations (n=31)	12 (38.7%)	
Cumulative size of glioma		
<40 mm (n=90)	24 (26.7%)	0.856
≥40 mm (n=80)	23 (28.8%)	
WHO grade		
Grade II (n=18)	10 (55.6%)	**0.002**
Grade III (n=41)	20 (48.8%)	
Grade IV (n=163)	35 (21.5%)	
Karnofsky PS		
≤70 (n=65)	16 (24.6%)	0.407
≥80 (n=136)	42 (30.9%)	
Gender		
Female (n=92)	27 (29.3%)	0.980
Male (n=136)	38 (29.2%)	
Age		
≤59 Years (n=119)	41 (34.5%)	0.123
≥60 Years (n=103)	24 (23.3%)	
Upfront resection		
No (n=44)	18 (40.9%)	0.113
Yes (n=178)	47 (26.4%)	

RT: Radiotherapy; WHO: World Health Organization; PS: performance score; bold *p*-values were significant.

Results

Pre-radiotherapy seizures were reported for 65 of the 222 patients, *i.e.* the prevalence was 29.3%. A significant positive correlation with pre-radiotherapy seizures was found for WHO grade II gliomas when compared to grade III and grade IV tumors (55.6% *vs.* 48.8% and 21.5%, $p=0.002$). Trends for positive correlations with pre-radiotherapy seizures were observed for age ≤59 years ($p=0.123$) and lack of upfront resection ($p=0.113$). The complete analyses of potential risk factors of pre-radiotherapy seizures are shown in Table II.

Significant positive associations with survival on univariate analyses (Table III) were found for unifocal gliomas ($p<0.001$), WHO grade II tumors ($p=0.045$) and upfront resection ($p<0.001$). Trends were observed for pre-radiotherapy seizures ($p=0.075$) and age ≤59 years ($p=0.091$). In the multivariate analysis, grade II ($p=0.002$)

Table III. *Survival rates up to 3 years after radiotherapy (univariate analyses).*

Factor	1 year (%)	2 years (%)	3 years (%)	*p*-Value
Symptoms prior to RT				
No symptoms (n=12)	80	69	55	0.361
Seizures only (n=21)	90	83	69	
Seizures+others (n=44)	92	66	59	
Others only (n=145)	79	67	61	
Seizures prior to RT				
No (n=157)	79	67	60	0.075
Yes (n=65)	91	71	62	
Number of glioma sites				
Unifocal (n=179)	85	72	63	**<0.001**
Mutifocal (n=32)	65	39	39	
Main location of glioma				
Frontal (n=62)	81	64	51	0.130
Parietal (n=38)	88	74	74	
Temporal (n=91)	87	76	67	
Other locations (n=31)	70	51	51	
Cumulative size of glioma				
<40 mm (n=90)	83	62	56	0.642
≥40 mm (n=80)	84	73	63	
WHO grade				
Grade II (n=18)	100	94	94	**0.045**
Grade III (n=41)	90	73	57	
Grade IV (n=163)	78	62	57	
Karnofsky PS				
≤70 (n=65)	83	60	53	0.235
≥80 (n=136)	84	70	62	
Gender				
Female (n=92)	82	66	63	0.543
Male (n=136)	83	69	59	
Age				
≤59 Years (n=119)	87	74	65	0.091
≥60 Years (n=103)	77	60	55	
Upfront resection				
No (n=44)	65	47	39	**<0.001**
Yes (n=178)	87	72	65	

RT: Radiotherapy; WHO: World Health Organization; PS: performance score; bold *p*-values were significant.

and upfront resection (p=0.004) maintained significance; unifocal gliomas showed a trend (p=0.062) (Table IV).

Discussion

In many glioma patients, the occurrence of seizures is the first clinical manifestation of their brain tumor (8). Seizures can have a considerable negative impact on the patients' quality of life (19, 20). A better understanding of the role of seizures for glioma patients may contribute to improvement of their treatment. The current study was initiated to contribute to the knowledge of the clinical meaning of seizures for patients irradiated for WHO grade II-IV gliomas. It investigated the prevalence of pre-radiotherapy seizures, potential risk factors

Table IV. *Multivariate analysis using the Cox proportiona hazard model.*

Factor	Hazard ratio	95%-Confidence interval	*p*-Value
Number of glioma sites	1.95	0.97-3.72	0.062
WHO grade	1.96	1.26-3.30	**0.002**
Upfront resection	2.54	1.36-4.57	**0.004**

WHO: World Health Organization; bold *p*-values were significant.

and a potential association with survival. The prevalence of seizures prior to radiotherapy was 29.3%, which was well within the range of 9-87% in the literature (3, 9-15). The prevalence for glioblastoma patients was 21.5%, which also corresponded well to the previously reported rates of 9-45% (9-13). Similarly, the prevalence of pre-radiotherapy seizures (55.6%) in our patients with WHO grade II tumors was also within the range of 30-87% reported in the literature (9-12). Less data are available specifically for pre-treatment seizures in patients with WHO grade III gliomas. However, in a systematic review, seizure rates of 29-67% have been reported for patients with grade III tumors during the course of their neurological disease (3). The prevalence of 48.8% found in the present study was within this range.

