Aus der Klinik für Strahlentherapie

der Universität zu Lübeck

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Entwicklung von Scores zur Abschätzung der Prognose von Patienten mit Hirnmetastasen

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I. EINLEITUNG

Hirnmetastasen bilden mit bis zu 40% die Gruppe mit dem höchsten Anteil an allen intrakraniellen Neoplasien [4, 6]. Ältere Daten beschreiben für die USA eine jährliche Inzidenz von 8,3-11,1/100.000 Patienten [6, 17]; genaue und aktuelle Daten für Deutschland liegen bisher nicht vor. Es ist anzunehmen, dass die jährliche Inzidenz durch die demographische Entwicklung, die effektivere systemische Tumortherapie und die präzisere Bildgebung steigt [13]. Am häufigsten liegt mit 50-65% den Hirnmetastasen ein Lungenkarzinom als Primärtumor zugrunde. Andere häufige Primärtumoren sind das Mammakarzinom (≥ 15%) sowie das maligne Melanom, das kolorektale Karzinom, das Nierenzellkarzinom und unbekannte Primärtumoren (CUP-Syndrom = Cancer of Unknown Primary) mit jeweils 5-10% [4, 18].

Bei etwa 30% der Patienten fällt die Tumorerkrankung erst durch die klinischen Symptome der Hirnmetastasen auf [18]. Diese sind von Lage, Größe, Wachstumsgeschwindigkeit der Metastasen sowie dem Ausmaß des begleitenden Ödems abhängig und zeigen sich unter anderem durch Kopfschmerzen (38-65%), motorische Defizite (34%), Desorientierung (25%), Krampfanfälle (21-30%), Übelkeit und Erbrechen (10%), Vergesslichkeit, zerebrale Herdstörungen, wie Sprech- und Sehstörungen (30%) sowie Gleichgewichtsstörungen [4, 18].

Ohne Therapie beträgt die durchschnittliche Überlebenszeit von Patienten mit multiplen (> 3) Hirnmetastasen nur etwa einen Monat [18]. Durch eine Behandlung kann diese um einige Monate verlängert werden. Die weltweit am häufigsten verwendete Therapie ist die Ganzhirnbestrahlung mit 10 x 3 Gy über zwei Wochen [3]. Es gibt aber auch kürzere (5 x 4 Gy über eine Woche) oder längere (20 x 2 Gy über vier Wochen) Strahlentherapiekonzepte [8, 12]. Des

Weiteren besteht bei einer geringen Anzahl von Hirnmetastasen (≤ 3 Metastasen) die Möglichkeit, diese aggressiver durch eine radiochirurgische, fraktioniert stereotaktische oder neurochirurgische Therapie zu behandeln. Diese Therapieformen können alleinig oder auch in Kombination mit einer Ganzhirnbestrahlung appliziert werden [7, 16].

Die Diagnose einer zerebralen Metastasierung stellt den behandelnden Arzt vor die schwierige Entscheidung, für jeden Patienten die richtige Therapie in dieser palliativen Situation auszuwählen. Zum einen möchte man den Patienten nicht mehr als nötig belasten und ihm so wenig wie möglich von seiner verbleibenden Lebenszeit durch mitunter sehr anstrengende Therapien nehmen. Andererseits können die Überlebenszeit und künftig auch die Lebensqualität durch eine passende Therapie deutlich gesteigert werden. Die Wahl der Therapie für den einzelnen Patienten sollte auf jeden Fall unter Berücksichtigung der zu erwartenden Überlebensprognose erfolgen.

Viele Patienten mit Hirnmetastasen haben eine sehr geringe Lebenserwartung von nur wenigen Monaten. Für diese Patienten wäre eine einfache Bestrahlungstechnik (Ganzhirnbestrahlung) mit einer kurzen Behandlungszeit zu bevorzugen. Eine Kurzzeit-Strahlentherapie über eine Woche ist hinsichtlich Überleben und intrazerebraler Kontrolle genauso effektiv wie das ‚Standardregime' mit 10 x 3 Gy [8, 11]. Ein Auftreten von therapieassoziierten Langzeitfolgen ist bei diesen Patienten aufgrund der kurzen Überlebenszeit nicht zu erwarten [8].

Bei Patienten mit Hirnmetastasen und einer vergleichsweise guten Überlebensprognose hingegen steht die optimale Schonung des gesunden Gewebes im Vordergrund, da diese Patienten mögliche Spätfolgen der Strahlentherapie wie zum Beispiel neurokognitive Defizite erleben können. Es ist

bei Patienten mit sehr guter Überlebensprognose (≥ 1 Jahr) sogar eine Erhöhung der Gesamtdosis auf > 30 Gy mit einer Dosis pro Fraktion von < 3 Gy zu erwägen. Durch eine Langzeit-Strahlentherapie mit einer Gesamtdosis > 30 Gy kann bei dieser Patientengruppe eine bessere lokale Kontrolle und durch Einzeldosen < 3 Gy ein niedrigeres Risiko für das Auftreten von radiogenen neurokognitiven Defiziten erreicht werden [1, 12].

Die Überlebensprognose ist ein sehr wichtiger Faktor bei der Auswahl der richtigen Therapie für den individuellen Patienten. Insofern wäre es für die behandelnden Ärzte von großer Bedeutung, die Überlebensprognose von Patienten mit Hirnmetastasen möglichst genau abschätzen zu können. Eine solche Abschätzung kann durch entsprechende Instrumente (Überlebensscores) erheblich erleichtert werden. Wesentliche Ziele der vorliegenden Arbeit waren es, einen neuen validierten Überlebensscore für Patienten mit Hirnmetastasen zu entwickeln und einen bestehenden Score zu validieren.

Die Prognose von Patienten mit Hirnmetastasen hängt auch von der Art des Primärtumors ab. So wurde im Rahmen dieser Arbeit in einem weiteren Schritt das unterschiedliche klinische Verhalten der verschiedenen Tumorentitäten berücksichtigt, um eine noch bessere Personalisierung der Therapie zu ermöglichen. Es wurden daher eigene Prognosescores für die häufigsten zerebral metastasierenden Primärtumoren entwickelt: für das nicht-kleinzellige Lungenkarzinom (NSCLC = Non-Small Cell Lung Cancer), das kleinzellige Lungenkarzinom (SCLC = Small Cell Lung Cancer), das Mammakarzinom und für wenig strahlensensible Tumoren (malignes Melanom, Nierenzellkarzinom, kolorektales Karzinom).

II. Ein neuer validierter Score zur Abschätzung der Überlebens-prognose (und der intrazerebralen Kontrolle) von Patienten mit Hirnmetastasen

Rades D, Dziggel L, Haatanen T, Veninga T, Lohysnka R, Dunst J, Schild SE (2011) Scoring systems to estimate intracerebral control and survival rates of patients irradiated for brain metastases. Int J Radiation Oncol Biol Phys. 80(4):1122-7. [Impact Factor 2013: 4,176]

Ziel dieser Studie war es, Scoringsysteme für das Gesamtüberleben und die intrazerebrale Kontrolle bei Patienten mit Hirnmetastasen zu entwickeln und zu validieren. Dazu wurden die Daten von 1797 Patienten retrospektiv ausgewertet. Zunächst wurden die Patienten randomisiert in zwei Gruppen eingeteilt: eine Testgruppe (N = 1198) und eine Validierungsgruppe (N = 599). Es wurden zwei Scoringsysteme entwickelt, eines für das Gesamtüberleben und eines für die intrazerebrale Kontrolle.

Mittels multivariater Analysen wurden jeweils Prognosefaktoren ermittelt, die signifikant mit dem Gesamtüberleben bzw. mit der lokalen Kontrolle assoziiert waren. Bei dem Gesamtüberleben waren es folgende fünf Faktoren: Alter, Karnofsky Index, extrakranielle Metastasierung, Anzahl der Hirnmetastasen und das Intervall zwischen der Tumordiagnose und der Strahlentherapie. Bei der lokalen Kontrolle waren es: Tumorentität, Karnofsky Index, Anzahl der Hirnmetastasen sowie das Intervall zwischen der Tumordiagnose und der Strahlentherapie.

Für jeden Faktor wurde ein Punktwert ermittelt, indem die jeweilige Rate für das Überleben bzw. die lokale Kontrolle nach sechs Monaten (in %) durch 10 dividiert wurde (Tabelle 1). Der Gesamtscore für jeden Patienten wiederum wurde aus der Summe der Punktwerte für jeden Faktor gebildet und lag für das Gesamtüberleben zwischen 15 und 30 Punkten sowie für die intrazerebrale

Kontrolle zwischen 14 und 27 Punkten. Aus den Gesamtscores wurden sowohl für das Gesamtüberleben als auch für die intrazerebrale Kontrolle je drei Prognosegruppen A-C gebildet. Dies erfolgte sowohl für die Test- als auch für die Validierungsgruppe.

Tabelle 1: 6-Monatsraten für die intrazerebrale Kontrolle und die entsprechenden Punktwerte

	Intrazerebrale Kontrolle nach 6 Monaten (%)	**Punktwert**
Karnofsky Index		
< 70	21	2
= 70	59	6
> 70	73	7
Primärtumor		
Mammakarzinom	65	7
Nicht-kleinzelliges Lungenkarzinom	56	6
Kleinzelliges Lungenkarzinom	56	6
Nierenzellkarzinom	53	5
Malignes Melanom	49	5
CUP-Syndrom	33	3
Kolorektales Karzinom	43	4
Andere Tumoren	53	5
Anzahl an Hirnmetastasen		
1	73	7
2-3	63	6
≥ 4	39	4
Intervall zwischen Tumordiagnose und Ganzhirnbestrahlung		
≤ 6 Monate	49	5
> 6 Monate	59	6

Es ergaben sich 6-Monatsraten für das Gesamtüberleben der Testgruppe von 9% in Gruppe A (Gesamtscore von 15-19 Punkten), 41% in Gruppe B (Gesamtscore von 20-25 Punkten) und 78% in Gruppe C (Gesamtscore von 26-30 Punkten). In der Validierungsgruppe lagen die entsprechenden 6-Monatsraten für

das Gesamtüberleben bei 7%, 39% und 79% und waren den drei entsprechenden Prognosegruppen der Testgruppe vergleichbar.

Die 6-Monatsraten der intrazerebralen Kontrolle der Testgruppe waren 17% in Gruppe A (Gesamtscore von 14-18 Punkten), 49% in Gruppe B (Gesamtscore von 19-23 Punkten) und 77% in Gruppe C (Gesamtscore von 24-27 Punkten). Die entsprechenden 6-Monatsraten der Validierungsgruppe waren 19%, 52% und 77% und damit ebenfalls den drei Gruppen der Testgruppe vergleichbar (Abbildung 1).

Da die Raten für das Gesamtüberleben und die lokale Kontrolle der Validierungsgruppe ähnlich denen der Testgruppe waren, können diese Scoringsysteme als valide und reproduzierbar angesehen werden.

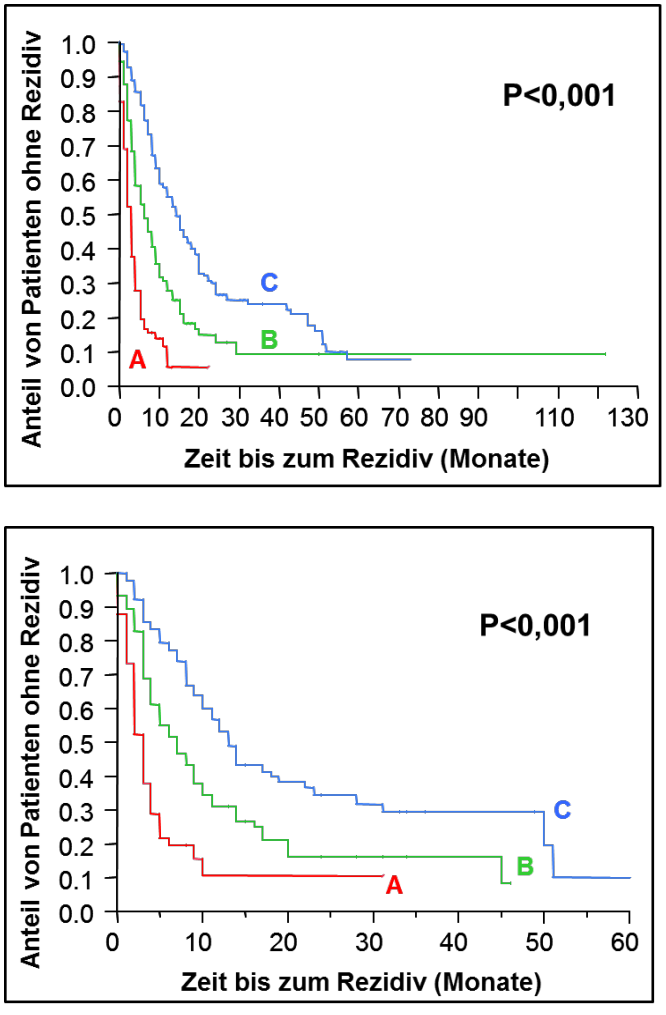


Abbildung 1: Kaplan-Meier Kurven für die intrazerebrale Kontrolle der drei Prognosegruppen A (14-18 Punkte), B (19-23 Punkte) und C (24-27 Punkte) der Test- (oben) und der Validierungsgruppe (unten)

III. Validierung eines Überlebensscores für Patienten mit Hirnmetastasen nach Ganzhirnbestrahlung

Dziggel L, Segedin B, Podvrsnik NH, Oblak I, Schild SE, Rades D (2013) Validation of a survival score for patients treated with whole-brain radiotherapy for brain metastases. Strahlenther Onkol. 189(5):364-6. [Impact Factor 2013: 2,733]

Ziel dieser Studie war die Validierung eines im Jahre 2008 publizierten Prognosescores für Patienten mit Hirnmetastasen nach alleiniger Ganzhirnbestrahlung [9]. Hier wurden die Daten von 350 Patienten, die eine alleinige Ganzhirnbestrahlung bei zerebralen Metastasen erhielten, retrospektiv untersucht und mit den Daten der 1085 Patienten der vorherigen Studie verglichen. Die 350 Patienten bildeten die Validierungsgruppe und die 1085 Patienten der vorherigen Studie die Testgruppe.

In der 2008 publizierten Studie wurden Daten von 1085 Patienten retrospektiv untersucht und anhand von multivariaten Analysen vier Prognosefaktoren identifiziert, die signifikant mit dem Überleben assoziiert waren. Diese Prognosefaktoren waren: Alter (≤ 60 Jahre vs. ≥ 61 Jahre), Karnofsky Index (< 70 vs. ≥ 70), extrakranielle Metastasierung zum Zeitpunkt der Strahlentherapie (nein vs. ja) sowie das Intervall zwischen der Tumordiagnose und der Ganzhirnbestrahlung (≤ 8 Monate vs. > 8 Monate).

Für jeden dieser Prognosefaktoren wurde ein Punktwert errechnet, indem die jeweilige Überlebensrate nach sechs Monaten (in %) durch 10 dividiert wurde (Tabelle 2). Die prognostischen Gesamtscores ergaben sich aus der Summe der Punktwerte für jeden Faktor und lagen zwischen 9 und 18 Punkten.

Daraus abgeleitet wurden vier prognostische Gruppen gebildet: Gruppe A (9-10 Punkte), Gruppe B (11-13 Punkte), Gruppe C (14-16 Punkte) und Gruppe D (17-18 Punkte) (Abbildung 2). Patienten der Gruppe A hatten die schlechteste

Überlebensprognose, während Patienten der Gruppe D die beste Prognose aufwiesen. Die vier Gruppen wurden mit Hilfe des Kaplan-Meier-Verfahrens und des Log-rank-Tests verglichen und unterschieden sich hiernach signifikant hinsichtlich des Überlebens ($p < 0{,}001$).

Tabelle 2: Überlebensraten 6 Monate nach Ganzhirnbestrahlung und die entsprechenden Punktwerte

	Überleben nach 6 Monaten (%)	**Punktwert**
Alter		
≤ 60 Jahre	43	4
≥ 61 Jahre	25	3
Karnofsky Index		
< 70	8	1
≥ 70	53	5
Extrakranielle Metastasen zur Zeit der Ganzhirnbestrahlung		
Nein	51	5
Ja	24	2
Intervall zwischen Tumordiagnose und Ganzhirnbestrahlung		
≤ 8 Monate	32	3
> 8 Monate	36	4

Mit derselben Methode wurden die Daten der 350 Patienten der Validierungsgruppe analysiert und ebenfalls vier Prognosegruppen mit einem Gesamtscore von 9 bis 18 Punkten gebildet. In der Validierungsgruppe betrugen die Überlebensraten nach sechs Monaten 8% für Patienten der Gruppe A (Gesamtscore 9 bis 10 Punkte), 24% für Patienten der Gruppe B (Gesamtscore 11 bis 13 Punkte), 51% für Patienten der Gruppe C (Gesamtscore 14 bis 16 Punkte) und 82% für Patienten der Gruppe D (Gesamtscore 17 bis 18 Punkte). Hinsichtlich des Überlebens waren die vier Prognosegruppen signifikant unterschiedlich ($p < 0{,}001$).

Die Überlebensraten der 1085 Patienten der vorherigen Studie betrugen 6% in Gruppe A, 15% in Gruppe B, 43% in Gruppe C und 76% in Gruppe D ($p < 0{,}001$).

Um eine Validität des Prognosescores beurteilen zu können, wurden die jeweiligen Gruppen A, B, C und D der vorherigen und der aktuellen Studie mittels des Chi-Quadrat-Tests miteinander verglichen. Dabei zeigten sich zwischen den jeweiligen Gruppen keine signifikanten Unterschiede. Die P-Werte für den Vergleich der Gruppen waren: $p = 0{,}81$ für die Gruppen A, $p = 0{,}18$ für die Gruppen B, $p = 0{,}29$ für die Gruppen C und $p = 0{,}75$ für die Gruppen D.

Damit konnte gezeigt werden, dass der initial entwickelte Prognosescore für Patienten mit Hirnmetastasen nach Ganzhirnbestrahlung valide und reproduzierbar ist.

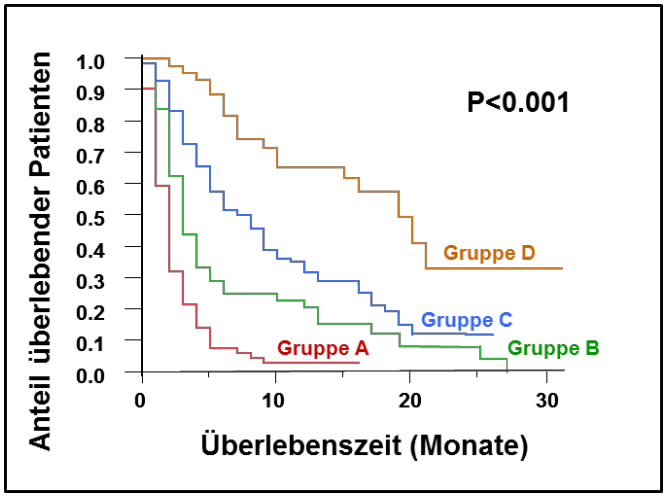


Abbildung 2: Kaplan-Meier Kurven für das Überleben in den vier Gruppen A, B, C und D der aktuellen Studie

IV. Überlebensscore für Patienten mit Hirnmetastasen eines nicht-kleinzelligen Lungenkarzinoms (NSCLC)

Rades D, Dziggel L, Segedin B, Oblak I, Nagy V, Marita A, Schild SE, Trang NT, Khoa MT (2013) A new survival score for patients with brain metastases from non-small cell lung cancer (NSCLC). Strahlenther Onkol. 189(9):777-81. [Impact Factor 2013: 2,733]

Um die biologischen und klinischen Unterschiede von verschiedenen Tumorentitäten zu berücksichtigen und die Therapie von Patienten mit Hirnmetastasen weiter zu individualisieren, wurde unter anderem für das nicht-kleinzellige Lungenkarzinom (NSCLC) ein separater Überlebensscore entwickelt. Dazu wurden Daten von 514 Patienten mit Hirnmetastasen eines NSCLC, die alleinige Ganzhirnbestrahlung erhalten haben, in eine Testgruppe (N = 257) und eine Validierungsgruppe (N = 257) eingeteilt.

Zunächst wurden sieben mögliche prognostische Faktoren hinsichtlich des Gesamtüberlebens analysiert: Regime der Ganzhirnbestrahlung, Alter, Geschlecht, Karnofsky Index, Anzahl der Hirnmetastasen, extrakranielle Metastasierung und das Intervall zwischen Tumordiagnose und Strahlentherapie. Die Faktoren, die in der univariaten Analyse signifikant waren, wurden anschließend mit einer multivariaten Analyse (Cox Proportional Hazard Modell) untersucht. Dabei ergaben sich drei unabhängige Prognosefaktoren für das Gesamtüberleben: Geschlecht (weiblich vs. männlich), Karnofsky Index (< 70 vs. ≥ 70) und extrakranielle Metastasierung (nein vs. ja).

Für jeden der drei Prognosefaktoren wurde ein Punktwert berechnet, indem die Überlebensrate nach sechs Monaten (in %) durch 10 dividiert wurde (Tabelle 3). Entsprechend dem prognostischen Gesamtscore, der sich aus der Summe der Punktwerte für jeden Faktor ergab und zwischen 5 und 15 Punkten

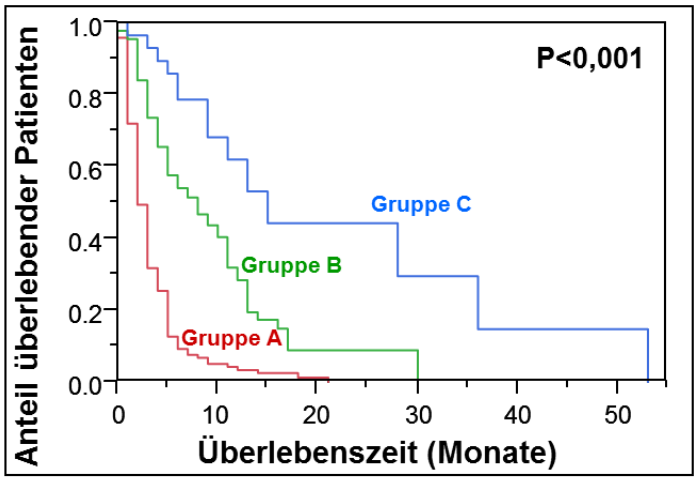
lag, wurden drei prognostische Gruppen gebildet: Gruppe A (5-9 Punkte), Gruppe B (11-12 Punkte) und Gruppe C (15 Punkte).

Tabelle 3: Überlebensraten 6 Monate nach Ganzhirnbestrahlung und die entsprechenden Punktwerte

	Überleben nach 6 Monaten (%)	**Punktwert**
Geschlecht		
weiblich	45	5
männlich	24	2
Karnofsky Index		
< 70	8	1
≥ 70	48	5
Extrakranielle Metastasierung		
Nein	51	5
Ja	20	2

Die Überlebensraten nach 6 Monaten waren in der Testgruppe 9% (Gruppe A), 54% (Gruppe B) und 79% (Gruppe C) ($p < 0,001$). Die entsprechenden Überlebensraten der Validierungsgruppe betrugen 14%, 56% und 78% ($p < 0,001$). Zum Vergleich der drei prognostischen Gruppen A, B und C der Test- und der Validierungsgruppe wurde der Chi-Quadrat-Test angewendet. Es konnten keine signifikanten Unterschiede festgestellt werden: $p = 0,30$ für den Vergleich beider Gruppen A, $p = 0,92$ für den Vergleich beider Gruppen B und $p = 0,99$ für den Vergleich beider Gruppen C.

Die geringen Unterschiede zwischen den einzelnen Gruppen der Test- und der Validierungsgruppe sprechen für die Validität und Reproduzierbarkeit des neuen Scores für Patienten mit Hirnmetastasen eines nicht-kleinzelligen Lungenkarzinoms.



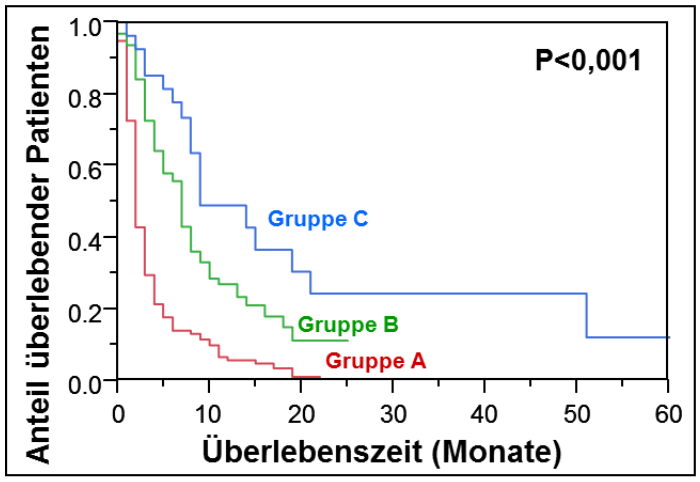


Abbildung 3: Kaplan-Meier Kurven für das Überleben in den drei Prognosegruppen A, B, und C der Testgruppe (oben) und der Validierungsgruppe (unten)

V. Überlebensscore für Patienten mit Hirnmetastasen eines kleinzelligen Lungenkarzinoms (SCLC)

Rades D, Dziggel L, Segedin B, Oblak I, Nagy V, Marita A, Schild SE (2013) The first survival score for patients with brain metastases from small cell lung cancer (SCLC). Clin Neurol Neurosurg. 115(10):2029-32. [Impact Factor 2013: 1,248]

Um auch auf das unterschiedliche Verhalten des kleinzelligen Lungenkarzinoms (SCLC) im Vergleich zu anderen Tumorentitäten einzugehen, wurde für eine optimale Personalisierung der Therapie auch für diese Gruppe von Patienten ein separater Überlebensscore erstellt.

Dazu wurden Daten von 172 Patienten retrospektiv untersucht und in zwei Gruppen, eine Testgruppe (N = 86) und eine Validierungsgruppe (N = 86), eingeteilt. Sechs mögliche Prognosefaktoren wurden hinsichtlich des Überlebens in der Testgruppe untersucht, wovon drei Faktoren identifiziert werden konnten, die mit dem Überleben signifikant assoziiert waren: Karnofsky Index (< 70 vs. ≥ 70), Anzahl der Hirnmetastasen (1-3 vs. ≥ 4) und extrakranielle Metastasierung (nein vs. ja).

Tabelle 4: Überlebensraten 6 Monate nach Ganzhirnbestrahlung und die entsprechenden Punktwerte

	Überleben nach 6 Monaten (%)	**Punktwert**
Karnofsky Index		
< 70	5	1
≥ 70	51	5
Anzahl der Hirnmetastasen		
1-3	50	5
≥ 4	21	2
Extrakranielle Metastasierung		
Nein	45	5
Ja	20	2

Für jeden dieser drei Prognosefaktoren wurden Punktwerte gebildet, indem die Überlebensrate nach sechs Monaten (in %) durch 10 dividiert wurde (Tabelle 4). Die Gesamtscores, die aus der Summe der Punktwerte für jeden Faktor gebildet wurden, lagen zwischen 5 und 15 Punkten (Abbildung 4). Entsprechend dieser Gesamtscores wurden drei prognostische Gruppen gebildet: Gruppen A (5-8 Punkte), B (9-12 Punkte) und C (15 Punkte). Die Überlebensraten nach sechs Monaten der Testgruppe waren 3% in Gruppe A, 40% in Gruppe B und 89% in Gruppe C ($p < 0,001$). Die jeweiligen Überlebensraten der Validierungsgruppe waren 3%, 41% und 89% ($p < 0,001$).

Auch in dieser Studie wurden die drei prognostischen Gruppen A, B und C der Testgruppe mit den entsprechenden Gruppen A, B und C der Validierungsgruppe mit Hilfe des Chi-Quadrat-Tests verglichen. Dabei zeigten sich keine signifikanten Unterschiede: $p = 0,99$ für den Vergleich beider Gruppen A, $p=0,98$ für den Vergleich beider Gruppen B und $p = 1,00$ für den Vergleich beider Gruppen C. Somit kann auch dieser Score zur Abschätzung des Überlebens von Patienten mit Hirnmetastasen eines kleinzelligen Lungenkarzinoms als valide und reproduzierbar angesehen werden.

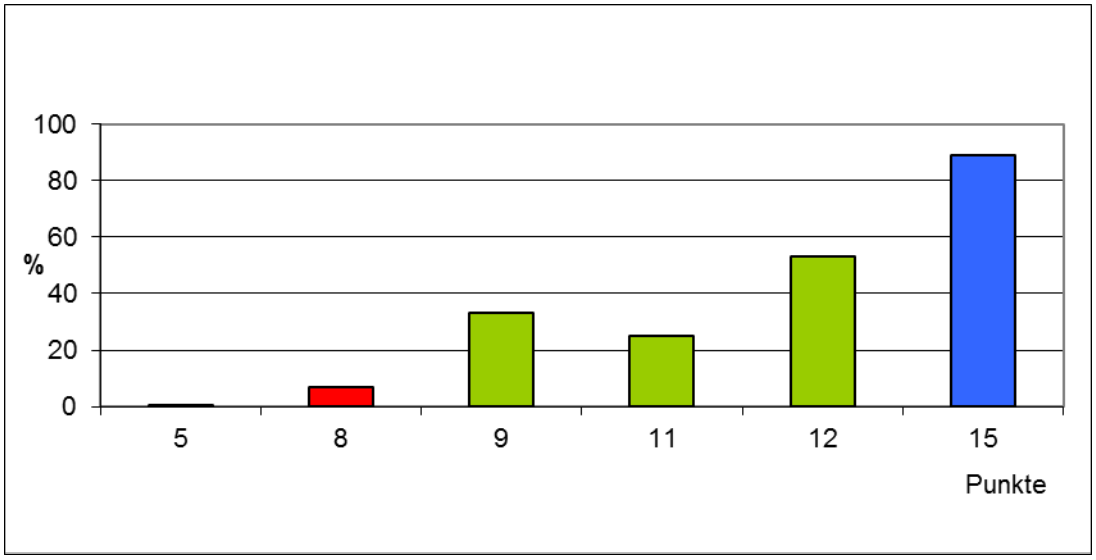


Abbildung 4: Die 6-Monats-Überlebensraten (in %) bezogen auf die entsprechenden Gesamtscores

VI. Überlebensscore für Patientinnen mit Hirnmetastasen eines Mammakarzinoms

Rades D, Dziggel L, Segedin B, Oblak I, Nagy V, Marita A, Schild SE, Trang NT, Khoa MT (2013) A simple survival score for patients with brain metastases from breast cancer. Strahlenther Onkol. 189(8):664-7. [Impact Factor 2013: 2,733]

Mit etwa 15% ist Brustkrebs der zweithäufigste Primärtumor nach dem Lungenkarzinom bei Patienten mit Hirnmetastasen [4]. Daher scheint ein spezifischer Überlebensscore für Patientinnen mit Hirnmetastasen eines Mammakarzinoms wünschenswert, um die Therapie dieser Patientinnen optimal individualisieren zu können.

In dieser Arbeit wurden die Daten von 230 Patientinnen, die aufgrund ihrer Hirnmetastasen des Mammakarzinoms mit alleiniger Ganzhirnbestrahlung behandelt wurden, eingeschlossen. Es wurden wiederum zwei Gruppen, eine Testgruppe (N = 115) und eine Validierungsgruppe (N = 115), gebildet. In der Testgruppe wurden zunächst sechs mögliche prognostische Faktoren hinsichtlich ihrer Assoziation mit dem Überleben analysiert: Regime der Ganzhirnbestrahlung, Alter, Karnofsky Index, Anzahl der Hirnmetastasen, extrakranielle Metastasierung und das Intervall zwischen der Tumordiagnose und der Ganzhirnbestrahlung. Die Faktoren, die sich in der univariaten Analyse als signifikant erwiesen, wurden anschließend in einer multivariaten Analyse weitergehend untersucht. Dabei war der Karnofsky Index signifikant mit dem Überleben assoziiert ($p < 0,001$) und die extrakranielle Metastasierung zeigte einen Trend ($p = 0,06$), so dass diese zwei Faktoren in das Scoring-System eingeschlossen wurden. Der Punktwert für jeden Faktor wurde wiederum gebildet, indem die Überlebensrate nach sechs Monaten (in %) durch 10 dividiert wurde (Tabelle 5).

Tabelle 5: Überlebensraten 6 Monate nach Ganzhirnbestrahlung und die entsprechenden Punktwerte

	Überleben nach 6 Monaten (%)	Punktwert
Karnofsky Index		
< 70	10	1
≥ 70	63	6
Extrakranielle Metastasierung		
Nein	61	6
Ja	32	3

Die prognostischen Gesamtscores ergaben sich wiederum aus der Summe der Punktwerte für jeden dieser zwei Faktoren und lagen zwischen 4 und 12 Punkten (Abbildung 5). Anhand der Gesamtscores wurden drei Gruppen gebildet: Gruppe A (4-7 Punkte), Gruppe B (9 Punkte) und Gruppe C (12 Punkte).

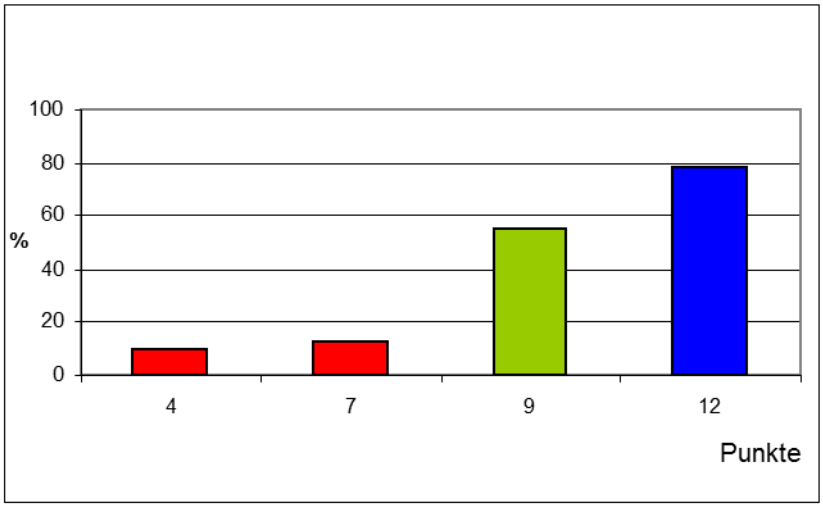


Abbildung 5: Die 6-Monats-Überlebensraten (in %) bezogen auf die entsprechenden Gesamtscores

Die Überlebensraten nach sechs Monaten waren in der Testgruppe 10% in Gruppe A, 55% in Gruppe B und 78% in Gruppe C ($p < 0{,}001$). In der Validierungsgruppe betrugen die entsprechenden Überlebensraten 11%, 54% und 75% ($p < 0{,}001$). Die drei prognostischen Gruppen A, B und C der Testgruppe wurden mittels des Chi-Quadrat-Tests mit den entsprechenden Gruppen A, B und C der Validierungsgruppe verglichen. Dabei wurden keine signifikanten

Unterschiede festgestellt: $p = 0,98$ für den Vergleich beider Gruppen A, $p = 0,99$ für den Vergleich beider Gruppen B und $p = 0,97$ für den Vergleich beider Gruppen C.

Damit kann von der Validität und Reproduzierbarkeit dieses Scores für Patientinnen mit Hirnmetastasen eines Mammakarzinoms ausgegangen werden.

VII. Überlebensscore für Patienten mit Hirnmetastasen wenig strahlensensibler Tumoren nach alleiniger Ganzhirnbestrahlung

Dziggel L, Segedin B, Podvrsnik NH, Oblak I, Schild SE, Rades D (2013) A survival score for patients with brain metastases from less radiosensitive tumors treated with whole-brain radiotherapy alone. Strahlenther Onkol. 190(1):54-8. [Impact Factor 2013: 2,733]

Patienten mit Hirnmetastasen von wenig strahlensensiblen Tumoren, wie dem malignen Melanom, dem Nierenzellkarzinom und dem kolorektalen Karzinom, haben insgesamt eine schlechte Prognose. Da dieser Situation ein unterschiedliches biologisches und klinisches Verhalten im Vergleich zu anderen Tumorentitäten zugrunde liegt, ist auch hier die Entwicklung eines separaten Prognosescores indiziert.

Dazu wurden die Daten von 176 Patienten nach alleiniger Ganzhirnbestrahlung bei Hirnmetastasen von wenig strahlensensiblen Tumoren (65 Patienten mit malignem Melanom, 45 Patienten mit Nierenzellkarzinom und 66 Patienten mit kolorektalem Karzinom) in die Studie eingeschlossen. Es wurden eine Test- und eine Validierungsgruppe mit je 88 Patienten gebildet. In der Testgruppe wurden die folgenden acht möglichen Prognosefaktoren mit Hilfe des Kaplan-Meier-Verfahrens und des Log-rank-Tests bezüglich einer signifikanten Assoziation mit dem Überleben untersucht: Regime der Ganzhirnbestrahlung, Geschlecht, Alter, Karnofsky Index, Primärtumor, Anzahl der Hirnmetastasen, extrakranielle Metastasierung und das Intervall zwischen der Tumordiagnose und der Ganzhirnbestrahlung. Die Faktoren, die in dieser univariaten Analyse signifikant mit dem Überleben assoziiert waren, wurden anschließend in einer multivariaten Analyse mittels des Cox Proportional Hazard Modells weiterführend untersucht. Das Alter, der Karnofsky Index und die extrakranielle Metastasierung zeigten sich dabei mit dem Überleben signifikant assoziiert und wurden in das

Scoring-System eingeschlossen. Indem die Überlebensrate nach sechs Monaten (in %) durch 10 dividiert wurde, wurde der Punktwert für jeden Faktor ermittelt (Tabelle 6). Entsprechend dem prognostischen Gesamtscore, der sich aus der Summe der Punktwerte für jeden Faktor ergab und von 5 bis 14 Punkten reichte, wurden drei Prognosegruppen gebildet: Gruppe A (5-8 Punkte), Gruppe B (9-11 Punkte) und Gruppe C (12-14 Punkte).