According to the results of the present study, the WHO grade was significantly associated with the occurrence of pre-radiotherapy seizures. The highest prevalence of seizures was found for low-grade gliomas. These findings agree with the results of previous studies and reviews. In a retrospective study of 492 patients with primary and metastatic brain tumors including 334 glioma patients, the occurrence of pre-operative seizures was significantly associated with WHO grade I-II glioma when compared to grade III-IV glioma (odds ratio=4.0, p<0.001) (15). In another retrospective study of 190 patients with astrocytic tumors, the rates of preoperative seizures were 34%, 29% and 18%, respectively, in patients with grade II, III and IV tumors (11). The same group presented another study of 101 patients aged ≥45 years with supratentorial astrocytic tumors and reported pre-operative seizures in 35% (grade II), 11% (grade III) and 9% (grade IV) of these patients, respectively (12). In the review article of Fan *et al*., 30-87% of patients with low-grade gliomas and 21-33% of glioblastoma patients had seizures at first presentation (10). Moreover, in a larger retrospective study of 1,028 patients, the prevalence of seizures during the entire course of the disease was 85% (322 of 379 patients) for patients with low-grade gliomas, 69% (95 of 137 patients) for patients with anaplastic gliomas and 49% (251 of 512 patients) for glioblastoma patients, respectively (21).

In addition to the WHO grade, trends for correlations with pre-radiotherapy seizures were found for age ≤59 years and

lack of upfront resection. Younger age has been previously described as risk factor for pre-treatment seizures. In the study of Hwang *et al.*, patients <40 years had a higher risk of pre-operative seizures than older patients (odds ratio=3.08, p=0.013) (11). In the study of Kaloshi *et al.*, who compared 62 patients with supratentorial low-grade gliomas aged ≥60 years to 704 younger patients, seizures as initial symptom of glioma were found in 85% and 47% of the patients, respectively (p<0.001) (22). In the study of Skardelly *et al.*, that included also patients with brain metastases, patients ≤60 years had a higher risk of pre-operative seizures than patients >60 years (odds ratio=1.66, p=0.020) (15). Lote *et al.* have reported an inverse correlation between pre-treatment seizures and age for glioblastoma patients (p<0.01) (21). However, in younger patients with low-grade glioma (<40 years), the risk of seizures increased with age (p<0.01) developing a plateau in patients ≥40 years. The association between pre-radiotherapy seizures and lack of upfront resection can be explained by the fact that resection of glioma leads to a significant reduction of seizures with post-operative rates of freedom from seizures of 43-87% (23, 24). In addition, some authors have reported tumor location as risk factor for glioma-related seizures, although the reports showed some disagreement regarding the site. In the review articles of Kerkhof & Vecht and Englot *et al.*, temporal location was associated with the highest prevalence of seizures, whereas in the study of Skardelly *et al.*, the highest seizure rate was found for frontal location (8, 9, 15). In the present study, a significant association between pre-radiotherapy seizures and location of the glioma was not detected, similar to several previous studies (11-13).

In the current study, pre-radiotherapy seizures showed a trend for an association with survival. A significant association has been previously reported in a large study of 1,028 glioma patients including 649 patients with high grade tumors for the entire cohort and patients with high-grade tumors but not for patients with low-grade tumors (21). However, other studies have found significant associations between seizures and improved survival for patients with low-grade gliomas (9, 25-27). Moreover, in the present study, improved survival was independently associated with lower WHO grade and upfront resection. In addition, unifocal glioma showed a trend in the multivariate analysis and age ≤59 years a trend on univariate analysis. These four factors have been previously demonstrated to be significantly associated with more favorable survival prognoses (6, 10, 27-29). This agreement with previous data revealed consistency of the findings of the current study. Despite this, the retrospective study design and the risk of a hidden selection bias should be considered during the interpretation of this study.

In summary, the prevalence of pre-radiotherapy seizures was 29.3% in the entire cohort, 55.6% in patients with low grade (WHO grade II) gliomas, 48.8% in patients with anaplastic (grade III) gliomas and 21.5% in patients with glioblastomas (grade IV). Occurrence of pre-radiotherapy seizures appeared to be correlated with lower WHO grade, younger age and lack of upfront resection, and seizures appeared to be associated with more favorable survival. The findings of this study will contribute to the knowledge regarding the meaning of pre-radiotherapy seizures in patients irradiated for WHO grade II-IV gliomas.

Conflicts of Interest

The Authors state that there are no conflicts of interest regarding this study.

Authors' Contributions

J.W., T.W.K., S.T., S.E.S. and D.R. participated in the design of the study. J.W. collected the data that were analyzed by J.W., S.E.S. and D.R. Interpretation of the data was performed by all Authors. J.W., S.E.S. and D.R. drafted the manuscript, which was reviewed and approved in its final form by all Authors.