Tabelle 6: Überlebensraten 6 Monate nach Ganzhirnbestrahlung und die entsprechenden Punktwerte

	Überleben nach 6 Monaten (%)	**Punktwert**
Alter		
< 65 Jahre	38	4
≥ 65 Jahre	16	2
Karnofsky Index		
< 70	10	1
≥ 70	43	4
Extrakranielle Metastasierung		
Nein	59	6
Ja	21	2

Die Überlebensraten nach sechs Monaten waren in der Testgruppe 11% in Gruppe A, 38% in Gruppe B und 83% in Gruppe C ($p < 0,001$). In der Validierungsgruppe waren die entsprechenden Überlebensraten 12%, 31% und 75% ($p = 0,003$) (Abbildung 6). Mit dem Chi-Quadrat-Test wurden die jeweiligen drei Gruppen A, B und C der Test- und der Validierungsgruppe miteinander verglichen. Dabei zeigten sich keine signifikanten Unterschiede: $p = 0,97$ für den Vergleich beider Gruppen A, $p = 0,82$ für den Vergleich beider Gruppen B und $p = 0,95$ für den Vergleich beider Gruppen C.

Der Score für Patienten mit Hirnmetastasen von wenig strahlensensiblen Tumoren erscheint aufgrund der jeweils sehr ähnlichen Gruppen A, B und C der Test- und der Validierungsgruppe valide und reproduzierbar.

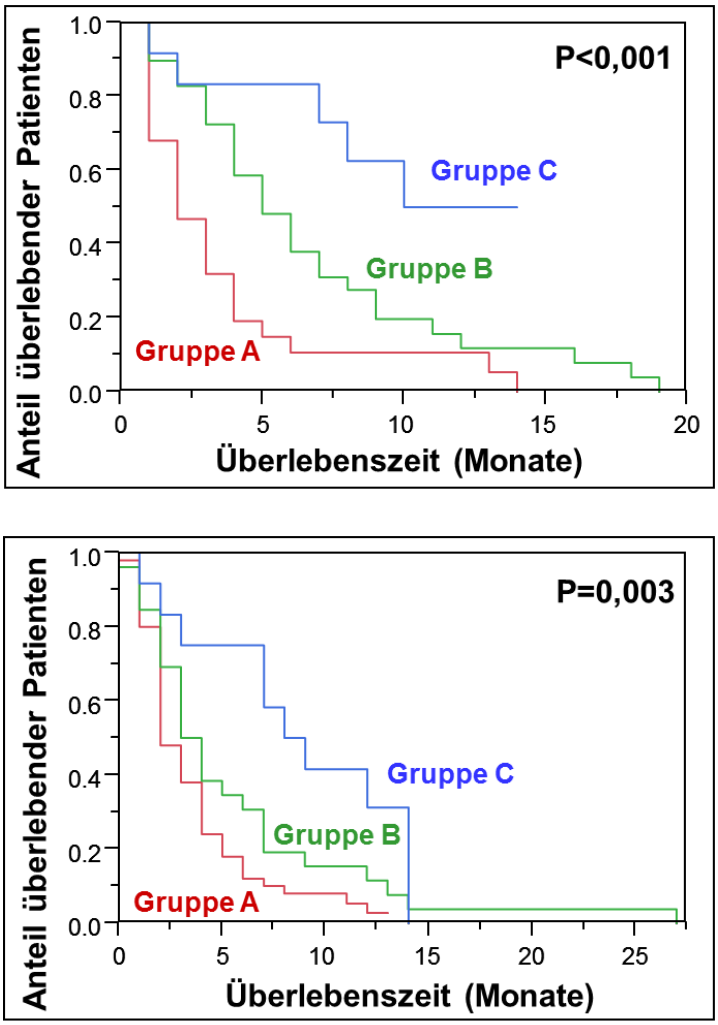


Abbildung 6: Kaplan-Meier Kurven für das Überleben in den drei Gruppen A, B, und C der Testgruppe (oben) und der Validierungsgruppe (unten)

VIII. Diskussion und Ausblick

Patienten mit Hirnmetastasen leiden oft unter starken Beschwerden durch die zerebrale Metastasierung und haben bei Vorliegen von mehr als drei Läsionen eine durchschnittliche Überlebensprognose von nur wenigen Monaten. In dieser Situation ist die Wahl der passenden Therapie zur Verbesserung der Lebensqualität und/oder Verlängerung der Lebenszeit eine große Herausforderung, nicht nur für den behandelnden Arzt, sondern auch für den Patienten und seine Angehörigen. Die Wahl der am besten geeigneten Behandlung hängt unter anderem von den verfügbaren Therapiemöglichkeiten und der Erfahrung des behandelnden Arztes ab, sollte aber auch die Prognose der Erkrankung und die Wünsche des Patienten mit berücksichtigen. Patienten mit Hirnmetastasen hoffen in der Regel auf eine Besserung der Symptome und der Lebensqualität und möchten zudem so wenig Zeit wie möglich mit Therapien verbringen.

Vor allem Patienten mit einer schlechten Prognose von nur wenigen Wochen bis Monaten sollten daher eine kurze und zugleich effektive Therapie erhalten, insbesondere da ein Krankenhausaufenthalt von den Patienten häufig nicht gewünscht wird und eine lange ambulante Therapie sehr anstrengend sein kann. In retrospektiven Studien wurde gezeigt, dass eine kurze Therapie mit beispielsweise 5 x 4 Gy in einer Woche hinsichtlich Überleben und intrazerebraler Kontrolle genauso effektiv ist, wie eine Therapie über zwei oder mehr Wochen [8, 11]. Bei einer höheren Dosis pro Fraktion ist zwar das Risiko für radiogene Spätnebenwirkungen erhöht, jedoch ist bei Patienten mit einer schlechten Prognose mit einem Erleben dieser Nebenwirkungen in den meisten Fällen nicht mehr zu rechnen [1].

Im Gegensatz hierzu scheinen Patienten mit einer sehr guten Prognose von einer Langzeittherapie mit Einzeldosen < 3 Gy zu profitieren. Das Risiko für radiogene Spätfolgen steigt mit zunehmender Lebensdauer. Da das Risiko für das Auftreten von Spätfolgen wie neurokognitive Defizite bei Einzeldosen < 3 Gy deutlich geringer ist als bei Einzeldosen ≥ 3 Gy, ist bei Patienten mit einer höheren Lebenserwartung eine längere Therapiezeit akzeptabel [1].

Die Wahl des geeigneten Bestrahlungs-Regimes hängt also in hohem Maße von der Überlebensprognose ab. Zum Abschätzen der Prognose sind Überlebensscores eine bedeutende und große Hilfe.

In der ersten Studie im Rahmen dieser Dissertation wurden Daten von 1797 Patienten mit Hirnmetastasen von verschiedenen Primärtumoren, die mit unterschiedlichen Therapieformen und Fraktionierungen behandelt wurden, untersucht. Es waren fünf Faktoren signifikant mit dem Überleben assoziiert: Alter, Karnofsky Index, extrakranielle Metastasierung, Anzahl der Hirnmetastasen und das Intervall zwischen der Tumordiagnose und der Strahlentherapie. In dieser Arbeit wurde ebenfalls die lokale (= intrazerebrale) Kontrolle untersucht. Assoziiert mit der lokalen Kontrolle waren vier Faktoren: Tumorentität, Karnofsky Index, Anzahl der Hirnmetastasen und das Intervall zwischen der Tumordiagnose und der Strahlentherapie. Basierend auf den signifikanten Faktoren wurden ein Überlebensscore sowie ein Score für die lokale Kontrolle für Patienten mit Hirnmetastasen entwickelt. Beide Scores wurden in dieser Studie validiert und erwiesen sich als gut reproduzierbar.

Bereits 2008 wurde ein Score basierend auf einem nur mit alleiniger Ganzhirnbestrahlung behandelten Patientenkollektiv publiziert [9]. Der Score wurde allerdings bislang nicht validiert. Dies erfolgte jetzt an einer

Patientenkohorte von 350 Patienten; Validität und Reproduzierbarkeit des 2008 publizierten Scores konnten eindeutig nachgewiesen werden.

Die genannten Scores beinhalten die Daten von Patienten mit Hirnmetastasen von diversen Primärtumoren. Um auch auf Unterschiede hinsichtlich der Biologie und des klinischen Verhaltens der einzelnen Tumorentitäten einzugehen, wurden im Rahmen dieser Dissertation Subgruppenanalysen zu den häufigsten Tumorentitäten, die für Hirnmetastasen verantwortlich sind, durchgeführt. Diese Entitäten waren das nicht-kleinzellige Lungenkarzinom, das kleinzellige Lungenkarzinom, das Mammakarzinom und weniger strahlensensible Tumoren (malignes Melanom, kolorektales Karzinom und Nierenzellkarzinom). Um das Risiko für einen möglichen Selektionsbias durch die Therapie (Ganzhirnbestrahlung, Radiochirurgie, Operation oder Kombinationstherapien) zu minimieren, wurden nur Patienten, die mit alleiniger Ganzhirnbestrahlung behandelt worden waren, eingeschlossen. In allen vier Subgruppenanalysen war der Karnofsky Index mit dem Überleben signifikant assoziiert. Auch konnte eine extrakranielle Metastasierung jeweils als Faktor mit in die Überlebensscores eingeschlossen werden.

Die Entwicklung von Überlebensscores für Patienten mit Hirnmetastasen ist schon seit einigen Jahren von Interesse. Der wohl bekannteste und aufgrund seiner einfachen Handhabung bisher am häufigsten genutzte Score ist die RPA-(Recursive Partitioning Analysis)-Klassifikation von Gaspar et al., anhand dessen Patienten in drei Prognosegruppen eingeteilt werden können [2]. Die vier Prognosefaktoren, die sich in der Studie von Gaspar et al. signifikant mit dem Überleben assoziiert zeigten und in die RPA-Klassifikation eingeschlossen wurden, waren der Karnofsky Index, das Alter, die Kontrolle des Primärtumors und die extrakranielle Metastasierung. Allerdings basiert die RPA-Klassifikation neben

Patienten, die mit alleiniger Ganzhirnbestrahlung behandelt worden waren, auch auf Patienten, die zusätzlich eine Chemotherapie oder einen Radiosensitizer erhalten hatten. Somit besteht durch die unterschiedlichen Therapien ein gewisses Risiko für einen Selektionsbias. Bei dem 2008 publizierten GPA-(Graded Prognostic Assessment)-Score waren ebenfalls vier Faktoren mit dem Überleben assoziiert: Alter, Karnofsky Index, Anzahl der Metastasen und extrakranielle Metastasierung [14]. In den GPA-Score gingen neben Patienten mit Behandlung mittels alleiniger Ganzhirnbestrahlung und Ganzhirnbestrahlung plus Chemotherapie/Radiosensitizer auch Patienten ein, die eine Ganzhirnbestrahlung nach Radiochirurgie erhalten hatten. Dadurch wurde das Bias-Risiko noch verstärkt. Rücksicht auf die unterschiedlichen Tumorentitäten wurde bei dem 2010 erweiterten DS-(Diagnosis Specific)-GPA-Score genommen, wobei für das kleinzellige und das nicht-kleinzellige Lungenkarzinom dieselben Prognosefaktoren gefunden wurden wie im initialen GPA-Score [15]. Beim malignen Melanom und dem Nierenzellkarzinom waren zwei Faktoren signifikant mit dem Überleben assoziiert, der Karnofsky Index und die Anzahl der Hirnmetastasen [15]. Als einziger Prognosefaktor war beim Mammakarzinom und bei gastrointestinalen Tumoren nur der Karnofsky Index mit dem Überleben assoziiert [15]. Bei dem BSBM (basic score for brain metastases) für Patienten nach Radiochirurgie wurden drei Prognosefaktoren in den Score mit eingeschlossen: Karnofsky Index, Kontrolle des Primärtumors und extrakranielle Metastasierung [5].

2013 erschien eine Arbeit über den Vergleich der verschiedenen Scoringsysteme (unter anderem die RPA-Klassifikation, der GPA-Score, der DS-GPA-Score, der BSBM und der hier vorgestellte Score aus dem Jahre 2011) anhand einer Patientenkohorte von 380 Patienten, die mit alleiniger Radiochirurgie

behandelt worden waren [19]. Es konnte gezeigt werden, dass alle Scoringsysteme gut mit dem Überleben korrelieren. Der Kritikpunkt, dass die einzelnen Prognoseklassen eine unausgeglichene Anzahl von Patienten aufwiesen, lässt sich am ehesten durch die wahrscheinlich bessere Prognose der untersuchten Patienten (Behandlung mit Radiochirurgie bei 1-3 Hirnmetastasen) erklären.

Bei allen genannten Scoringsystemen, inklusive den hier vorgestellten Scores für die einzelnen Tumorentitäten, waren zwei Faktoren immer mit dem Überleben signifikant assoziiert, der Karnofsky Index und die extrakranielle Metastasierung [2, 5, 14, 15].

In dem Score dieser Arbeit aus dem Jahr 2011 wurden erstmals fünf prognostische Faktoren eingeschlossen und auch ein Score für die lokale Kontrolle gebildet, was bezüglich der Symptomatik von Hirnmetastasen ebenfalls ein sehr wichtiger Endpunkt ist. Ein Kritikpunkt an den meisten bisherigen Scores ist, wie bereits erwähnt, der Einschluss von Patienten, die mit verschiedenen Therapien behandelt wurden. Die Arbeit zur Validierung des Prognosescores von Patienten nach alleiniger Ganzhirnbestrahlung geht auf diesen Punkt ein. Und auch bei den im Verlauf durchgeführten Subgruppenanalysen für die verschiedenen Primärtumorentitäten wurden nur Patienten eingeschlossen, die eine alleinige Ganzhirnbestrahlung erhalten hatten. Dadurch war die jeweils untersuchte Patientenkohorte homogener und die Ergebnisse dieser Studien weniger durch die Therapie beeinflusst.

Bei der Anwendung der hier vorgestellten Scores muss jedoch der retrospektive Charakter der Studien und somit die Gefahr versteckter Selektionsbias berücksichtigt werden. Es muss außerdem bedacht werden, dass in den hier präsentierten Studien unterschiedliche Regime bei der

Ganzhirnbestrahlung verwendet wurden. Um eine noch höhere Homogenität hinsichtlich der Behandlung der Patienten zu gewährleisten, wurde mittlerweile ein weiterer Überlebens-Score (WBRT-30) basierend ausschließlich auf Patienten, die eine Ganzhirnbestrahlung mit 10 x 3 Gy erhielten, entwickelt [10]. Um beim WBRT-30 Subgruppenanalysen für einzelne Tumorentitäten durchführen zu können, sind allerdings noch größere Patientenzahlen erforderlich. Ebenso sind prospektive Studien erforderlich, unter anderem auch, um die Ergebnisse der hier präsentierten Studien zu überprüfen.

Bis dahin können die im Rahmen dieser Arbeit entwickelten Scores, die sich alle als valide und reproduzierbar erwiesen haben, bei der Einschätzung der Überlebensprognose von Patienten mit Hirnmetastasen maßgeblich unterstützen. Die hier vorgestellten Scores tragen zu einer personalisierten Behandlung von Patienten mit Hirnmetastasen unter Berücksichtigung der individuellen Überlebensprognose bei. Auch können die signifikanten Prognosefaktoren zur Stratifizierung bei zukünftigen randomisierten Studien herangezogen werden.

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X. Anhang

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SCORING SYSTEMS TO ESTIMATE INTRACEREBRAL CONTROL AND SURVIVAL RATES OF PATIENTS IRRADIATED FOR BRAIN METASTASES

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Purpose: To create and validate scoring systems for intracerebral control (IC) and overall survival (OS) of patients irradiated for brain metastases.

Methods and Materials: In this study, 1,797 patients were randomly assigned to the test (n = 1,198) or the validation group (n = 599). Two scoring systems were developed, one for IC and another for OS. The scores included prognostic factors found significant on multivariate analyses. Age, performance status, extracerebral metastases, interval tumor diagnosis to RT, and number of brain metastases were associated with OS. Tumor type, performance status, interval, and number of brain metastases were associated with IC. The score for each factor was determined by dividing the 6-month IC or OS rate (given in percent) by 10. The total score represented the sum of the scores for each factor. The score groups of the test group were compared with the corresponding score groups of the validation group.

Results: In the test group, 6-month IC rates were 17% for 14–18 points, 49% for 19–23 points, and 77% for 24–27 points ($p < 0.0001$). IC rates in the validation group were 19%, 52%, and 77%, respectively ($p < 0.0001$). In the test group, 6-month OS rates were 9% for 15–19 points, 41% for 20–25 points, and 78% for 26–30 points ($p < 0.0001$). OS rates in the validation group were 7%, 39%, and 79%, respectively ($p < 0.0001$).

Conclusions: Patients irradiated for brain metastases can be given scores to estimate OS and IC. IC and OS rates of the validation group were similar to the test group demonstrating the validity and reproducibility of both scores. © **2011 Elsevier Inc.**

Brain metastases, Radiation therapy, Local control, Survival, Prognostic scores.

INTRODUCTION

Brain metastases occur in up to 40% of all cancer patients during the course of their disease. The vast majority of these patients receive radiotherapy. For patients with a poor expected survival, short-course whole-brain radiotherapy (WBRT) such as 5 × 4 Gy given in 1 week appears an appropriate treatment, because it is convenient for the patients and takes only little time from their limited life span. For patients with a relatively favorable survival prognosis, longer course WBRT programs such as 10 × 3 Gy in 2 weeks or 20 × 2 Gy in 4 weeks may be considered preferable because a lower dose per fraction reduces the risk of radiation induced neurocognitive deficits (1). Furthermore, there is a subset of favorable survivors who may live for years. These patients may benefit from more aggressive therapies including longer courses of external beam radiotherapy, radiosurgery, or neurosurgical resection. A scoring system that helps predict survival could be used to select the most appropriate treatment regimen for the individual patient and properly stratify patients in future randomized trials.

In addition to survival, intracerebral control (IC) of metastatic disease is an important endpoint. Several trials suggested that an intracerebral recurrence is the major cause of posttreatment neurocognitive deficits (2–4). In the study of Aoyama *et al*., the average interval until deterioration of neurocognitive function was 7.6 months in patients receiving radiosurgery alone group and 16.5 months in patients receiving WBRT plus radiosurgery (p = 0.05). The authors concluded that IC is the most important factor for stabilizing neurocognitive function. In contrast to the previous trials, a more recent Phase III trial demonstrated that patients receiving radiosurgery plus upfront WBRT were significantly more likely to show neurocognitive

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dysfunction at 4 months than patients receiving radiosurgery alone, whereas IC at 1 year was significantly better after WBRT plus radiosurgery than after radiosurgery alone (73% vs. 27%, $p = 0.0003$) (5).

IC is an important endpoint in the treatment of brain metastases. A scoring system predicting IC may further guide the physician to select the appropriate treatment regimen for the individual patient. Patients with a relatively favorable survival prognosis and an unsatisfying probability of IC may in particular benefit from more aggressive therapies.

This study is the first that aimed at developing a scoring system predictive for both survival and IC with the same cohort of patients.

METHODS AND MATERIALS

The scoring system is based on a retrospective analysis of 1,797 patients who were irradiated for brain metastases: 1,346 patients received WBRT alone, 131 radiosurgery alone, 61 WBRT plus a radiosurgery boost, and 259 neurosurgical resection followed by WBRT ± boost. The patients receiving radiosurgery or neurosurgery generally had a limited number (from 1 to 3) of brain metastases, whereas patients of the WBRT alone group had either a limited number (from 1 to 3) or multiple (≥4) lesions. The selection of the treatment regimen was based on the physician's decision, waiting lists, and availability of treatment modalities. Patients with leptomeningeal carcinomatosis and patients receiving prophylactic cranial irradiation were not included in this study. The patients were followed until death or for at least 6 months with respect to both intracerebral control (IC) and overall survival (OS). Patients in whom IC and OS were not known were excluded from the analysis. The patients were randomly assigned to either the test group ($n = 1,198$ corresponding to two thirds of the entire cohort) or the validation group ($n = 599$). In the test group, univariate and multivariate analyses were performed for IC and OS. In this test group, the following seven potential prognostic factors were investigated with respect to outcomes: age (≤60 vs. >60 years), sex, Karnofsky performance score (KPS, <70 vs. 70 vs. >70), primary tumor type (breast cancer vs. non–small cell lung cancer vs. small-cell lung cancer vs. renal cell carcinoma vs. malignant melanoma vs. cancer of unknown primary vs. colorectal cancer vs. other tumors), number of brain metastases (1 vs. 2–3 vs. ≥4), extracerebral metastases (no vs. yes), and the time between the first diagnosis of the malignant disease and radiotherapy of brain metastases (≤6 vs. >6 months). These potential prognostic factors were first univariately analyzed with the log-rank test. Those factors found to be significantly associated with intracerebral control or survival, respectively, in the univariate analysis were evaluated in multivariate analyses, which were performed with the Cox proportional hazards model. On the basis of the results of the multivariate analyses of the test group, two scoring systems were developed, one for IC and another for OS. The scores included the prognostic factors found significant on multivariate analysis. The score for each factor was determined by dividing the 6-month IC or OS rate (given in %) by 10 (see Tables 1 and 2). The total score represented the sum of the scores for each factor. The score groups of the test group were compared with the corresponding score groups of the validation group to investigate the validity and reproducibility of both scoring systems.

The comparisons with respect to intracerebral control and survival have been performed using the Kaplan-Meier method (6). The Kaplan-Meier curves were compared using the log-rank test. The difference was considered significant, if $p < 0.05$.

Table 1. IC rates at 6 months and the corresponding scores

	IC at 6 months (%)	Score
Karnofsky Performance Score		
< 70	21	2
= 70	59	6
> 70	73	7
Primary tumor type		
Breast cancer	65	7
Non–small cell lung cancer	56	6
Small-cell lung cancer	56	6
Renal cell carcinoma	53	5
Malignant melanoma	49	5
Cancer of unknown primary	33	3
Colorectal cancer	43	4
Other tumors	53	5
Number of brain metastases		
1	73	7
2–3	63	6
≥4	39	4
Interval from tumor diagnosis to WBRT		
≤6 months	49	5
>6 months	59	6

Abbreviations: IC = intracerebral control; WBRT = whole-brain radiotherapy.

RESULTS

In the test group, performance status (risk ratio (RR) 0.57; 95% confidence Interval (CI), 0.51–0.64; $p < 0.001$), primary tumor type (RR 1.04; 95% CI, 1.01–1.07; $p = 0.006$), number of brain metastases (RR 1.22; 95% CI, 1.14–1.30; $p < 0.001$), and interval from tumor diagnosis to radiotherapy (RR 0.81;

Table 2. OS rates at 6 months and the corresponding scores

	OS at 6 months (%)	Score
Age		
≤60 years	52	5
>60 years	35	4
Karnofsky Performance Score		
<70	9	1
= 70	47	5
>70	70	7
Extracranial metastases at the time of RT		
No	62	6
Yes	30	3
Number of brain metastases		
1	65	7
2–3	56	6
≥4	26	3
Interval from tumor diagnosis to WBRT		
≤6 months	41	4
>6 months	45	5

Abbreviations: OS = overall survival; RT = radiotherapy; WBRT = whole-brain radiotherapy.

95% CI, 0.69–0.95; $p = 0.010$) were significantly associated with IC. Age (RR 1.39; 95% CI, 1.24–1.55; $p < 0.001$), performance status (RR 0.52; 95% CI, 0.48–0.56; $p < 0.001$), extracerebral metastases (RR 1.51; 95% CI, 1.34–1.70; $p < 0.001$), number of brain metastases (RR 1.09; 95% CI, 1.03–1.15; $p = 0.002$), and interval from tumor diagnosis to RT (RR 0.80; 95% CI, 0.72–0.89; $p < 0.001$) were significantly associated with OS. For IC, the total scores ranged from 14 to 27 points (Fig. 1, top), and the patients were divided into three groups (14–18, 19–23, and 24–27 points). For OS, the total scores ranged from 15 to 30 points (Fig. 1, bottom), and the patients were divided into three groups (15–19, 20–25, and 26–30 points).

In the test group, the actuarial 6-month IC rates were 17% for patients with a score of 14–18 points, 49% for those with a score of 19–23 points, and 77% for those with a score of 24–27 points ($p < 0.0001$, Fig. 2). The corresponding IC rates in the validation group were 19%, 52%, and 77%, respectively ($p < 0.0001$, Fig. 2). The results of the comparison of each of the score Groups A, B, and C of the test group and the corresponding groups of the validation group with respect to IC are summarized in Table 3.

In the test group, the actuarial 6-month OS rates were 9% for patients with a score of 15–19 points, 41% for those with a score of 20–25 points, and 78% for those with a score of 26–30 points ($p < 0.0001$, Fig. 3). The OS rates in the validation group were 7%, 39%, and 79%, respectively ($p < 0.0001$, Fig. 3). The results of the comparison of each of the score Groups A, B and C of the test group and of the corresponding groups of the validation group with respect to OS are summarized in Table 3.

An additional analysis has been performed that compared the treatment regimens with respect to IC an OS. At 6 months, the IC rates were 46% after WBRT alone, 71% after radiosurgery alone, 89% after WBRT followed by radiosurgery, and 74% after neurosurgical resection followed by WBRT ± boost, respectively ($p < 0.001$). The 6-month OS rates were 34%, 70%, 77%, and 71%, respectively ($p < 0.001$).

DISCUSSION

The treatment for patients with brain metastases is controversial. Several therapies are available including short-course WBRT, long-course radiotherapy, radiosurgery, and neurosurgery. Prognostic scoring systems can help guide the physician to select the optimal treatment regimen for the individual patient. Two very important endpoints regarding the treatment of brain metastases are IC and OS. An intracerebral recurrence has been reported by several authors to lead to severe neurocognitive deficits and should be avoided if possible (2–4). Aoyama *et al*. (4) reported relevant neurocognitive decline at 1 year following treatment in 41% of patients who received stereotactic radiosurgery alone and in 59% of patients who received stereotactic radiosurgery plus upfront WBRT. At 2 years, the rates were 31% and 48%, respectively. At 3 years the rates were 85% and 48%, respectively. However, because at 3 years only 4 patients were at risk, the

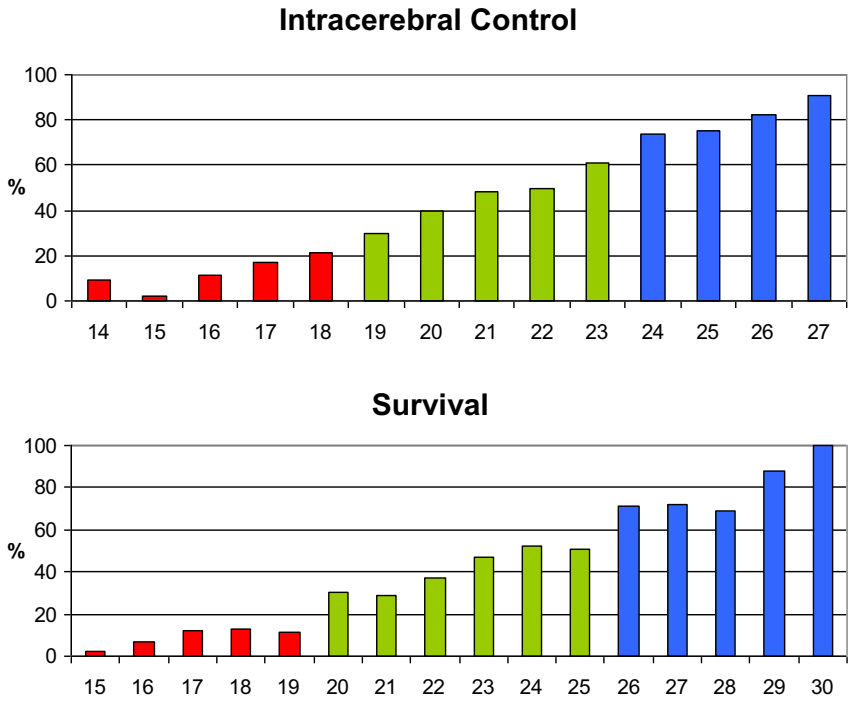

Fig. 1. The 6-month intracerebral control rates (top) and 6-month survival rates (bottom) of the test group related to the different scores.

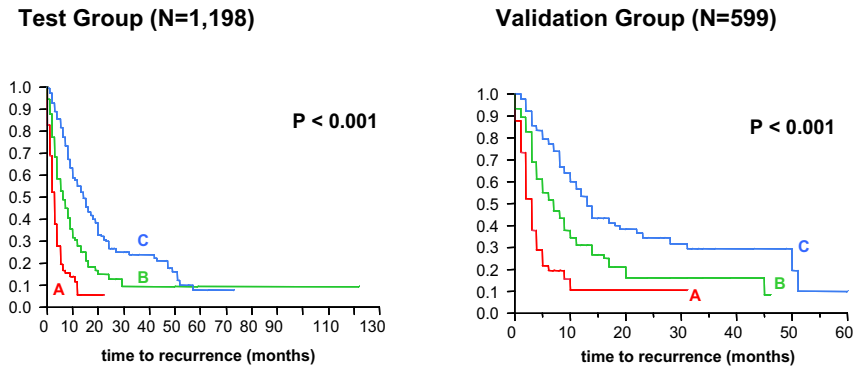

Fig. 2. Kaplan-Meier curves for intracerebral control of the three score Groups A (14–18 points), B (19–23 points), and C (24–27 points) of both the test group (left) and the validation group (right).

3-year results of this study must be interpreted with caution. Aoyama *et al*. concluded that intracerebral control is the most important factor for stabilizing neurocognitive function. In contrast to the previous trials, a more recent Phase III trial demonstrated that patients receiving radiosurgery plus upfront WBRT were significantly more likely to show a decline in learning and memory function at 4 months following treatment than patients receiving radiosurgery alone (5). Unexpectedly, survival at 4 months was better after radiosurgery alone than after radiosurgery plus upfront WBRT (87% vs. 71%). However, intracerebral control at 1 year was significantly better after WBRT plus radiosurgery than after radiosurgery alone (73% vs. 27%, $p = 0.0003$). Because the authors did not investigate neurocognitive function at 1 year and because neurocognitive function becomes more important in long-term survivors, the interpretation of the study of Chang *et al*. (5) is difficult, and the results should not be overestimated.

This presents the first scoring system that allows one to predict the intracerebral control of patients irradiated for brain metastases. The intracerebral control rates of the three prognostic groups in the test group were significantly different. Furthermore, the three prognostic groups of the validation groups were similar to those of the test group, as shown in Table 3. This finding demonstrates the high validity and reproducibility of this new scoring system in predicting intracerebral control. Patients with a poor expected local control (Groups A and B) and a relatively favorable survival prognosis may benefit from an intensification of their treatment including more aggressive modalities such as longer courses of WBRT, radiosurgery, or neurosurgical resection. Scoring systems predictive of survival in patients with brain metastases would be of substantial value. However, several scoring systems already exist for survival of patients with brain metastases. These scores include a maximum of four prognostic factors. The most commonly used scoring system is the Recursive Partitioning Analysis (RPA) classification presented by Gaspar *et al*. (7). The RPA classification was based on 1,200 patients from three RTOG trials who had received different types of treatment including WBRT and radiosurgery. The RPA classification included four prognostic factors, age, KPS, extracerebral metastases, and control of the primary tumor. However, the RPA Class III has been defined primarily by one factor, a KPS <70. Therefore, prognostic Group III is quite inhomogeneous. Furthermore, the score is 12 years old, and treatment strategies have changed during this period of time.

Table 3. Comparison of scores for Groups A, B, and C of the test group and the corresponding groups of the validation group with respect to intracerebral control (IC) and survival (OS)

	Intracerebral control rates at 6 months		
	Test group	Validation group	*p* value
Group A (14–18 points)	16%	19%	0.52
Group B (19–23 points)	49%	52%	0.65
Group C (24–27 points)	77%	77%	0.98
	Survival rates at 6 months		
	Test group	Validation group	*p* value
Group A (15–19 points)	9%	7%	0.62
Group B (20–25 points)	41%	39%	0.76
Group C (26–30 points)	78%	79%	0.92

In 1999, the Rotterdam Score, based on the data of 1,292 patients, was presented. However, this system has not achieved wide acceptance (8). The Score Index for Radiosurgery (SIR) was published in 2000 (9). However, this score was obtained from the data from only 65 patients treated with radiosurgery between 1993 and 1997 and does not appear representative for the majority of patients with brain metastases. In 2004, a group from Belgium presented the Basic Score for Brain Metastases (BSBM) (10). The score can be applied to patients treated with WBRT alone, WBRT plus radiosurgery, or neurosurgical resection followed by WBRT. However, the BSBM was based on data from only 110 patients, which may result in limited applicability due to the large confidence intervals found when

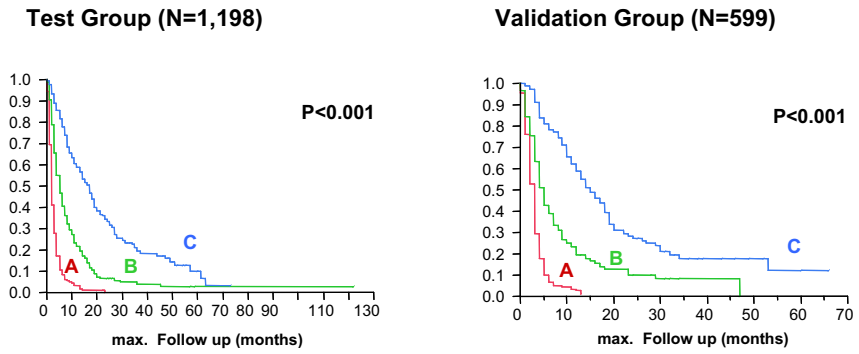

Fig. 3. Kaplan-Meier curves for survival of the three score Groups A (15–19 points), B (20–25 points), and C (26–30 points) of both the test group (left) and the validation group (right).

analyzing small cohorts of patients. In 2008, two further scoring systems predictive of survival of patients with brain metastases were presented, our score based on the data from 1,085 patients treated with WBRT alone, and the Graded Prognostic Assessment (GPA) score based on 1,960 patients from five RTOG trials who had received different types of treatment (11, 12). Both scores included four prognostic factors. Our own score included age, KPS, extracerebral metastases, and the interval from tumor diagnosis to WBRT. THE GPA score included age, KPS, number of brain metastases, and extracerebral metastases. Our new score is the first scoring system that included five prognostic factors including age, KPS, extracerebral metastases, the interval from tumor diagnosis to WBRT, and the number of brain metastases. Thus, it may be considered something of a hybrid between the GPA and our previous scoring system. Furthermore, a score including five instead of four prognostic factors is likely to be a more discriminating tool to predict survival of patients with brain metastases. According to a large retrospective analysis of 4,259 eligible patients from 11 institutions, the prognostic factors for patients with brain metastases vary with the type of primary tumor (13). Therefore, it appears reasonable to collect data of additional patients in the future, which would enable us to perform further analyses and to apply both of our scoring systems to subgroups of patients with a particular primary tumor type.

The survival rates of the three prognostic groups in the test group were significantly different from each other, and those from the three prognostic groups of the validation groups were very similar to those of the test group. The latter finding demonstrates the validity and reproducibility of this scoring system. Moreover, it appeared advantageous to develop a survival scoring system from the same cohort of patients who formed the basis of the score predicting intracerebral control to optimally integrate the use of both scores for patient care.

Patients with a poor survival prognosis are candidates for short-course WBRT with 5 × 4 Gy in 1 week, because short-course WBRT has been demonstrated to be as effective as longer WBRT programs and requires less of the patient's limited life span. However, patients with brain metastases who are expected to live longer than 6 months are at greater risk of experiencing late radiation related toxicity such as neurocognitive dysfunction. The risk of developing neurocognitive toxicity is decreased with the use of lower doses per fraction. DeAngelis *et al.* (1) observed neurocognitive deficits after WBRT alone with doses per fraction of 3–6 Gy. Therefore, patients with a relatively favorable survival prognosis appear better treated with longer-course WBRT including doses per fraction of <3 Gy. Patients with a favorable survival prognosis may also benefit from more aggressive modalities such as radiosurgery and neurosurgery, as demonstrated in the additional analysis of our study. This applies in particular to patients who have an expected IC that must be improved. However, in the test group of our study, no patient was identified who had a favorable survival prognosis (Group C) and a poor expected IC (Group A). Fifty-six patients (5%) were identified with both a favorable survival prognosis (Group C) and an intermediate prognosis of IC (Group B).