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Re-Evaluation of Prognostic Factors for Survival After Radiotherapy of Cerebral Gliomas: A Supplementary Analysis to a Previous Study

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Abstract. *Background/Aim: Previously, we identified predictors of survival after irradiation of grade II-IV cerebral gliomas. In this supplementary analysis, survival was calculated in a more appropriate way than the original study. Patients and Methods: Ten factors were re-evaluated for survival in patients of the original study including pre-radiotherapy seizures. In the original study, survival was calculated from the end of the last radiotherapy course (primary or re-irradiation). After re-review, this approach was considered inappropriate. Survival should have always been calculated from the first radiotherapy course, as done in this supplementary analysis. Results: On multivariate analysis, WHO-grade II (p=0.006) and upfront resection (p=0.001) were associated with better survival. Unifocal glioma was significant on univariate analysis (p=0.001), where a trend could be identified for age ≤59 years (p=0.057) and seizures (p=0.060). Conclusion: The findings of this supplementary analysis regarding the identification of prognostic factors for survival agree with the results of the original study.*

Cerebral gliomas can be associated with seizures that mainly occur prior to treatment (1). Previous studies suggested that pre-treatment seizures are associated with better survival prognoses (2-5). Possible explanations include that seizures may lead to earlier diagnosis of a glioma, that slower-growing gliomas have a greater tendency to be associated with seizures, and that gliomas associated with seizures may be a special glioma subtype (3-6).

Recently, we presented a study focusing on pre-radiotherapy seizures in patients irradiated for cerebral gliomas of grade II-IV, according to the World Health Organization (WHO) classification (7). In this original study, a trend was found for a positive association between pre-radiotherapy seizures and survival (7). However, survival was calculated from the end of the last radiotherapy course (primary radiotherapy or re-irradiation). After additional review, this approach was considered inappropriate. Survival should have always been calculated from the first radiotherapy course administered for treatment of cerebral glioma. Therefore, this supplementary analysis was performed and death was calculated from the last day of the initial radiotherapy.

Patients and Methods

This supplementary analysis was performed in the cohort of 222 patients receiving radiotherapy for grade II-IV cerebral gliomas analyzed in the previous study, which was approved by the ethics committee of the University of Lübeck (reference: 20-120A) (7). As in the previous study, ten factors were analyzed for associations with survival including symptoms prior to radiotherapy (none, seizures only, seizures plus other symptoms, other symptoms only), pre-radiotherapy seizures (no, yes), number of sites (unifocal glioma, multifocal glioma), main site(s) of glioma (frontal, parietal, temporal, other sites), cumulative diameter (<40mm, ≥40mm), WHO-grade (II, III, IV), Karnofsky performance score (≤70%, ≥80%), gender (female, male), age (≤59 years, ≥60 years) and upfront resection (no, yes) (Table I). In this new analysis, time to death was calculated in all patients from the last day of the first radiotherapy course given to treat a cerebral glioma. In the original study, survival was calculated from the end of the last radiotherapy course, which could have been the end of primary radiotherapy or the end of re-irradiation for recurrent or new gliomas (7).

In the current analysis, the Kaplan-Meier method and Wilcoxon-test were applied for univariate analyses. A p-value <0.05 indicated

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Key Words: Cerebral glioma, radiotherapy, survival, prognostic factors, re-evaluation.

Table I. *Univariate analyses of survival.*

Factor		1 year (%)	2 years (%)	3 years (%)	*p*-Value
Symptoms prior to radiotherapy	No symptoms (n=12)	82	72	72	0.30
	Seizures only (n=21)	90	84	70	
	Seizures+others (n=44)	95	68	57	
	Others only (n=145)	79	69	62	
Seizures prior to radiotherapy	No (n=157)	79	70	64	0.060
	Yes (n=65)	93	74	61	
Number of glioma sites	Unifocal (n=179)	85	74	66	**0.010**
	Mutifocal (n=32)	71	52	37	
Main location of glioma	Frontal (n=62)	81	65	52	0.11
	Parietal (n=38)	88	80	80	
	Temporal (n=91)	87	77	69	
	Other locations (n=31)	74	56	50	
Cumulative size of glioma	<40 mm (n=90)	83	68	59	0.77
	≥40 mm (n=80)	83	73	63	
WHO-grade	Grade II (n=18)	100	94	94	**0.035**
	Grade III (n=41)	93	76	58	
	Grade IV (n=163)	79	66	61	
Karnofsky performance score	≤70% (n=65)	83	64	59	0.28
	≥80% (n=136)	85	73	64	
Gender	Female (n=92)	82	69	63	0.54
	Male (n=136)	84	72	62	
Age	≤59 Years (n=119)	88	77	68	0.057
	≥60 Years (n=103)	78	62	54	
Upfront resection	No (n=44)	65	49	41	**<0.001**
	Yes (n=178)	88	75	67	

WHO: World Health Organization; bold *p*-values indicate significance. If the sum of the numbers of patients for a factor is less than 222, no data were available for the missing patients regarding this factor.

a significant association with survival. In case of a *p*-value <0.10, the situation was defined as showing a trend. Significant factors were additionally analyzed with a multivariate Cox proportional hazard model, where *p*-values <0.05 were considered significant.