In conclusion, patients irradiated for brain metastases can be grouped with these scores to estimate both intracerebral control and survival rates. The IC and OS rates of each of the three prognostic groups in the patients belonging to the validation group were similar to the corresponding rates in the patients of the test group. These findings demonstrate the validity and reproducibility of both scores. Patients with a poor expected survival are candidates for short-course WBRT, and those with a relatively favorable survival prognosis are candidates for long-course radiotherapy, which is associated with less late-radiation-related toxicity. Patients in whom the expected IC needs to be improved but have a reasonably favorable expected survival may benefit from a more aggressive treatment regimen including longer courses of external beam radiotherapy, radiosurgery, and neurosurgery. These scoring systems are not only useful in predicting survival and intracerebral control but also in 2aiding the choice of rational treatment and the stratification of patients in future trials.

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Validation of a survival score for patients treated with whole-brain radiotherapy for brain metastases

Up to 40% of all cancer patients develop brain metastasis during the course of their disease [10]. Whole brain radiotherapy (WBRT) alone is the most common treatment for these patients, in particular for those patients with multiple lesions, although other treatment approaches are available for selected patients with a small number of lesions [4, 6, 9]. Short-course WBRT such as 5 fractions of 4 Gy given in 1 week can be considered preferable to longer-course programs such as 10 fractions of 3 Gy in 2 weeks or 20 fractions of 2 Gy in 4 weeks for patients with a short survival time [6]. In contrast, long-term survivors are better treated with longer-course WBRT and lower doses per fraction, since the risk of neurocognitive deficits due to WBRT increases with the dose per fraction [1]. Scoring systems predicting survival can help select the appropriate WBRT schedule for the individual patient. Several scoring systems already exist [2, 5]. However, these scores did not focus specifically on patients receiving WBRT alone but also included patients treated with other approaches. Therefore, we developed a survival score specifically for patients treated with WBRT alone for brain metastases in 2008 [7]. However, this scoring system, which was based on a study of 1,085 patients receiving WBRT alone between 1992 and 2005, has not yet been validated. The present study was performed to validate our score in 350 new patients from Germany and Slovenia who received WBRT alone for brain metastases.

Materials and methods

The present study included 350 patients who received WBRT for brain metastases between 2005 and 2011. This retrospective cohort represents the validation group for our previously developed survival score. In that previous score, the following four independent prognostic factors for survival were included: age (≤60 vs. ≥61 years, Karnofsky Performance Score (KPS ≥70 vs. <70), presence of extracranial metastases at the time of WBRT (no versus yes), and the interval between the first diagnosis of cancer and WBRT (>8 months versus ≤8 months; **Tab. 1**). For each of these factors, a separate score was calculated based on the 6-month survival rate (in %) divided by 10. The total prognostic score represented the sum of the scores from each factor. The total scores ranged between 9 and 18 points (**Fig. 1**). Four groups were formed according to the total score: 9–10 points (group A), 11–13 points (group B), 14–16 points (group C), and 17–18 points (group D). The four groups were compared for survival using the Kaplan–Meier method [3]. The Kaplan–Meier curves were compared using the log-rank test. The difference was considered significant with $p<0.001$. This scoring system was applied in the same way to the 350 patients of the present validation study. Each the prognostic groups A, B, C, and D of the present study was compared to each of the prognostic groups A, B, C, and D of the previous study using the χ^2 test.

Results

In the present validation study, the scores also ranged from 9–18 points (**Fig. 2**) and were similar to those of the previous study (**Fig. 1**). The actuarial 6-month survival rates in the present study were 8% for patients with a total score of 9–10 points, 24% for those with a score of 11–13 points, 51% for those with a score of 14–16 points, and 82% for those with a score of 17–18 points (**Fig. 3**, $p<0.001$). The corresponding survival rates in the previous study of 1,085 patients were 6%, 15%, 43%, and 76%, respectively (**Fig. 4**, $p<0.001$). The comparisons of each the prognostic groups A, B, C, and D of the present study to each of the prognostic groups A, B, C, and D of the previous study did not show a significant difference. The p values were 0.81 for groups A,

Tab. 1 Survival rates 6 months after WBRT and the corresponding scores

	Survival at 6 months (%)	Score
Age		
≤60 years	43	4
≥61 years	25	3
Karnofsky Performance Score		
<70	8	1
≥70	53	5
Extracranial metastases at the time of RT		
No	51	5
Yes	24	2
Interval from tumor diagnosis to WBRT		
≤8 months	32	3
>8 months	36	4

RT radiotherapy, *WBRT* whole-brain radiotherapy.

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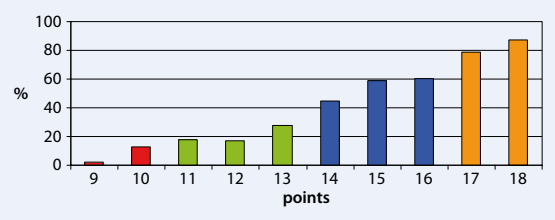

Fig. 1 ▲ The 6-month survival rates (in %) related to the corresponding scores of the present study

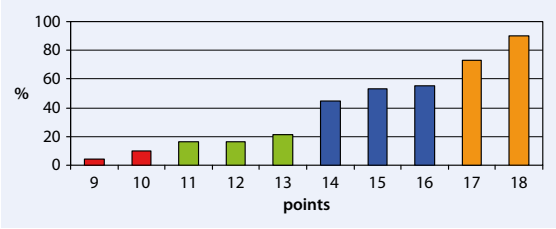

Fig. 2 ▲ The 6-month survival rates (in %) related to the corresponding scores of the previous study [7]

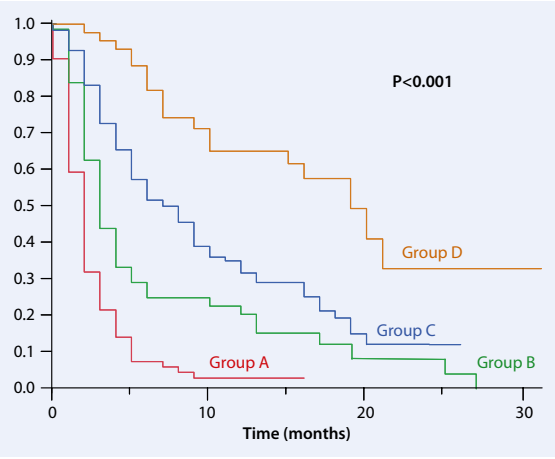

Fig. 3 ▲ Kaplan–Meier curves for survival of the four groups A, B, C, and D of the present study

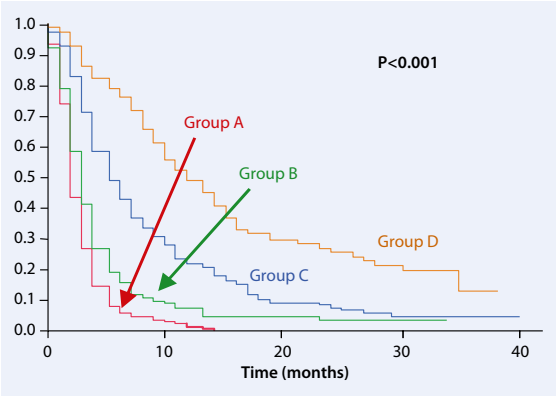

Fig. 4 ▲ Kaplan–Meier curves for survival of the four groups A, B, C, and D of the previous study [7]

0.18 for groups B, 0.29 for groups C, and 0.75 for groups D.

Discussion

In patients with brain metastases with a very poor survival prognosis, short-course WBRT appears preferable to longer programs, since a short radiation program requires less of a patient's limited lifespan for cancer therapy [6]. Patients who live longer than 6 months are at greater risk of experiencing radiation related neurocognitive problems. Since DeAngelis et al. [1] observed neurocognitive deficits only after doses per fraction of 3 Gy or higher, patients with a favorable prognosis appear better treated with longer-course WBRT including doses per fraction of <3 Gy. Thus, it is important to be able to estimate the patient's survival prognosis in order to select the most appropriate treatment regimen. A few years ago, we presented a new scoring system particularly designed for patients receiving WBRT alone for brain metastases [7]. However, until now that score has not been validated.

The present series represents the validation cohort for our previously developed survival score. The 6-month survival rates of the four prognostic groups in the 350 patients of the validation cohort were not significantly different from the survival rates observed in the previous study of 1,085 patients [7]. This demonstrates the validity and reproducibility of our survival score. However, both the previous and the present study were based on retrospective data which may have led to hidden biases.

The validated score allows grouping the patients according to their survival prognosis. Patients with a score of 9–13 points (groups A and B) had 6-month survival rates of less than 25%, and may be treated with 5 fractions of 4 Gy in 1 week. In patients with a score of 14–16 points (group C), short-course WBRT may at least be considered, since about 50% of these patients died within 6 months. Patients with a score of 17–18 points (group D) had a 6-month survival probability of >80% and, therefore, appear better treated with longer-course WBRT in order to minimize the potential risk of late radiation toxicity.

Conclusion

Our previously designed survival score for patients receiving WBRT alone for brain metastases was valid and reproducible in another patient cohort. The validated score can help tailor the treatment of brain metastases to an individual patient. Additionally, this scoring system can also be used in stratifying patients when designing clinical trials.

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Original article

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Abstract · Zusammenfassung

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Validation of a survival score for patients treated with whole-brain radiotherapy for brain metastases

Abstract

Background. This study was performed to validate a scoring system published in 2008 to predict the survival of patients receiving whole-brain radiotherapy (WBRT) alone for brain metastases.

Methods. The scoring system included four independent prognostic factors: age, performance status, extracranial metastases, and interval between first diagnosis of cancer and WBRT. The score for each prognostic factor was determined by dividing the 6-month survival rate (in %) by 10. The total score represented the sum of the scores for each prognostic factor. Total scores ranged from 9–18 points, and patients were divided into four groups. In the present study, 350 new patients were evaluated in order to validate the previously developed score.

Results. In the present validation study, the 6-month survival rates were 8% for patients with a score of 9–10 points (group A), 24% for those with a score of 11–13 points (group B), 51% for those with a score of 14–16 points (group C), and 82% for those with scores of 17–18 points (group D), respectively ($p<0.001$). In our previous study published in 2008, the 6-month survival rates were 6%, 15%, 43%, and 76%, respectively ($p<0.001$). The comparisons between each of the four prognostic groups of both series did not reveal a significant difference.

Conclusion. In this study, the 6-month survival rates of the four prognostic groups were not significantly different from those of the preceding study. This demonstrates the validity and reproducibility of this score. The score can help select the appropriate treatment for the individual patient and help design prospective trials.

Keywords
Brain metastases · Whole-brain radiotherapy · Survival · Score · Validation

Validierung eines Überlebensscores für Patienten mit Hirnmetastasen nach Ganzhirnbestrahlung

Zusammenfassung

Hintergrund. Ziel dieser Studie war die Validierung eines 2008 publizierten Scores zur Abschätzung der Überlebensprognose von Patienten mit Hirnmetastasen nach alleiniger Ganzhirnbestrahlung (WBRT).

Methoden. Der Score beinhaltete die vier unabhängigen Prognosefaktoren Alter, Allgemeinzustand, extrakranielle Metastasen zur Zeit der WBRT und Intervall von der Erstdiagnose der Tumorerkrankung bis zur WBRT. Der Score für jeden Prognosefaktor wurde ermittelt, indem die Überlebensrate nach 6 Monaten (in %) durch 10 dividiert wurde. Der Gesamtscore entsprach der Summe der vier Einzelscores und lag zwischen 9 und 18 Punkten. Entsprechend dem Gesamtscore wurden vier prognostische Gruppen gebildet. Um den initialen Score zu validieren, wurden 350 neue Patienten in die aktuelle Studie eingeschlossen.

Ergebnisse. In der aktuellen Serie betrugen die 6-Monats-Überlebensraten 8% bei einem Score von 9–10 Punkten (Gruppe A), 24% bei 11–13 Punkten (Gruppe B), 51% bei 14–16 Punkten (Gruppe C) und 82% bei 17–18 Punkten (Gruppe D; $p<0{,}001$). In der Studie aus dem Jahr 2008 waren die 6-Monats-Überlebensraten jeweils 6%, 15%, 43% und 76% ($p<0{,}001$). Die Vergleiche zwischen den einzelnen Prognosegruppen beider Serien ergaben keinen signifikanten Unterschied.

Schlussfolgerung. In der aktuellen Studie waren die 6-Monats-Überlebensraten der vier Prognosegruppen im Vergleich zur vorherigen Studie nicht signifikant unterschiedlich. Dies zeigt die Validität und Reproduzierbarkeit des Scores. Der Score kann bei der Wahl des geeigneten Therapieregimes für den individuellen Patienten hilfreich sein, ebenso bei der Entwicklung prospektiver Studien.

Schlüsselwörter
Hirnmetastasen · Ganzhirnbestrahlung · Überleben · Score · Validierung

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A new survival score for patients with brain metastases from non-small cell lung cancer

Non-small cell lung cancer (NSCLC) is the most common primary tumor in patients presenting with brain metastases and accounts for about 40% of these patients [4, 6]. The vast majority of patients with brain metastases from NSCLC are treated with whole-brain radiotherapy (WBRT) alone. The most common WBRT schedule worldwide is 10 fractions of 3 Gy in 2 weeks. In addition, short-course WBRT mainly with 5 fractions of 4 Gy in 1 week or longer-course WBRT programs such as 14–15 fractions of 2.5 Gy in 3 weeks and 20 fractions of 2 Gy in 4 weeks are used. The choice of the WBRT schedule for the individual patient is likely to be influenced by the patient's survival prognosis. Patients with a poor expected survival may be appropriately treated with 5 fractions of 4 Gy in 1 week instead of 10 fractions of 3 Gy in 2 weeks to avoid these patients spending more of their remaining life time with radiotherapy than necessary. Retrospective studies have suggested that patients with a much more favorable prognosis benefit from longer-course WBRT with total doses higher than 30 Gy and doses per fraction of <3 Gy in terms of better outcomes and less neurocognitive deficits [2, 7, 14]. These patients should receive 14–15 fractions of 2.5 Gy in 3 weeks or 20 fractions of 2 Gy in 4 weeks instead of 10 fractions of 3 Gy in 2 weeks. Therefore, scoring systems which help estimate the patient's survival time are important for selecting the appropriate WBRT schedule for the individual patient. Since different primary tumors may vary with respect to biology and course of the disease, it appears reasonable to create specific survival scores for the most common primary tumors in patients with brain metastasis such as NSCLC.

Patients and methods

This study included data of 514 patients who received WBRT alone for brain me-

Tab. 1 Potential prognostic factors in the test group (n=257) and in the validation group (n=257). The comparison was performed with the χ^2 test

	Test group n (%)	Validation group n (%)	p value
WBRT schedule			
5 fractions of 4 Gy	73 (28)	70 (27)	
10 fractions of 3 Gy	184 (72)	187 (73)	0.89
Age			
≤61 years	134 (52)	139 (54)	
≥62 years	123 (48)	118 (46)	0.81
Gender			
Female	101 (39)	104 (40)	
Male	156 (61)	153 (60)	0.89
Karnofsky Performance Score			
<70	106 (41)	104 (40)	
≥70	151 (59)	153 (60)	0.91
Brain metastases (n)			
1–3	87 (34)	95 (37)	
≥4	170 (66)	162 (63)	0.60
Extracranial metastases			
No	101 (39)	111 (43)	
Yes	156 (61)	146 (57)	0.54
Interval tumor diagnosis to WBRT			
<3 months	140 (54)	148 (58)	
≥3 months	117 (46)	109 (42)	0.65

WBRT whole brain radiotherapy.

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Tab. 2 Univariate analysis of survival at 6 months and at 12 months

	Survival rate at 6 months (%)	Survival rate at 12 months (%)	p value
WBRT schedule			
5 fractions of 4 Gy	30	16	
10 fractions of 3 Gy	33	19	0.64
Age			
≤61 years	40	23	
≥62 years	24	12	**0.007**
Gender			
Female	45	27	
Male	24	12	**0.003**
Karnofsky Performance Score			
<70	8	2	
≥70	48	29	**<0.001**
Brain metastases (n)			
1–3	41	23	
≥4	27	15	**0.023**
Extracranial metastase			
No	51	30	
Yes	20	10	**<0.001**
Interval tumor diagnosis to WBRT			
<3 months	31	19	
≥3 months	33	17	0.19

Tab. 3 Results of the multivariate analysis of survival

	Risk ratio	95% confidence interval	p value
Age			
≤61 vs. ≥62 years	1.26	0.95–1.67	0.10
Gender			
Female vs. male	1.42	1.07–1.92	**0.015**
Karnofsky Performance Score			
≥70 vs. <70	2.67	1.98–3.60	**<0.001**
Brain metastases (n)			
1–3 vs. ≥4	1.01	0.91–1.12	0.85
Extracranial metastases			
No vs. Yes	1.98	1.47–2.69	**<0.001**

Tab. 4 Survival rates 6 months after whole brain radiotherapy and the corresponding scores

	Survival at 6 months (%)	Score
Gender		
Female	45	5
Male	24	2
Karnofsky Performance Score		
<70	8	1
≥70	48	5
Extracranial metastases		
No	51	5
Yes	20	2

tastases from NSCLC. The patients were divided into a test group (n=257) and a validation group (n=257). In the test group, seven potential prognostic factors were analyzed with respect to survival. These factors included the WBRT schedule (5 fractions of 4 Gy vs. 10 fractions of 3 Gy), age (≤61 years vs. ≥62 years, median age 61 years), gender, Karnofsky Performance Score (KPS <70 vs. ≥70), number of brain metastases (1–3 vs. ≥4), extracranial metastases (no vs. yes), and the interval between tumor diagnosis and WBRT (<3 months vs. ≥3 months). The potential prognostic factors in the test group and the validation group are shown in **Tab. 1**.

In the test group, the univariate analyses of survival were performed with the Kaplan–Meier method [5] and the log-rank test (**Tab. 2**). Prognostic factors found to be significant on univariate analysis pP<0.05) were included in a multivariate analysis performed with the Cox proportional hazards model. In the multivariate analysis, gender, KPS, and extracranial metastases were significantly associated with survival (**Tab. 3**). These three independent prognostic factors were included in the scoring system. The score for each factor was determined by dividing the 6-month survival rate (in %) by 10 (**Tab. 4**). The total prognostic score represented the sum of the scores from each factor. The total scores were 5, 8, 9, 11, 12, and 15 points (**Fig. 1**). Three groups were formed according to the total score: 5–9 points (group A), 11–12 points (group B), and 15 points (group C). The three prognostic groups A, B and C of the test group were compared to the corresponding groups of the validation group by using the χ^2 test. The study was approved by the local ethics committee.