Results

Median follow up was 14.5 (0-123) months in the entire cohort and 17 (3-123) months in those patients alive at the last contact. Median survival was 60 months, and survival rates at 1, 2 and 3 years were 83%, 71% and 62%, respectively. On univariate analyses (Table I), unifocal glioma (p=0.010), WHO-grade II (p=0.035) and upfront resection (p<0.001) were significantly associated with better survival. Trends were found for pre-radiotherapy seizures (p=0.060) and age ≤59 years (p=0.057). WHO-grade [hazard ratio (HR)=1.98, 95%-confidence interval (CI)=1.27–3.37, p=0.002] and resection (HR=2.67, 95%-CI=1.45–4.74, p=0.004) were significant in the multivariate analysis, where unifocal glioma was not significant (HR=1.70, 95%-CI=0.85–3.18, p=0.11). Survival rates of grade IV gliomas appeared very high. Since of the 115 surviving patients with grade IV glioma 47, 86 and 100 patients, respectively, had follow up times of <1 year, <2 years and <3 years, several deaths might have been missed in this retrospective study.

Discussion

Seizures can be the first symptom that leads to the diagnosis of a cerebral glioma (1). Pre-treatment seizures have been reported to be associated with improved survival. In the study of Lote *et al.* including both low-grade and high-grade gliomas, a significant association between seizures and survival was found in the multivariate analyses of the entire cohort (relative risk of death=0.83, 95%-confidence interval=0.70-0-98, $p<0.03$) and in patients with high-grade gliomas (relative risk of death=0.80, 95%-confidence interval=0.66-0-96, $p<0.02$) (2). In the group with low-grade tumors, a significant association was not even observed on univariate analysis ($p>0.2$). In contrast to Lote *et al.*, other studies found a positive association between seizures and survival in patients with low-grade gliomas (6, 8, 9). In our original study, occurrence of pre-radiotherapy seizures showed a trend ($p=0.075$) for an association with better survival on univariate analysis (7). In our original study, WHO-grade II (HR=1.96, 95%-CI=1.26-3.30, $p=0.002$) and upfront resection (HR=2.54, 95%-CI=1.36-4.57, $p=0.004$) were identified as independent predictors of survival in the multivariate analysis. In addition, unifocal glioma was significant on univariate

analysis ($p<0.001$) and showed a trend in the multivariate analysis (HR=1.96, 95%-CI=0.97-3.72, $p=0.062$). For age ≤59 years, a trend was found on univariate analysis ($p=0.091$). Positive associations between these factors and survival of glioma patients were previously described (10-14), consistent with the results of our study (7). However, in our original study, survival was calculated from the end of the last radiotherapy course, which was re-irradiation for recurrent or new gliomas in some patients, but should have always been calculated from the end of the first radiotherapy course for cerebral glioma (7). Therefore, the survival data of the original study were re-evaluated by calculating the time to death from the last day of the initial radiotherapy course in all patients. As in the original study, WHO-grade II and upfront resection proved to be independent predictors of better survival in the current supplementary analysis (7). For occurrence of pre-radiotherapy seizures and age ≤59 years, trends for improved survival were found on univariate analysis, which agreed well with our original study. On univariate analysis, unifocal glioma was significantly associated with better survival in both the original and the current study. Unifocal glioma showed a trend for better survival in the multivariate analysis of the original study (p=0.062), which was not observed in this analysis (p=0.11). However, both results were not significant.

In conclusion, the findings of the current analysis regarding the identification of prognostic factors for survival agree with the results of the original study. The identified prognostic factors can contribute to better treatment personalization in future patients with cerebral gliomas and can be used for proper stratification in future clinical trials.

Conflicts of Interest

The Authors state that there are no conflicts of interest regarding this study.

Authors' Contributions

J.W., T.W.K., S.T., S.E.S. and D.R. participated in the design of this additional study. Data were collected by J.W., analyzed by S.E.S. and D.R. and interpreted by all Authors. S.E.S. and D.R. drafted the manuscript that has been reviewed and finally approved by all Authors.

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STUDY PROTOCOL Open Access

A prospective interventional study evaluating seizure activity during a radiotherapy course for high-grade gliomas (SURF-ROGG)

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Abstract

Background: Gliomas are often associated with symptoms including seizures. Most patients with high-grade gliomas are treated with radiotherapy or radio-chemotherapy. Since irradiation causes inflammation, it may initially aggravate symptoms. Studies focusing on seizure activity during radiotherapy for gliomas are not available. Such knowledge may improve patient monitoring and anti-epileptic treatment. This study evaluates seizure activity during radiotherapy for high-grade gliomas.