Results

In the test group, the 6-month survival rates were 9% in group A, 54% in group B, and 79% in group C (p<0.001; **Fig. 2**). In the validation group the 6-month survival rates were 14% in group A, 56% in group B, and 78% in group C (p<0.001; **Fig. 2**).

The comparisons between each of the three prognostic groups A, B, and C of the test and the validation group did not show a significant difference. The p values were p=0.30 for the comparison of both groups A, p=0.92 for the comparison of both groups B, and p=0.99 for the comparison of both groups C, respectively.

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Discussion

WBRT alone is still the most common treatment of brain metastasis [6]. The appropriate WBRT regimen depends on the patient's survival prognosis. Patients with a poor prognosis would benefit from a short course of WBRT such as 5 fractions of 4 Gy given in 1 week, which has been reported to be similarly effective with respect to survival and local control as longer WBRT programs such as 10 fractions of 3 Gy in 2 weeks [11]. Acute toxicity was not significantly greater with 5 fractions of 4 Gy when compared to 10 fractions of 3 Gy. However, the risk of developing radiotherapy-related neurocognitive deficits increases with the dose per fraction [2, 7]. Patients with a relatively favorable survival prognosis are better treated with longer course WBRT including doses per fraction of <3 Gy, because these patients may live long enough to experience such deficits. Therefore, it is important to be able to estimate the patient's survival prognosis in order to administer the most appropriate treatment regimen.

Estimating the patient's survival time can be facilitated with the help of prognostic scores. Several survival scores already exist for patients with brain metastasis but have been developed in heterogeneously treated series of patients and in series of patients with many different primary tumors [3, 9, 10]. Since the biological behavior of the various primary tumors may be quite different, it appears reasonable to create separate survival scores for the most common tumor entities associated with brain metastasis. In the current study, a survival score has been designed for patients with brain metastasis from NSCLC. NSCLC is the most common primary tumor in patients with brain metastasis and accounts for about 40% of these patients [6].

The current score included three independent predictors of survival, gender, KPS, and extracranial metastases. Gender has not yet been included in previous scores, which demonstrates the need for separate scores for different tumor entities. Based on the individual scores evaluated for each of the three independent prognostic factors, three prognostic groups were designed. The 6-month survival rates of the three groups were very different. Patients of group A had the worst survival prognosis with a 6-month survival rate of only 9% and, therefore, should be considered for short-course WBRT such as 5 fractions of 4 Gy in 1 week. The patients of group B had an intermediate survival prognosis; the

Abstract · Zusammenfassung

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D. Rades · L. Dziggel · B. Segedin · I. Oblak · V. Nagy · A. Marita · S.E. Schild · N.T. Trang · M.T. Khoa

A new survival score for patients with brain metastases from non-small cell lung cancer

Abstract

Background and purpose. Non-small cell lung cancer (NSCLC) is the most common primary tumor in patients developing brain metastasis. This study was performed to develop and validate a survival score particularly for this group of patients.

Patients and methods. In this study, the data of 514 patients treated with whole-brain radiotherapy (WBRT) alone for brain metastasis from NSCLC were retrospectively analyzed. The patients were divided into a test group (n=257) and a validation group (n=257). In the multivariate analysis of the test group, gender, performance status, and extracranial metastases were independent predictors of survival and, therefore, included in the scoring system. The score for each of the three factors was obtained from the 6-month survival rate (in %) divided by 10. The total scores that represented the sum of the three scores were 5, 8, 9, 11, 12, or 15 points. Three prognostic groups were formed according to the total scores.

Results. The 6-month survival rates in the test group were 9% for 5–9 points (group A), 54% for 11–12 points (group B), and 79% for 15 points (group C). In the validation group the 6-month survival rates were 14, 56, and 78%, respectively. The comparisons between the prognostic groups A, B, and C of the test and the validation group did not reveal any significant differences.

Conclusion. This new score appears valid and reproducible. It can help predict the survival of patients with brain metastasis from NSCLC.

Keywords

Brain metastasis · Whole-brain radiotherapy · Non-small cell lung cancer · Survival prognosis · Score

Ein neuer Überlebensscore für Patienten mit Hirnmetastasen eines nicht-kleinzelligen Lungenkarzinoms

Zusammenfassung

Hintergrund und Ziel. Das NSCLC ist der häufigste Primärtumor bei Patienten mit Hirnmetastasen. Ziel dieser Studie war es, speziell für diese Patientengruppe einen Überlebensscore zu entwickeln und zu validieren.

Patienten und Methoden. In dieser Studie wurden die Daten von 514 Patienten, die eine alleinige Ganzhirnbestrahlung (WBRT) bei Hirnmetastasen eines NSCLC erhielten, retrospektiv analysiert. Die Patienten wurden in eine Testgruppe (n=257) und eine Validierungsgruppe (n=257) unterteilt. In der Multivarianzanalyse der Testgruppe erwiesen sich das Geschlecht, der Karnofsky-Index und extrakranielle Metastasierung als signifikante Prognosefaktoren für das Überleben und wurden in dem Scoringsystem berücksichtigt. Der Score für jeden Faktor wurde ermittelt, indem die Überlebensrate nach 6 Monaten (in %) durch 10 dividiert wurde. Der jeweilige Gesamtscore entsprach der Summe der 3 Einzelscores und betrug 5, 8, 9, 11, 12 oder 15 Punkte. Unter Berücksichtigung der Gesamtscores wurden 3 Prognosegruppen gebildet.

Ergebnisse. Die Überlebensraten nach 6 Monaten in der Testgruppe waren 9% bei 5–9 Punkten (Gruppe A), 54% bei 11–12 Punkten (Gruppe B) und 79% bei 15 Punkten (Gruppe C). In der Validierungsgruppe betrugen die Überlebensraten 14, 56 und 78%. Die Vergleiche der 3 Prognosegruppen A, B und C zwischen der Testgruppe und der Validierungsgruppe ergaben keine signifikanten Unterschiede.

Schlussfolgerungen. Dieser neue Score erscheint valide und reproduzierbar. Er kann dazu beitragen, die Überlebensprognose von Patienten mit Hirnmetastasen eines NSCLC abzuschätzen.

Schlüsselwörter

Hirnmetastasen · Ganzhirnbestrahlung · Nicht-kleinzelliges Bronchialkarzinom · Überlebensprognose · Score

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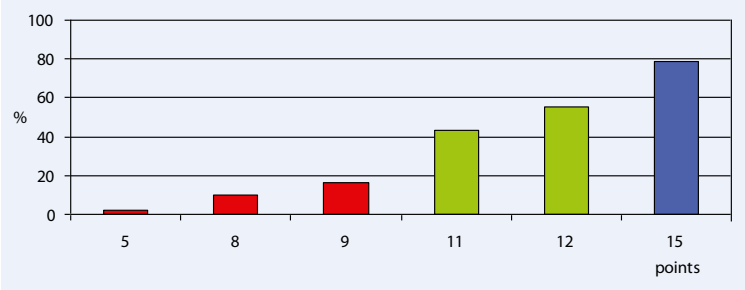

Fig. 1 ▲ The 6-month survival rates (in %) related to the corresponding scores

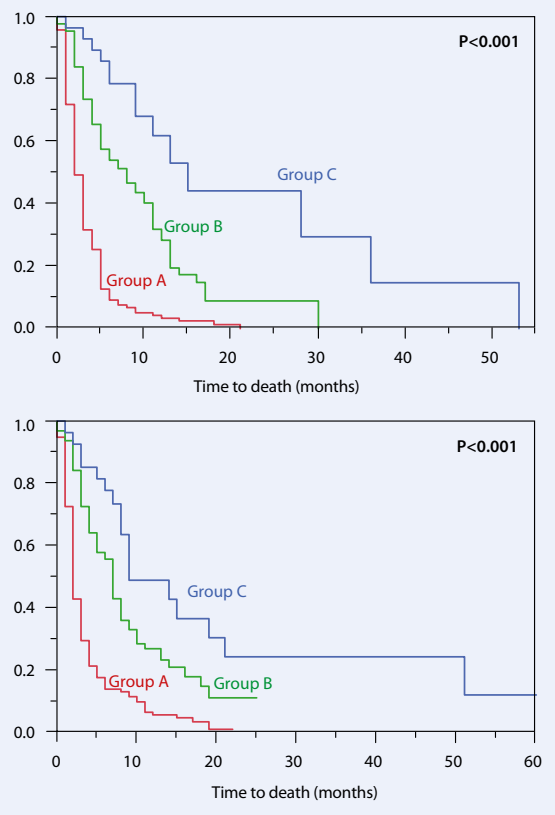

Fig. 2 ◀ Kaplan–Meier curves for survival of the three prognostic groups A, B, and C of the test group (*top*) and the validation group (*bottom*)

6-month survival rate was 54%. These patients may be candidates for the most common WBRT regimen, 10 fractions of 3 Gy in 2 weeks. The patients of group C, the most favorable prognostic group with a 6-month survival rate of 79% should be considered for long-course WBRT with doses per fraction of <3 Gy such as 20 fractions of 2 Gy in 4 weeks or 14–15 fractions of 2.5 Gy in 3 weeks. In patients with a favorable prognosis, such long-course WBRT programs are likely to result in less late toxicity and improved outcomes. In patients of the prognostic groups B and C who have only a limited number of brain metastases the option of radiosurgery or neurosurgery, either alone or in combination with WBRT, should be considered in order to offer the best available treatment [1, 8, 12, 13, 15].

The current score has been validated in another cohort of 257 patients. The 6-month survival rates of the three prognostic groups A, B, and C of this validation group were very similar to the survival rates of the prognostic groups A, B, and C of the test group. This finding demonstrates that this new survival score is both valid and well reproducible. When reviewing the results of this study, one should consider that the data were retrospectively analyzed. Retrospective studies always bear the risk of a hidden selection bias. Ideally, the score should also be validated in a prospective cohort of patients. However, such a validation study is not expected in the near future. Therefore, validating the score in a retrospective cohort of patients is the best option currently available.

Conclusion

This new score appeared valid and reproducible. It allows the survival of patients with brain metastases from NSCLC to be estimated, which can help the physician in selecting the most appropriate treatment for the individual patient.

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The first survival score for patients with brain metastases from small cell lung cancer (SCLC)

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ABSTRACT

Objective: Survival scores can help physicians select appropriate treatment for patients with brain metastasis. Primary tumors have different biological behavior justifying separate scoring systems for different tumors. In this study, a survival score was developed for patients with brain metastasis from SCLC.
Methods: Data of 172 patients receiving whole-brain radiotherapy alone for brain metastasis from SCLC were included. Patients were assigned to a test ($N = 86$) or a validation group ($N = 86$). In the test group, Karnofsky Performance Score, number of brain metastases, and extracranial metastasis were associated with survival and included in the score. Scores for each factor were obtained from the 6-month survival rate divided by 10. According to the total scores, which represented the sum of the three scores, three prognostic groups were formed.
Results: 6-Month survival rates in the test group were 3% for 5–8 points, 40% for 9–12 points, and 89% for 15 points ($p < 0.001$). In the validation group, 6-month survival rates were 3%, 41%, and 89% ($p < 0.001$). The comparisons between the three prognostic groups of the test group and the validation group did not show significant differences.
Conclusions: This new score appears valid and reproducible. It can be used to personalize the treatment to patients with brain metastasis from SCLC.

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1. Introduction

Brain metastases develop in up to 40% of adult cancer patients during the course of their disease [1]. Personalization of cancer treatment has been recognized more during recent years, particularly for a palliative situation such as brain metastasis. Most patients with brain metastasis have a poor prognosis, surviving only a few months [1,2]. These patients should receive a less burdensome treatment with a short overall treatment time such as 5×4 Gy of whole-brain radiotherapy (WBRT) alone given over one week. WBRT with 5×4 Gy in one week has been reported to be similarly effective in most patients as 10×3 Gy in two weeks, which is the most frequently used WBRT regimen [3]. Since the risk of radiation-related late toxicity such as neurocognitive deficits increases with the dose per fraction, 5×4 Gy is likely to result in more neurocognitive deficits than 10×3 Gy [4,5]. Since patients with an expected survival time of more than very few months have a higher risk of experiencing neurocognitive deficits, they appear better treated with 10×3 Gy than with 5×4 Gy. In cases with a very limited number of brain metastases, the option of radiosurgery or resection of the lesions should also be considered [6–10].

If the survival prognosis is very favorable, patients appear to benefit from an escalation of the total radiation dose beyond 30 Gy in terms of improved intracerebral control and survival [11]. If doses per fraction of less than 3 Gy are used, the risk of developing neurocognitive deficits further decreases [4]. Therefore, patients with a very favorable prognosis, who are not candidates for radiosurgery or neurosurgery, should receive WBRT with total dose greater than 30 Gy and doses per fraction of less than 3 Gy, e.g. with 20×2 Gy over four weeks. The considerations demonstrate that the selection of the appropriate treatment and WBRT regimen for the individual patient depends on his survival prognosis. Therefore, it is very important to be able to estimate the patient's survival prognosis, which can be facilitated by using survival scores. Because primary tumors vary with respect to biology, there is a rationale for

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Table 1
Potential prognostic factors in the test group ($N=86$) and in the validation group ($N=86$). The comparison was performed with the Chi-square test.

	Test group N (%)	Validation group N (%)	p-Value
WBRT schedule			
5 × 4 Gy	25 (29)	27 (31)	
10 × 3 Gy	61 (71)	59 (69)	0.91
Age			
≤61 years	43 (50)	41 (48)	
≥62 years	43 (50)	45 (52)	0.90
Gender			
Female	31 (36)	27 (31)	
Male	55 (64)	59 (69)	0.78
Karnofsky Performance Score			
<70	41 (48)	38 (44)	
≥70	45 (52)	48 (56)	0.84
Number of brain metastases			
1–3	24 (28)	23 (27)	
≥4	62 (72)	63 (73)	0.95
Extracranial metastases			
No	31 (36)	27 (31)	
Yes	55 (64)	59 (69)	0.78

WBRT: whole-brain radiotherapy.

separate survival scores for different primary tumors. The present study aimed to develop and validate a survival score for patients with brain metastasis from small-cell lung cancer (SCLC).

2. Patients and methods

In this study, the data of 172 patients receiving WBRT alone for brain metastases from SCLC were retrospectively evaluated. The patients were assigned either to a test group ($N=86$) or a validation group ($N=86$). In the test group, the following six potential prognostic factors were analyzed with respect to survival: WBRT schedule (5 × 4 Gy vs. 10 × 3 Gy), age (≤61 years vs. ≥62 years, median age: 61.5 years), gender, Karnofsky Performance Score (KPS <70 vs. ≥70), number of brain metastases (1–3 vs. ≥4), and extracranial metastases (no vs. yes). The distribution of these factors in both the test group and the validation group is given in Table 1.

The analyses of survival in the test group were performed with the Kaplan–Meier method [12] and the log-rank test (Table 2). Karnofsky Performance Score, number of brain metastases, and extracranial metastases were significantly associated with survival. These three prognostic factors were included in the scoring system.

Table 2
Univariate analysis of survival at 6 months and at 12 months.

	Survival rate at 6 months (%)	Survival rate at 12 months (%)	p-Value
WBRT schedule			
5 × 4 Gy	32	17	
10 × 3 Gy	28	14	0.54
Age			
≤61 years	35	16	
≥62 years	23	17	0.20
Gender			
Female	32	22	
Male	27	10	0.38
Karnofsky Performance Score			
<70	5	2	
≥70	51	26	<0.001
Number of brain metastases			
1–3	50	30	
≥4	21	9	0.033
Extracranial metastases			
No	45	36	
Yes	20	3	0.004

WBRT: whole-brain radiotherapy.

Table 3
Survival rates 6 months after whole-brain radiotherapy and the corresponding scores.

	Survival at 6 months (%)	Score
Karnofsky Performance Score		
<70	5	1
≥70	51	5
Number of brain metastases		
1–3	50	5
≥4	21	2
Extracranial metastases		
No	45	5
Yes	20	2

The score for each of the three factors was determined by dividing the 6-months survival rate (in %) by 10 (Table 3). The total scores represented the sum of the scores from each factor and were 5, 8, 9, 11, 12 or 15 points (Fig. 1). Three prognostic groups were designated according to the total score: 5–8 points (group A), 9–12 points (group B), and 15 points (group C). The survival of groups A, B and C of the test group were compared to the corresponding groups of the validation group using the Chi-square test. This study has been approved by the local ethics committee.

3. Results

In the test group, the 6-month survival rates were 3% in group A, 40% in group B, and 89% in group C, respectively ($p<0.001$). In the validation group the 6-month survival rates were 3% in group A, 41% in group B, and 89% in group C, respectively ($p<0.001$). The comparisons with respect to the 6-months survival rates between each of the three prognostic groups A, B and C of the test group and the corresponding prognostic groups A, B and C of the validation group did not show significant differences.

The p-values were $p=0.99$ (6-month survival rates: 3% vs. 3%) for the comparison of both groups A, $p=0.98$ (6-month survival rates: 40% vs. 41%) for the comparison of both groups B, and $p=1.00$ (6-month survival rates: 89% vs. 89%) for the comparison of both groups C, respectively.

4. Discussion

Primary and secondary malignant lesions within the brain play an important role in the field of oncology. Brain metastases are ten times as common as primary brain tumors [13–28]. The vast majority of cancer patients who have developed brain metastasis are treated with WBRT alone [1,29,30]. If WBRT alone is administered, one may choose between different WBRT regimens. The most commonly used WBRT regimens take between one week and four weeks. For patients with a very poor survival prognosis, it is important that the treatment is not more burdensome than necessary. Thus, neurosurgical resection should not be performed in these patients; in particular if all lesions cannot be completely removed. Radiosurgery may also be too stressful for these patients, since they

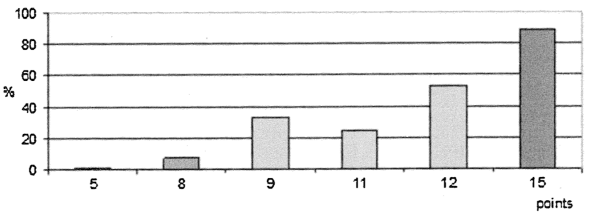

Fig. 1. The 6-months survival rates (in %) related to the corresponding scores.

have to tolerate a tight head mask and to lie flat and motionless for about half an hour or longer. Therefore, patients with a very poor survival prognosis are generally candidates for WBRT alone. If WBRT alone is administered, it is very important for these patients that the overall treatment time is not longer than necessary, since their remaining life time is quite short. Therefore, these patients should receive a short course of WBRT such as 5 × 4 Gy over one week, which has been reported to be similarly effective with respect to survival and local control as longer WBRT programs regimens in most patients [3]. Furthermore, radiation-related acute toxicity was not significantly greater with 5 × 4 Gy than with 10 × 3 Gy.