Methods: The primary objective this prospective interventional study is the evaluation of seizure activity during a course of radiotherapy for high-grade gliomas. Progression of seizure activity is defined as increased frequency of seizures by > 50%, increased severity of seizures, or initiation/increase by ≥25% of anti-epileptic medication. Seizure frequency up to 6 weeks following radiotherapy and electroencephalography activity typical for epilepsy will also be evaluated. Patients keep a seizure diary during and up to 6 weeks following radiotherapy. Every day, they will document number (and type) of seizures and anti-epileptic medication. Once a week, the findings of the diary are checked and discussed with a neurologist to initiate or adjust anti-epileptic medication, if necessary. Patients complete a questionnaire regarding their satisfaction with the seizure diary. If the dissatisfaction rate is > 40%, the seizure diary will be considered not suitable for the investigated indication. Thirty-five patients (32 patients plus drop-outs) should be enrolled. With this sample size, a one-sample binomial test with a one-sided significance level of 2.5% has a power of 80% to yield statistical significance, if the rate of patients with progression of seizure activity is 30% (rate under the alternative hypothesis), assuming a 'natural' background progression-rate of 10% without radiotherapy (null hypothesis).

Discussion: If an increase in seizure activity during a course of radiotherapy for high-grade glioma occurs, the findings of this study may pave the way for a larger prospective trial and will likely lead to closer patient monitoring and better anti-epileptic treatment.

Trial registration: clinicaltrials.gov (NCT04552756); registered on 16th of September, 2020.

Keywords: High-grade glioma, Seizures, Radiotherapy, Radio-chemotherapy, Seizure diary

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Background

Gliomas represent the most common type of primary brain tumors and are frequently associated with clinical symptoms including seizures [1–7]. The majority of patients with high-grade gliomas (grade III or IV according to the classification of the World Health Organization) receive radiotherapy with or without chemotherapy, either as adjuvant treatment after neurosurgical resection or as definitive treatment after biopsy. Due to an acute inflammatory reaction associated with edema in the irradiated area of the brain and subsequent increase of intracranial pressure, radiotherapy may lead to onset or progression of clinical symptoms including seizures during the course of treatment [8, 9]. To our knowledge, no studies are available that focused on the subacute effect of radiotherapy on seizure activity during a course of radiation treatment in glioma patients. These data would be important to improve monitoring and anti-epileptic treatment of these patients. This study evaluates the seizure activity during radiotherapy for high-grade (grade III or IV) gliomas.

Methods and design

This single-arm prospective interventional study performed at a single academic center will evaluate the seizure activity during radiotherapy of high-grade gliomas. The study has been approved by the local ethics committee (University of Lübeck, no. 20–311) and registered at clinicaltrials.gov (identifier: NCT04552756).

Objectives and endpoints

Primary objective is the evaluation of seizure activity during a course of radiotherapy for high-grade gliomas. Progression of seizure activity during the course of radiotherapy compared to baseline is defined as increase of frequency of seizures by more than 50%, increase of severity of seizures (i.e. increase of generalized seizures by more than 50%), or increase of the dose of anti-epileptic medication by at least 25% or initiation of anti-epileptic medication. The latter criterion was defined in accordance with another situation in radiation oncology, radiotherapy of painful bone metastases [10]. These parameters will be assessed using a seizure diary kept by the patients during the course of radiotherapy. In addition, seizure frequency up to 6 weeks following radiotherapy (seizure diary), patient satisfaction with the seizure diary, and electroencephalography (EEG) activity typical for epilepsy will be evaluated.

Eligibility criteria

Inclusion criteria include histologically proven newly diagnosed or recurrent grade III or IV glioma (associated or not associated with seizures), indication for normofractionated radiotherapy, Eastern Cooperative Oncology Group performance score 0–2, age ≥ 18 years, written informed consent (taken by physicians registered as investigators for this trial), and capacity of the patient to cooperate (including the use of a seizure diary). Exclusion criteria include pregnancy/lactation and limited legal capacity or being under legal supervision.

Assessments

Parameters assessed prior radiotherapy include demographics (age, date of birth, gender), medical history, concomitant diseases, concomitant medication including anti-epileptic treatment, physical examination, histology and grade of glioma, upfront surgery, and planned radiotherapy/radio-chemotherapy.

The following parameters will be assessed during the trial (Fig. 1):

1. Seizure frequency

The patients keep a seizure diary during radiotherapy and up to 6 weeks following radiotherapy. Every day, the patients document the number and type of seizures and intake of anti-epileptic medication. At the end of radiotherapy, the patients are asked to complete a questionnaire regarding their satisfaction with the seizure diary.

2. Objective assessment of seizure activity

To obtain an objective assessment of seizure activity in addition to patient reported outcomes, an EEG is performed during the first and sixth week of radiotherapy, and during the sixth week following radiotherapy.

3. Adverse Events

Adverse events other than seizures will be assessed on an ongoing basis according to CTCAE v5.0 [11].

In addition, potential prognostic factors regarding the increase of seizure activity during the course of radiotherapy will be evaluated including seizure activity at baseline, age, gender, glioma grade, recurrent glioma, isocitrate dehydrogenase (IDH1/2) mutation status, methylation of the O^6-methylguanine-DNA methyltransferase (MGMT) gene promoter, tumor site, tumor size, cortical involvement and extent of upfront surgery.

Interventions

Patients receive the same standard treatment for high-grade glioma as they would have received without participation in this study. If necessary, any care and interventions are permitted during the trial for treatment-related events and other types of comorbidity.

	STUDY PERIOD					
	Enrolment	Allocation Baseline	Post-Allocation			Close-out
TIMEPOINT	Month -1 to Month 0	Month -1 to Month 0	Weekly during RT (weeks 1 - 6-6.5, depending on duration of RT*)	End of RT*	Weekly during weeks 7 - 12 (weeks 1-6 following RT*)	6 weeks after RT*
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
Radiotherapy*			◆———			
Seizure diary		X	X	X	X	X
Electroecephalpography (EEG)			X[a]		X[b]	
ASSESSMENTS:						
Demographics, medical history, concomitant diseases and medication, physical examination, histology, grade of glioma, upfront surgery, planned radiotherapy and chemotherapy		X				
Patient-reported seizure activity (seizure diary)		X	X	X	X	X
Objective assessment of seizure activity (EEG)			X[a]		X[b]	
Adverse events			X	X	X	X
Treatment given as planned?			X	X	X	X
Satisfaction with seizure diary				X		

*RT= radiotherapy; a = during the first and the sixth week of radiotherapy; b = during the sixth week following radiotherapy

Fig. 1 Timeline of enrolment, interventions and assessments of the SURF-ROGG trial

Glioblastoma (grade IV)

The treatment of glioblastomas includes resection or biopsy of the tumor followed by radiotherapy of the tumor region plus margins. Radiotherapy is performed with a high-precision technique, i.e. volumetric modulated arc therapy (VMAT). Glioblastoma patients with a Karnofsky performance score ≥ 70 and younger than 70 years generally receive normo-fractionated radiotherapy [12]. This applies also to patients aged ≥70 years with methylation of the MGMT gene promoter [12]. The dose-fractionation regimen depends on the proximity of the tumor to structures and organs at risk and is either 30 × 2.0 Gy over 6 weeks or 33 × 1.8 Gy over 6.5 weeks. Tolerance doses of the structures and organs at risk will be considered using the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) [13].

Radiotherapy should be combined with temozolomide (TMZ), whenever reasonable. TMZ is given concurrently with radiotherapy plus sequentially following radiotherapy. The dose of concurrent TMZ is 75 mg/m2/day, administered on 7 days per week during the entire course of radiotherapy. Concurrent treatment is followed by 6 courses of sequential TMZ (150–200 mg/m2/day on 5 consecutive days every 4 weeks).

Anaplastic astrocytoma and anaplastic oligodendroglioma (grade III)

The treatment of grade III gliomas also includes resection or biopsy of the tumor. Postoperative treatment varies between anaplastic astrocytomas and anaplastic oligodendrogliomas. Most patients receive postoperative radiotherapy. Anaplastic astrocytomas with IDH1/2 wild type are generally treated like glioblastomas. If anaplastic astrocytomas show an IDH1/2 mutation, postoperative treatment starts with radiotherapy alone followed by sequential chemotherapy with TMZ (150–200 mg/m2/day on 5 consecutive days every 4 weeks) or 4 courses of PCV including procarbazine (60 mg/m2 on days 8–21),

lomustine (110 mg/m2/day on day 1) and vincristine (1.4 mg/m2/day, maximum absolute dose = 2.0 mg, on days 8 and 29, every (6-)8 weeks) [12]. To reduce toxicity, vincristine may be omitted. In case of an IDH1 mutation, astrocytomas and oligodendrogliomas can be differentiated by the 1p/19q co-deletion. Astrocytomas do not have a 1p/19q co-deletion, whereas the co-deletion is present in oligodendrogliomas. Postoperative treatment of anaplastic oligodendrogliomas with IDH mutation and 1p/19q co-deletion starts with radiotherapy alone followed by chemotherapy with 4 courses of PCV [12]. Again, vincristine may be omitted to reduce treatment-related toxicity.

Seizure diary

The patients keep a seizure diary during the period of radiotherapy and up to 6 weeks following radiotherapy. Every day, the patients document the number and type of seizures and intake of anti-epileptic medication.

Once a week during the radiotherapy course, the seizure diary will be reviewed by a medical staff member. During the 6 weeks following radiotherapy, the patients are contacted by phone (to minimize the number of visits to the hospital) once a week to obtain the information from the seizure diary. During and following radiotherapy, the weekly findings of the seizure diary are discussed with a neurologist to initiate or adjust anti-epileptic medication, if necessary. At the end of radiotherapy, the patients are asked to complete a questionnaire regarding their satisfaction with the seizure diary. In case of a dissatisfaction rate > 40%, the seizure diary will be considered not suitable for patients with high-grade gliomas.

Electroencephalography (EEG)

The patients receive an EEG during the first and the sixth week of radiotherapy, as well as during the sixth week following radiotherapy. Activity typical for epilepsy includes spike waves, sharp waves and/or sharp slow waves and is classified as absent or present.