It has been reported that the risk of developing radiation-related neurocognitive deficits increases with the dose per fraction, in particular if the dose per fraction is 3 Gy or greater [4,5]. The risk of developing neurocognitive deficits also increases with the patient's survival time. Patients with an intermediate survival prognosis may be treated with the most common "standard" regimen, 10 × 3 Gy over two weeks. However, patients who have a very favorable survival prognosis may benefit even more from WBRT with a total dose greater than 30 Gy and doses per fraction less than 3 Gy. A retrospective study suggested that patients with a very favorable survival prognosis who received WBRT with total doses greater than 30 Gy achieved better intracerebral control and survival when compared to 10 × 3 Gy [11]. Patients with an intermediate or a very favorable survival prognosis who have only a very limited number of brain metastases (generally considered 1–3 lesions) may also be candidates for neurosurgery or radiosurgery, alone or in combination with WBRT [6–11,31,32].

Proper selection of the best treatment for the individual patient depends to a large extent on a clear understanding of the individual patient's survival prognosis. Therefore, it is critical to be able to estimate the patient's survival time in order to optimally tailor the treatment to the patient's individual situation. This goal can be achieved with prognostic scores. The first survival score for patients with brain metastasis, the recursive partitioning analysis (RPA) classification was first described in 1997 [33]. Since then, additional survival scores have been presented [34–36]. However, those scores were developed from data of heterogeneously treated patients with many different primary tumors. The biology of primary tumors may be quite different. Therefore, separate survival scores for the most common tumor entities associated with brain metastasis appear more desirable. Separate survival scores have already been successfully developed for other palliative situations such as metastatic spinal cord compression [37–40].

This study present a new survival score specifically designed for patients with brain metastasis from SCLC, the third most common primary tumor in patients with brain metastasis [1]. The new score included the three prognostic factors: Karnofsky Performance Score, number of brain metastases, and extracranial metastases. Based on the scores of these factors, three prognostic groups were created. Patients of group A had a 6-month survival rate of only 3%. We believe these patients should receive a short-course WBRT regimen such as 5 × 4 Gy in one week. Group B patients had an intermediate survival prognosis with a 6-month survival rate of 40%. Therefore, we believe that these patients would be best treated with the "standard" regimen 10 × 3 Gy over two weeks. Patients of group C who had a very favorable survival prognosis (6-month survival rate of 89%) appear most appropriately treated with a long-course WBRT regimen including total doses of >30 Gy and doses per fraction of <3 Gy, e.g. 20 × 2 Gy over four weeks. In patients with a favorable prognosis, such a long-course WBRT regimen will likely result in fewer neurocognitive deficits and improved treatment outcomes.

In the present study, the 6-month survival rates of the three prognostic groups A, B and C of the test group were almost identical with the 6-month survival rates of the corresponding prognostic groups of the validation group. Therefore, this new survival score can be considered valid and reproducible. The retrospective nature of the data included in this score should be considered when interpreting this analysis. However, a validation in a prospective series of patients is not be expected in the near future.

5. Conclusion

This new survival score was specifically designed for patients with brain metastasis from SCLC receiving WBRT alone. It can be considered valid and reproducible and can contribute to the personalization of the treatment in these patients.

Conflict of interest

There is no conflict of interest related to this study.

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A simple survival score for patients with brain metastases from breast cancer

Many primary tumors lead to the development of brain metastasis. Breast cancer patients represent the second largest group of such patients and have a more favorable survival prognosis than those patients with brain metastasis from other primary tumors [5]. The majority of patients with brain metastasis from breast cancer receive whole-brain radiotherapy (WBRT) alone, mostly with10 fractions of 3 Gy over 2 weeks. Other common WBRT regimens include 5 fractions of 4 Gy over 1 week, 14–15 fractions of 2.5 Gy over 3 weeks and 20 fractions of 2 Gy over 4 weeks. Personalizing cancer care has become much more important during recent years. In patients with brain metastasis, the survival prognosis is a very important—if not the most important—factor for selecting the optimal treatment for the individual patient. Patients with a short remaining life time may be candidates for 5 fractions of 4 Gy in 1 week in order to keep the overall treatment time as short as possible. In contrast, patients with a very favorable prognosis may be better treated with a WBRT regimen with a total dose higher than 30 Gy and doses per fraction of <3 Gy. Higher total doses have been suggested to be associated with better intracerebral control and survival [13]. If lower doses per fraction are used, the risk of developing radiation-induced neurocognitive deficits decreases [2, 6]. These considerations show that it is important to be able to predict the patient's survival prognosis. This goal can be achieved more easily with the use of survival scores. Primary tumors show different biological and clinical behavior. Therefore, specific survival scores for different primary tumors leading to brain metastasis are desirable. The present study aimed to create and validate a survival score specifically for patients with brain metastasis from breast cancer.

Patients and methods

In this study, a total of 230 patients who had been treated with WBRT alone for brain metastases from breast cancer were included. The 230 patients were divided into a test group and a validation group, each consisting of 115 patients. In the test group, the following six potential prognostic factors were evaluated for potential association with survival: WBRT schedule (5 fractions of 4 Gy vs. 10 fractions of 3 Gy), age (≤60 vs. ≥61 years, median age 60 years), Karnofsky Performance Score (KPS <70 vs. ≥70), number of brain metastases (1–3 vs. ≥4), extracranial metastases (no vs. yes), and the interval between tumor diagnosis and WBRT (<36 months vs. ≥36 months, median interval 36 months). The distribution of the potential prognostic factors in the test group and the validation group are given in **Tab. 1**.

In the test group, the univariate analyses of survival were performed with the Kaplan–Meier method [4] and the log-rank test (**Tab. 2**). Prognostic fac-

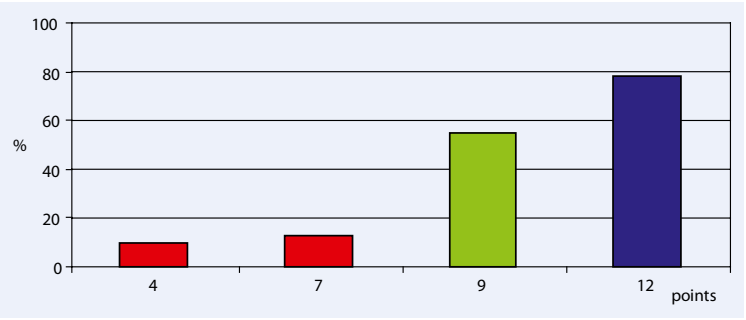

Fig. 1 ▲ The 6-month survival rates (in %) related to the corresponding scores

persönliches Exemplar für D. Rades

Tab. 1 Potential prognostic factors in the test group (n=115) and in the validation group (n=115). The comparison was performed with the χ^2 test

	Test group n (%)	Validation group n (%)	p value
WBRT schedule			
5 fractions of 4 Gy	33 (29)	38 (33)	
10 fractions of 3 Gy	82 (71)	77 (67)	0.75
Age			
≤60 years	58 (50)	57 (50)	
≥61 years	57 (50)	58 (50)	0.95
Karnofsky Performance Score			
<70	50 (43)	47 (41)	
≥70	65 (57)	68 (59)	0.86
Brain metastases (n)			
1–3	34 (30)	29 (25)	
≥4	81 (70)	86 (75)	0.75
Extracranial metastases			
No	31 (27)	28 (24)	
Yes	84 (73)	87 (76)	0.89
Interval tumor diagnosis to WBRT			
<36 months	59 (51)	62 (54)	
≥36 months	56 (49)	53 (46)	0.84

WBRT whole brain radiotherapy.

Tab. 2 Univariate analysis of survival at 6 and 12 months

	Survival rate at 6 months (%)	Survival rate at 12 months (%)	p value
WBRT schedule			
5 fractions of 4 Gy	48	34	
10 fractions of 3 Gy	37	23	0.28
Age			
≤60 years	43	30	
≥61 years	37	19	0.18
Karnofsky Performance Score			
<70	10	7	
≥70	63	40	**<0.001**
Brain metastases (n)			
1–3	47	31	
≥4	37	23	0.34
Extracranial metastases			
No	61	45	
Yes	32	17	**0.002**
Interval tumor diagnosis to WBRT			
<36 months	36	24	
≥36 months	45	26	0.33

Tab. 3 Results of the multivariate analysis of survival

	Risk ratio	95% confidence interval	p value
Karnofsky Performance Score			
≥70 vs. <70	3.63	2.26–5.88	**<0.001**
Extracranial metastases			
No vs. Yes	1.62	0.97–2.84	0.06

tors that were significant in the univariate analysis ($p<0.05$) were additionally included in a multivariate analysis, which was performed with the Cox proportional hazards model. In the multivariate analysis, the KPS was significantly associated with survival ($p<0.001$), and extracranial metastases showed a strong trend ($p=0.06$; **Tab. 3**). These two prognostic factors were included in the scoring system. The score for each factor was determined by dividing the 6-month survival rate (in %) by 10 as shown in **Tab. 4**. The total prognostic score represented the sum of the scores from each of the two factors. The total scores were 4, 7, 9, and 12 points (**Fig. 1**). Three prognostic groups were designed according to the total scores. These groups were 4–7 points (group A), 9 points (group B), and 12 points (group C), respectively. Additionally, the three prognostic groups A, B and C of the test group were compared to the corresponding prognostic groups of the validation group (χ^2 test). The study has been approved by the local ethics committee.

Results

In the test group, the 6-month survival rates were 10% in group A, 55% in group B, and 78% in group C ($p<0.001$). In the validation group, the 6-month survival rates were 11, 54, and 75% in group C, respectively ($p<0.001$). The comparisons between each of the three prognostic groups A, B, and C of the test and the validation group did not show significant differences. The p values were $p=0.98$ for the comparison of both groups A, $p=0.99$ for the comparison of both groups B, and $p=0.97$ for the comparison of both groups C, respectively.

Discussion

The majority of patients with brain metastasis from breast cancer are treated with WBRT alone [5]. In order to tailor the WBRT regimen to the individual patient, it is crucial to be able to estimate the patient's survival prognosis. Patients with a poor prognosis should receive a short course of WBRT such as 5 fractions of 4 Gy over 1 week, which has been

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Tab. 4 Survival rates 6 months after WBRT and the corresponding scores

	Survival at 6 months (%)	Score
Karnofsky Performance Score		
<70	10	1
≥70	63	6
Extracranial metastases		
No	61	6
Yes	32	3

suggested in a retrospective study to be similarly effective as the most common WBRT regimen 10 fractions of 3 Gy over 2 weeks [10]. According to that retrospective study, radiation-related the acute toxicities of 5 fractions of 4 Gy and 10 fractions of 3 Gy were also not significantly different. In another retrospective study, late toxicities such as neurocognitive deficits were more prominent, if the dose per fraction was 3 Gy or greater [2]. Since the risk of developing late toxicities increases with survival time, patients with a more favorable survival prognosis should receive a longer course of WBRT including doses per fraction of <3 Gy. Furthermore, a retrospective study has suggested that WBRT with total doses beyond 30 Gy and doses per fraction <3 Gy result in better intracerebral control and survival than 10 fractions of 3 Gy [13]. In that study, intracerebral control at 1 year was 28% after 10 fractions of 3 Gy and 44% after 20 fractions of 2 Gy. On multivariate analysis, 20 fractions of 2 Gy was significantly associated with improved intracerebral control (p=0.047). The 1-year survival rates were 50% after 10 fractions of 3 Gy and 61% after 20 fractions of 2 Gy. On multivariate analysis, 20 fractions of 2 Gy was associated with significantly better survival (p=0.008).

These data show that it is very important to have an instrument that helps estimating the patient's survival prognosis in order to select the optimal WBRT regimen for each patient. The survival scores that are already available for patients with brain metastasis were created in patients with a variety of primary tumors who had received different treatment regimens [3, 8, 9]. However, primary tumors may vary greatly with respect to their biological and clinical behavior. Therefore, specific survival scores

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A simple survival score for patients with brain metastases from breast cancer

Abstract

Background and purpose. Personalized cancer treatment considers the patient's survival prognosis. Therefore, it is important to be able to estimate the patient's survival time, particularly in a palliative situation such as brain metastasis. This study aimed to create and validate a survival score for patients with brain metastasis from breast cancer, which is the second most common primary tumor in these patients.

Patients and methods. Data of 230 patients treated with whole-brain radiotherapy (WBRT) alone for brain metastasis from breast cancer were retrospectively analyzed. Patients were assigned to a test (n=115) or a validation group (n=115). According to the results of the multivariate analysis of the test group, Karnofsky Performance Score and extracranial metastases were included in the scoring system. The score for each factor was obtained from the 6-month survival rate (in %) divided by 10. Total scores represented the sum of these scores and were 4, 7, 9, or 12 points. Three prognostic groups were formed.

Results. The 6-month survival rates in the test group were 10% for 4–7 points, 55% for 9 points, and 78% for 15 points (p<0.001). In the validation group the corresponding 6-month survival rates were 11, 54, and 75%, respectively (p<0.001). The comparisons between the prognostic groups of the test and the validation group did not show significant differences.

Conclusion. This simple survival score appears valid and reproducible. It can be used to estimate the survival time of patients with brain metastasis from breast cancer receiving WBRT alone.

Keywords

Brain metastasis · Whole-brain radiotherapy · Breast cancer · Survival prognosis · Score

Ein einfacher Überlebensscore für Patientinnen mit Hirnmetastasen eines Mammkarzinoms

Zusammenfassung

Hintergrund und Ziel. Die personalisierte Krebstherapie berücksichtigt die Überlebensprognose der Patienten. Deshalb ist es wichtig, die Prognose der Patienten abschätzen zu können, insbesondere in einer palliativen Situation wie dem Vorliegen von Hirnmetastasen. Ziel dieser Studie war es, einen Überlebensscore für Patientinnen mit Hirnmetastasen eines Mammakarzinoms, dem zweithäufigsten Primärtumor in dieser Situation, zu entwickeln und zu validieren.

Patienten und Methoden. Daten von 230 Patientinnen, die eine alleinige Ganzhirnbestrahlung (WBRT) bei Hirnmetastasen eines Mammakarzinoms erhielten, wurden retrospektiv analysiert. Die Patienten wurden einer Testgruppe (n=115) oder einer Validierungsgruppe (n=115) zugeteilt. Nach den Ergebnissen der Multivarianzanalyse der Testgruppe wurden der Karnofsky-Index und die extrakranielle Metastasierung in dem Scoringsystem berücksichtigt. Den Score für jeden Faktor erhielt man, indem die Überlebensrate nach 6 Monaten (in %) durch 10 dividiert wurde. Die Gesamtscores entsprachen der Summe dieser Scores und betrugen 4, 7, 9 oder 12 Punkte. Es wurden 3 Prognosegruppen gebildet.

Ergebnisse. Die 6-Monats-Überlebensraten in der Testgruppe betrugen 10% bei 4–7 Punkten, 55% bei 9 Punkten und 78% bei 12 Punkten (p<0,001). In der Validierungsgruppe waren die entsprechenden Überlebensraten 11, 54 und 75% (p<0,001). Die Vergleiche für die 3 Prognosegruppen zwischen der Testgruppe und der Validierungsgruppe zeigten keine signifikanten Unterschiede.

Schlussfolgerungen. Dieser einfache Score erscheint valide und reproduzierbar. Er kann verwendet werden, um die Überlebenszeit von Patientinnen mit Hirnmetastasen eines Mammakarzinoms nach alleiniger Ganzhirnbestrahlung abzuschätzen.

Schlüsselwörter

Hirnmetastasen · Ganzhirnbestrahlung · Mammakarzinom · Überlebensprognose · Score

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for the most common tumor entities associated with brain metastasis are desirable. In this study, such a score has been created and validated for patients with brain metastasis from breast cancer, the second most common primary tumor in patients with brain metastasis [5]. This new score included only two prognostic factors, the KPS and presence/absence of extracranial metastases, and, therefore, is easy to use during daily routine.

The 6-month survival rates of the three prognostic groups of this score were quite different. Patients of group A, who had the worst survival prognosis, may be considered candidates for a short-course WBRT program such as 5 fractions of 4 Gy. Group B patients who had an intermediate survival prognosis may be considered for 10 fractions of 3 Gy in 2 weeks, the most common "standard" WBRT regimen. Group C patients who had the best survival prognosis would likely benefit from WBRT with total doses beyond 30 Gy and doses per fraction of <3 Gy in terms of better treatment outcomes and fewer neurocognitive deficits. For patients of the prognostic groups B and C with only very few brain metastases, radiosurgery ± WBRT or neurosurgery ± WBRT may also be appropriate [1, 7, 11, 12, 14, 15].

This new score has been validated in a group of 115 patients. The finding that the 6-month survival rates of the three prognostic groups of both the test group and the validation group were very similar demonstrates that this score is valid and reproducible. The retrospective nature of the data of this study should be taken into account when using the score. However, a prospective study may not be available in the near future.

Conclusion

This simple score appears valid and reproducible. It can be used to estimate the survival time of patients with brain metastases from breast cancer receiving WBRT alone in order to select the most appropriate WBRT regimen for each individual patient.

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A survival score for patients with brain metastases from less radiosensitive tumors treated with whole-brain radiotherapy alone

Introduction

Brain metastases occur in up to 46% of patients with a malignant melanoma, in 4–11% of patients with renal cell carcinoma and in 0.3–23% of colorectal cancer patients [1, 4, 7, 13, 14, 19]. These primary tumors are considered to have a low radiosensitivity relative to many other solid tumors. The prognosis of these patients is poor, with median survival times of only a few months [1, 4, 7, 13, 14, 19]. The most common therapy for brain metastasis is whole-brain radiotherapy (WBRT) alone, particularly for patients with multiple lesions. The most frequently used WBRT schedule is 10×3 Gy in 2 weeks. However, there is also the possibility of using

Tab. 1 Distribution of the potential prognostic factors in the test (N=88) and validation (N=88) groups. The comparison was performed with the χ-square test

	Test group N (%)	Validation group N (%)	P-value
WBRT schedule			
5×4 Gy	32 (36)	29 (33)	0.84
10×3 Gy	56 (64)	59 (67)	
Age			
<65 years	50 (57)	47 (53)	0.84
≥65 years	38 (43)	41 (47)	
Gender			
Female	34 (39)	29 (33)	0.71
Male	54 (61)	59 (67)	
KPS			
<70 points	39 (44)	41 (47)	0.89
≥70 points	49 (56)	47 (53)	
Primary tumor type			
Renal cell carcinoma	23 (26)	22 (25)	0.95
Melanoma	31 (35)	34 (39)	
Colorectal cancer	34 (39)	32 (36)	
No. brain metastases			
1	15 (17)	16 (18)	0.87
2–3	18 (20)	14 (16)	
≥4	55 (63)	58 (66)	
Extracranial metastases?			
No	17 (19)	21 (24)	0.81
Yes	71 (81)	67 (76)	
Interval from tumor diagnosis to WBRT			
≤24 months	35 (40)	38 (43)	0.84
>24 months	53 (60)	50 (57)	

WBRT whole-brain radiotherapy, *KPS* Karnofsky Performance Score.