Sample size calculations

The main goal of the study is to generate objective data on the occurrence, frequency and severity of seizures and the use of anti-epileptic medication during the course of radiotherapy applying standardized questionnaires, in order to evaluate the potential effect of radiotherapy in patients with high-grade gliomas and generate hypotheses. Thirty-two patients are required for the statistical analyses. Assuming that 10% of patients do not fulfil these requirements, a total of 35 patients should be enrolled to this trial. With this sample size, a one-sample binomial test with a one-sided significance level of 2.5% has a power of 80% to yield statistical significance if the rate of patients with progression of seizure events during the course of radiotherapy is 30% (rate under the alternative hypothesis), assuming a 'natural' background progression-rate of 10% without radiotherapy (null hypothesis). The latter rate was chosen after discussions with experienced neurologists. If the natural course of the disease would lead to a progression-rate of 5% without radiotherapy, the power increases to 98%. Recruitment should be completed within 12 months. The radiotherapy period is 6–6.5 weeks, and follow up is 6 weeks. Thus, duration of the trial is about 15 months.

Statistical methods for investigated endpoints

The focus of the statistical analysis is descriptive and exploratory in nature. If statistical tests are applied, they are to be interpreted on an exploratory perspective. All data recorded in the case report forms describing the study population (demographic and clinical characteristics, at baseline) will be analyzed descriptively. Categorical data will be presented in tables with frequencies and percentages. Continuous data will be summarized with at least the following: Frequency (n), median, quartiles, mean, standard deviation (standard error), minimum and maximum. Number of patients with protocol deviations during the study and listings describing the deviations will be provided. The seizure frequency at baseline and during the course of radiotherapy will be calculated by summing the number of seizures in each period and dividing by the total duration (days), excluding days with no available diary data, and multiplying by 7 to normalize to a weekly rate. The resulting normalized frequencies form the basis for calculating the composite primary endpoint. The point estimate of the rate of progressors and the associated 95% confidence interval will be presented. To test whether the rate of progressions is significantly increased beyond 10%, the one-sided binomial test at a one-sided 2.5% significance level will be applied.

Furthermore, a logistic regression model including baseline seizure including seizure activity at baseline, age (≤59 vs. ≥60 years), gender, glioma grade (grade III vs. IV), recurrent glioma (no vs. yes), IDH1/2 mutation status (mutation vs. wild type), methylation of the MGMT gene promoter (yes vs. no), tumor site (frontal vs. temporal vs. parietal vs. other sites), tumor size (≤ median vs. > median), cortical involvement (yes vs. no) and extent of surgery (no resection/biopsy only vs. subtotal resection vs. gross total resection) will be fitted to identify potentially relevant prognostic factors [14].

Adjusted odds ratios and 95% confidence interval (Wald $\chi 2$) will be derived. In addition, each component of the primary composite endpoint will be subjected to a separate statistical analysis using the same methods

described above. For exploratory purposes, the analyses described above will also be conducted by focusing on the seizures classified as generalized and generalized/grand mal only.

In order to describe the time profiles of seizure frequencies in more detail, normalized seizure frequencies over time will be calculated within 3-week intervals, namely weeks 1–3 and 4–6 during radiotherapy, and weeks 1–3 (7–9 in total) and 4–6 (10–12 in total) following radiotherapy. These frequencies will be subjected to descriptive statistics as well as graphical presentations by means of box-and whisker diagrams. For exploratory purposes, the Wilcoxon signed-rank test will be applied to compare the two-time windows during the course of radiotherapy; the Friedman-Test will be applied to assess whether there is any difference in seizure frequencies between all of the time intervals during the course of radiotherapy and thereafter.

In addition, the percent change from baseline in seizure frequency will be considered and subjected to descriptive analysis. For further exploratory analysis, the rates of patients experiencing any seizure (yes/no) at baseline and at each time interval will be estimated together with their associated confidence intervals. Subsequent analyses focus on the clinically relevant generalized seizures only.

Patient satisfaction with the seizure diary will be assessed at the end of radiotherapy using a questionnaire and subjected to descriptive analysis. In case of a dissatisfaction rate > 40%, the seizure diary will be considered not suitable for patients with high-grade gliomas. EEG activity typical for epilepsy will be performed during the first and sixth week of radiotherapy, and the sixth week following radiotherapy. EEG activity typical for epilepsy is classified as absent or present. Statistical analysis is focused on data description only. A mean change to baseline (during first week of radiotherapy) by 50% regarding the number of patients with EEG activity typical for epilepsy will be considered clinically relevant.

Data management and monitoring

Patients can be identified only by the individual patient number, date of birth and gender. A patient list will be kept at the trial center alone. The data will be pseudonymized prior to analyses and handled in accordance with the General Data Protection Regulation. Originals of the key trial documents will be stored at the contributing center (sponsor's site) for at least 10 years following the final report. The principal investigator will store administrative documents, the patient list, signed informed consent forms, copies of documentation forms and general documentation. Original patient files must be kept for 30 years according to the German regulations for radioprotection. Initiation of the study and on-site monitoring will be performed by the ZKS Lübeck. Regular audits are not planned but may be performed if considered necessary. Since this trial is not related to the German pharmaceutical or medicinal product act, inspections of higher federal authorities are not scheduled. A data monitoring committee is not necessary, because the patients do receive the same treatment for high-grade glioma as outside this trial. The coordinating investigator will work towards comprehensive dissemination of the study findings. Coordinating investigator, biostatistician and staff members involved in the trial will provide a study report. Study results will be published in a peer-reviewed journal and are planned to be presented at scientific meetings. Publications will be coordinated with and supported by a professional biostatistician. For publications the acronym SURF-ROGG will be used. Data analysts and statisticians are blinded.

Discussion

Primary brain tumors such as gliomas can be associated with seizures. For patients with grade III or IV gliomas, pre-treatment seizure rates of 29–67% and 9–45%, respectively, were reported [3, 15–19]. Moreover, in a study from our group, the prevalence of seizures prior to radiotherapy was 48.8% in patients with grade III gliomas and 21.5% in patients with grade IV gliomas, respectively [14].

Radiotherapy improves long-term seizure outcomes in glioma patients. In a retrospective study of 43 patients with diffuse gliomas (33 patients with a grade II glioma and 10 patients with a grade III glioma), seizure reduction of ≥50% compared to baseline was observed in 31 patients (72%) at 3 months following radiotherapy [20]. Moreover, in a randomized trial comparing early radiotherapy with 54 Gy in 30 fractions to radiotherapy performed only at the time of progression, seizure control at 1 year was better in the early radiotherapy group [21]. However, during the course of radiotherapy, seizures may occur for the first time or the frequency of seizures may increase, because radiotherapy leads to an acute inflammatory reaction, which can be associated with edema and increased intracranial pressure [8, 9]. In 2004, Bhansali et al. reported 11 patients with radiation-induced brain disorders [8]. Four of these patients (36%) had developed generalized seizures. In a review article published in 2007, seizures were reported to be symptoms of both acute radiation encephalopathy and late radiation-related necrosis [9]. However, no study has been available so far that evaluated the effect of irradiation to the brain on seizure activity during the course of radiotherapy for high-grade gliomas. However, these data would be very important in order to improve the monitoring and, if required, the anti-epileptic treatment of these patients. Therefore, the SURF-ROGG trial has

been designed that will evaluate the seizure frequency during a course of radiotherapy for high-grade (grade III or IV) gliomas. Patients with low-grade (grade I or II) gliomas will not be included, because the treatment of these tumors and the dose-fractionation of radiotherapy are almost always different from the treatment of high-grade tumors [12].

In this trial, progression of seizure activity is defined as increase of seizure frequency by more than 50%, increase of severity of seizures (i.e. increase of generalized seizures by more than 50%), or initiation or increase of anti-epileptic medication by at least 25%. Evaluation of seizure activity is mainly based on patient-reported outcomes, i.e. on a seizure diary kept by the patients during the period of radiotherapy and up to 6 weeks following radiotherapy. Every day, the patients document the number and type of seizures, as well as the intake of anti-epileptic medication. At the end of radiotherapy, the patients are asked to complete a questionnaire regarding their satisfaction with the seizure diary. In addition to the patient-reported outcomes, EEG activity typical for epilepsy will be evaluated to receive also objective data.

If the SURF-ROGG trial shows an increase in seizure activity during the course of radiotherapy for high-grade gliomas, the findings of this trial may pave the way for a larger prospective trial and will likely contribute to closer patient monitoring and better anti-epileptic treatment.

Abbreviations

CTCAE: Common Terminology Criteria for Adverse Events; EEG: Electroencephalography; GCP: Good Clinical Practice; IDH: Isocitrate Dehydrogenase; MGMT: O^6-Methyl-Guanine-DNA Methyl-Transferase; PCV: Procarbazine, Lomustine and Vincristine; QUANTEC: Quantitative Analyses of Normal Tissue Effects in the Clinic; SURF-ROGG: SeizURe Frequency during a Radiotherapy cOurse for high-Grade Gliomas; TMZ: Temozolomide; VMAT: Volumetric Modulated Arc Therapy; ZKS: Zentrum für Klinische Studien (Centre for Clinical Trials)

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Authors' contributions

D.R., J.W., D.O., P.T., S.E.S., S.T. and T.W.K. participated in the development of the protocol. D.R. and S.E.S. drafted the manuscript. All authors have read and approved the manuscript.

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Availability of data and materials

Not applicable, because no data have been generated until now. The trial was registered at clinicaltrials.gov (NCT04552756).

Declarations

Ethics approval and consent to participate

The SURF-ROGG trial was approved by the local ethics committee (University of Lübeck, no. 20–311). The trial is performed according to the Declaration of Helsinki and the principles of Good Clinical Practice (GCP). Patients are included only after written informed consent.

Consent for publication

Not applicable.

Competing interests

Dirk Rades is associate editor of BMC Cancer. Otherwise, no competing interests exist regarding this trial.

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