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Tab. 2 Univariate analyses of survival at 6 months

	Survival rate at 6 months (%)	P-value
WBRT schedule		
5×4 Gy	28	0.97
10×3 Gy	29	
Age		
<65 years	38	0.013*
≥65 years	16	
Gender		
Female	32	0.28
Male	26	
KPS		
<70 points	10	
≥70 points	43	<0.001*
Primary tumor type		
Renal cell carcinoma	30	0.51
Melanoma	29	
Colorectal cancer	18	
No. brain metastases		
1	40	0.26
2–3	33	
≥4	24	
Extracranial metastases?		
No	59	0.013*
Yes	21	
Interval from tumor diagnosis to WBRT		
≤24 months	23	0.11
>24 months	32	

WBRT whole-brain radiotherapy, *KPS* Karnofsky Performance Score, *statistically significant p-value.

Tab. 3 Results of the multivariate survival analysis

	Risk ratio	95% confidence interval	P-value
Age			
<65 vs. ≥65 years	1.73	1.05–2.84	0.032*
KPS			
≥70 vs. <70 points	2.10	1.31–3.40	0.002*
Extracranial metastases			
No vs. yes	2.05	1.08–4.33	0.027*

KPS Karnofsky Performance Score, *statistically significant p-value.

Tab. 4 Survival rates 6 months after WBRT and the corresponding scores

	Survival at 6 months (%)	Score
Age		
<65 years	38	4
≥65 years	16	2
KPS		
<70 points	10	1
≥70 points	43	4
Extracranial metastases?		
No	59	6
Yes	21	2

WBRT whole-brain radiotherapy, *KPS* Karnofsky Performance Score

short-course WBRT (such as 5×4 Gy in 1 week) or longer-course WBRT (such as 20×2 Gy in 4 weeks). For patients with 1–3 lesions, more aggressive approaches are also available, including neuro- or radiosurgery [6, 15, 17]. Patients with a poor survival prognosis would likely benefit from a short course of therapy not requiring long stays in hospital or more frequent visits to the radiation oncology department than necessary. Since the risk of neurocognitive deficits increases with the dose per fraction, patients with a more favorable prognosis may benefit from a longer-course therapy with lower doses per fraction [2, 8].

Scoring systems that can predict the survival of patients with brain metastasis prior to the start of treatment are important to help identify the best treatment for each individual patient. Several scoring systems are already available for patients with brain metastasis [3, 10]. This new score has been specifically designed for patients with brain metastasis from less radiosensitive tumors. In contrast to most other scores, only one treatment modality—WBRT alone—was included in the analysis.

Patients and methods

This study included data from 176 patients who had received WBRT alone for brain metastases from a less radiosensitive tumor such as renal cell carcinoma (N=45), malignant melanoma (N=65) or colorectal cancer (N=66). The study was approved by the local ethics committee. The patients were divided into test and validation groups, each containing 88 patients. In the test group, the following potential prognostic factors were analyzed for a significant association with survival: WBRT schedule (5×4 vs. 10×3 Gy), gender, age (<65 vs. ≥65 years), Karnofsky Performance Score (KPS, <70 vs. ≥70 points), primary tumor type (renal cell carcinoma vs. malignant melanoma vs. colorectal cancer), number of brain metastases (1 vs. 2–3 vs. ≥4), extracranial metastases (yes vs. no) and the interval between tumor diagnosis and WBRT (≤24 vs. >24 months). The distributions of the potential prognostic factors

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in the test and validation groups are summarized in Tab. 1.

In the test group, the univariate survival analyses were performed using the Kaplan–Meier method [5] and the log-rank test (Tab. 2). Prognostic factors that were significant in univariate analyses ($p<0.05$) were included in a multivariate analysis performed with the Cox proportional hazards model. In the multivariate analysis, age, KPS and extracranial metastases were significantly associated with survival (Tab. 3). These three independent prognostic factors were included in the scoring system. The score for each factor was determined by dividing the 6-month survival rate (in %) by 10 (Tab. 4). The total prognostic score represented the sum of the scores from each individual factor. Total scores ranged between 5 and 14 points (Fig. 1). Three groups were created according to the total score: 5–8 points (group A), 9–11 points (group B) and 12–14 points (group C).

The three prognostic groups A, B and C of the test group were compared to the corresponding groups of the validation group using the χ-square test.

Results

In the test group, the 6-month survival rates were 11% in group A, 38% in group B and 83% in group C ($p<0.001$, Fig. 2). In the validation group, the 6-month survival rates were 12% in group A, 31% in group B and 75% in group C ($p=0.003$, Fig. 2).

The comparisons between the prognostic groups A, B and C of the test group with those of the validation group did not reveal any significant differences: $p=0.97$ for the comparison of the A groups; $p=0.82$ for the comparison of the B groups and $p=0.95$ for the comparison of the C groups.

Discussion

Many patients with brain metastases have a relatively poor survival prognosis, whereas some patients may go on to live for a few years. It is important to be able to estimate the survival of patients in order to identify the best therapy for each individual case. Patients with a very poor

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A survival score for patients with brain metastases from less radiosensitive tumors treated with whole-brain radiotherapy alone

Abstract

Background and purpose. This study aimed to develop and validate a scoring system to predict the survival of patients receiving whole-brain radiotherapy (WBRT) alone for brain metastases from less radiosensitive tumors.

Patients and methods. The study included data from 176 patients with brain metastasis from renal cell carcinoma, malignant melanoma or colorectal cancer. Patients were divided into a test group (N=88) and a validation group (N=88). In the multivariate analysis of the test group, age, Karnofsky Performance Status and extracranial metastasis were significantly associated with survival. These three factors were included in the scoring system. The score for each factor was determined by dividing the 6-month survival rate (in %) by 10. The total score represented the sum of the three scores. According to the total scores—which ranged from 5 to14 points—three prognostic groups were created.

Results. The 6-month survival rates in the test group were 11% for 5–8 points (N=47, group A), 38% for 9–11 points (N=29, group B) and 83% for 12–14 points (N=12, group C). In the validation group the 6-month survival rates were 12, 31 and 75%, respectively. Comparisons between the prognostic groups A, B and C of the test group with those of the validation group did not reveal any significant differences.

Conclusion. The new scoring system based on three independent prognostic factors can help to estimate the survival of patients with brain metastases from a less radiosensitive tumor. The score appears to be valid and reproducible.

Keywords

Metastasis · Karnofsky Performance Status · Radiosensitivity · Survival · Score

Ein Überlebensscore für Patienten mit Hirnmetastasen von gering strahlensensiblen Tumoren nach alleiniger Ganzhirnbestrahlung

Zusammenfassung

Hintergrund und Ziel. Ziel dieser Studie war es, einen Score zu entwickeln und zu validieren, mit dem die Überlebensprognose von Patienten mit Hirnmetastasen von gering strahlensensiblen Tumoren nach alleiniger Ganzhirnbestrahlung (WBRT) abgeschätzt werden kann.

Patienten und Methoden. Die Studie enthielt Daten von 176 Patienten mit Hirnmetastasen eines Nierenzellkarzinoms, eines malignen Melanoms oder eines kolorektalen Karzinoms, die in eine Testgruppe (n=88) und eine Validierungsgruppe (n=88) aufgeteilt wurden. In der Multivarianzanalyse der Testgruppe waren Alter, Karnofsky-Index und extrakranielle Metastasierung signifikant mit dem Überleben assoziiert. Diese 3 Faktoren wurden in dem Scoringsystem berücksichtigt. Der Score wurde für jeden Faktor ermittelt, indem die Überlebensrate nach 6 Monaten (in %) durch 10 dividiert wurde. Der jeweilige Gesamtscore entsprach der Summe der 3 Einzelscores. Unter Berücksichtigung der Gesamtscores, die zwischen 5 und 14 Punkten betrugen, wurden 3 Prognosegruppen gebildet.

Ergebnisse. Die Überlebensraten nach 6 Monaten in der Testgruppe betrugen 11% bei 5–8 Punkten (n=47, Gruppe A), 38% bei 9–11 Punkten (n=29, Gruppe B) und 83% bei 12–14 Punkten (n=12, Gruppe C). In der Validierungsgruppe lagen die Überlebensraten bei 12, 31 und 75%. Die Vergleiche zwischen der Test- und der Validierungsgruppe für die 3 Prognosegruppen A, B und C ergaben keine signifikanten Unterschiede.

Schlussfolgerungen. Dieses neue Scoringsystem, das auf 3 unabhängigen Prognosefaktoren beruht, kann dazu beitragen, die Überlebensprognose von Patienten mit Hirnmetastasen von gering strahlensensiblen Tumoren abzuschätzen. Der Score erscheint valide und reproduzierbar.

Schlüsselwörter

Metastasierung · Karnofsky-Performance-Status · Strahlensensitivität · Überleben · Score

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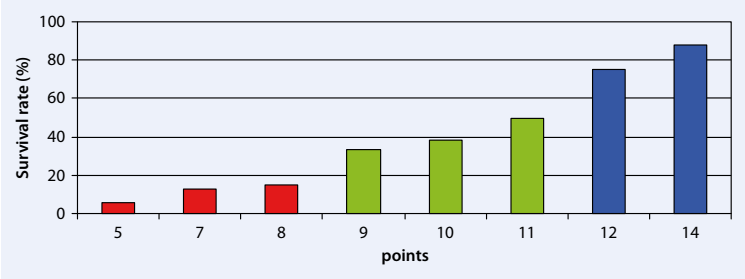

Fig. 1 ▲ The 6-month survival rates (in %) related to the corresponding scores. Three groups, A (*red*), B (*green*) and C (*blue*), were created on the basis of the scores

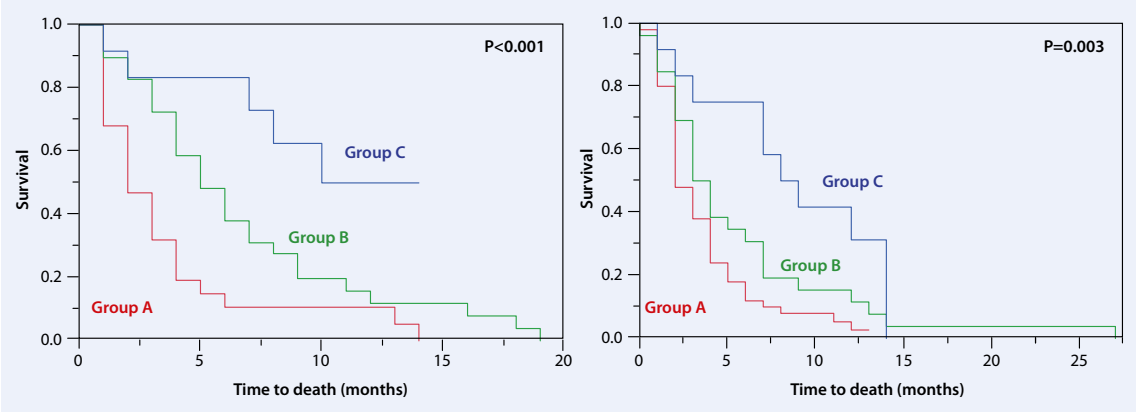

Fig. 2 ▲ Kaplan–Meier curves for survival of the three groups A (*red*), B (*green*) and C (*blue*) of the test group (*left*) and the validation group (*right*)

survival prognosis likely benefit from short-course WBRT, as this minimizes the time spent undergoing treatment and they are unlikely to experience neurocognitive deficits due to the radiotherapy [11]. Since patients with a better survival prognosis are at a higher risk of experiencing radiation-related neurocognitive deficits, a longer course of WBRT with lower fraction doses is advisable. DeAngelis et al. only observed neurocognitive deficits after doses per fraction of 3 Gy or higher. Therefore, patients with a favorable survival prognosis should be treated with longer-course WBRT with a dose per fraction of <3 Gy [2]. According to a recent review, altered WBRT fractionation regimens did not improve survival, neurological function or symptom control when compared to 10×3, 5×4 and 4×5 Gy schedules [20]. However, the latter review did not separately investigate patients with a favorable survival prognosis. A recent retrospective study suggested that patients with a favorable survival prognosis benefit from an escalation of WBRT dose beyond 10×3 Gy in terms of improved survival and intracerebral control [16].

In the present study, a scoring system has been developed to estimate the survival of patients with brain metastases from relatively radioresistant tumors treated with WBRT alone. Based on three independent prognostic factors for survival, three prognostic groups were identified. The three independent prognostic factors—age, KPS and extracranial metastases—have been identified previously in patients with brain metastases from less radiosensitive tumors [9]. In this previous study, patients receiving WBRT doses >30 Gy were also included. In order to develop the new score in a homogeneously treated series of patients, data from patients receiving WBRT doses >30 Gy were not considered. The fact that this new score was developed in patients who were treated quite homogeneously may confer an advantage over the Diagnosis-Specific Graded Prognostic Assessment (DS-GPA), which considered different primary tumor types [18]. Based on two prognostic factors—KPS and extracranial metastases—the DS-GPA for melanoma and renal cell carcinoma consists of four prognostic groups: DS-GPA 0–1, DS-GPA 1.5–2.5, DS-GPA 3.0 and DS-GPA 3.5–4.0 [18]. The patients included in the DS-GPA received various treatment regimens, including radiosurgery. Such treatment heterogeneity may have led to a selection bias when designing the DS-GPA. Applying the DS-GPA to the test group of the present study, 6-month survival rates were 22% (22/55) for DS-GPA 0–1, 38% (8/21) for DS-GPA 1.5–2.5, 55% (6/11) for DS-GPA 3.0 and 0% (0/1) for DS-GPA 3.5–4.0 ($p<0.001$). The differences between the prognostic groups of the DS-GPA are thus less prominent than for our new

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score. Considering the levels of statistical significance observed upon comparison of the 6-month survival rates between the prognostic groups, our new score again appeared to be superior to the DS-GPA. Applying the DS-GPA, no significant difference was observed between DS-GPA 0–1 and DS-GPA 1.5–2.5 (p=0.36), between DS-GPA 1.5–2.5 and DS-GPA 3.0 (p=0.71), or between DS-GPA 3.0 and DS-GPA 4.0 (p=0.95). Applying our new score, a significant difference was found between group A and group B (p=0.018) and a trend was observed when comparing group B to group C (p=0.14).

Since patients in group A of this new score had a 6-month survival probability of only 11%, these patients can be considered candidates for short-course WBRT schedules such as 5×4 Gy in 1 week. Group B patients had an intermediate survival prognosis and may be candidates for the most commonly applied standard WBRT schedule of 10×3 Gy in 2 weeks. Group C patients had a more favorable survival prognosis and may therefore be considered for a WBRT schedule with a total dose >30 Gy and a fraction dose <3 Gy, such as 20×2 Gy in 4 weeks [2, 16]. The latter group represented less than 15% of the entire cohort in the present study, which demonstrates the typically poor survival prognosis of patients with brain metastases from a less radiosensitive tumor. Patients of groups B and C with a limited number of brain metastases may also be selected for more intensive treatments such as neuro- and radiosurgery [6, 15, 17]. Since elderly patients have been reported to have a very poor survival prognosis, an additional survival score for this group of patients appears reasonable [12].

The fact that the comparisons between each of the three prognostic groups A, B and C of the test group with those of the validation group did not show any significant differences demonstrates the validity and reproducibility of this new scoring system. When using this score, the retrospective nature of the data should be taken into account. However, a scoring system based on prospective data will not be available in the near future.

Conclusion

This new score can help predict the survival of patients with brain metastases from a less radiosensitive tumor. The score appears valid and reproducible. It can facilitate the choice of treatment for individual patients and also be used to stratify patients in future clinical trials.

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Compliance with ethical guidelines

Conflict of interest. On behalf of all authors, the corresponding author states that there are no conflicts of interest.

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Ethikantrag:

Promotion Dreyer

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Datum: 22. Februar 2013

Überlebens-Scores bei Patienten und Patientinnen mit Hirnmetastasen nach Strahlentherapie
Hier: Anzeige - Ihr Schreiben vom 21. Februar 2013

Sehr geehrter Herr Prof. Rades,

mit Ihrem o.g. Schreiben informieren Sie die Ethik-Kommission über ein von Ihnen durchgeführtes Forschungsvorhaben, bei dem ausschließlich anonymisierte Daten verarbeitet wurden.

Im Nachhinein nimmt die Ethik-Kommission das von Ihnen in Ihrem Anschreiben beschriebene Vorhaben zur Kenntnis. Für zukünftige Vorhaben erwarten wir eine Anzeige vor Beginn der Forschungsaktivitäten

Mit freundlichem Gruß bin ich
Ihre

M. Schrader

Prof. Dr. med. Marianne Schrader
Mitglied der Ethik-Kommission

XI. Danksagung

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XII. Lebenslauf

Persönliche Daten

Name:	Liesa Dziggel
Geburtstag:	16.11.1983
Geburtsort:	Frankfurt/Main

Beruflicher Werdegang

Seit 12/2011	Assistenzärztin in der Klinik für Strahlentherapie, UKSH Lübeck

Studium

2004 – 2007	Vorklinischer Abschnitt und Physikum an der Universität zu Lübeck
2007 – 2010	Klinischer Abschnitt an der Universität zu Lübeck
2010 – 2011	Praktisches Jahr: Klinik für Radiologie, UKSH Lübeck Klinik für Innere Medizin, Asklepios Klinik Bad Oldesloe Klinik für Chirurgie, Schön Klinik Neustadt
05/2011	2. Staatsexamen

Schulische Ausbildung und weitere Tätigkeiten

1990 – 1994	Grundschule, Steinbach/Ts.
1994 – 2003	Gymnasium, Altkönig-Schule, Kronberg/Ts.
2003 – 2004	Freiwilliges soziales Jahr (FSJ), DRK-Mutter-Kind-Klinik, Wittdün/Amrum

Publikationen:

Rades D, Huttenlocher S, Dziggel L, Blanck O, Hornung D, Mai KT, Ngo TT, Pham TV, Schild S (2015) A new tool to predict survival after radiosurgery alone for newly diagnosed cerebral metastases. Asian Pac J Cancer Prev 16(7):2967-70

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Rades D, Panzner A, Dziggel L, Haatanen T, Lohynska R, Schild SE (2012) Dose-escalation of whole-brain radiotherapy for brain metastasis in patients with a favorable survival prognosis. Cancer 118(15):3852-9

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