Aus der Klinik für Strahlentherapie

der Universität zu Lübeck

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Überlebens-Scores bei Patienten mit metastatisch bedingter Rückenmarkskompression

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Inhaltsverzeichnis:

Abkürzungsverzeichnis:

CUP	(cancer of unknown primary)
ECOG	(Eastern Cooperative Oncology Group)
Gy	(Gray)
MSCC	(metastatic spinal cord compression)
SCC	(spinal cord compression)

I. Einleitung

Die metastatisch bedingte Rückenmarkskompression (MSCC) ist eine Komplikation, welche bei 5-10% aller Patienten mit einer malignen Tumorerkrankung vorkommt [1,2]. Zumeist wird die MSCC durch Wirbelkörpermetastasen verursacht, die das Rückenmark verdrängen, komprimieren oder infiltrieren. Mögliche klinische Symptome sind Schmerzen sowie neurologische Ausfälle wie Schwäche in den Beinen bis hin zur vollständigen Paraplegie, Sensibilitätsstörungen und Störungen der Blasen - und Mastdarmfunktion.

Die MSCC ist eine onkologische Notfallsituation und es muss so schnell wie möglich mit einer Therapie begonnen werden. Obligat ist die Gabe von Glukokortikoiden (häufig Dexamethason), sofern keine Kontraindikationen gegen Steroide vorliegt. Die alleinige Strahlentherapie ist die weltweit am häufigsten angewandte Therapie der MSCC [1,2]. Ausgewählte Patienten profitieren von einer vor der Strahlentherapie durchgeführten chirurgischen Intervention in Form einer Dekompression plus Stabilisierung [3].

Bei der Behandlung von Tumorpatienten gibt es allerdings zunehmend Bestrebungen, die Therapie zu personalisieren, das heißt auf den jeweiligen Patienten zu beziehen. Dies gilt in besonderem Maße auch für die Therapie von Metastasen. Die meisten Patienten mit einer MSCC haben eine sehr eingeschränkte Lebenserwartung von nur wenigen Monaten, während einige Patienten eine Lebenserwartung von bis zu mehreren Jahren aufweisen [1,2].

Jede einzelne Sitzung einer Strahlentherapie kann für die Patienten belastend sein, insbesondere bei starken Schmerzen und reduziertem Allgemeinzustand. Für diese Patienten wäre eine möglichst kurze Gesamtbehandlungszeit wünschenswert. Eine große retrospektive Analyse und eine prospektive Studie

haben gezeigt, dass eine Kurzzeit-Bestrahlung von bis zu einer Woche hinsichtlich Besserung der motorischen Funktion ähnlich effektiv ist wie eine Langzeit-Bestrahlung von 2-4 Wochen [4,5]. Allerdings kommt es nach einer Kurzzeit-Bestrahlung häufiger zu Rezidiven einer MSCC im alten Bestrahlungsfeld [5,6]. Patienten mit einer sehr schlechten Überlebensprognose versterben in der Regel, bevor es zu einem solchen Rezidiv kommt, und würden somit von einer Kurzzeit-Bestrahlung profitieren. Bei Patienten mit besserer Überlebensprognose ist die lokale Kontrolle von größerer Bedeutung. Bei dieser Patientengruppe wäre also eine Langzeit-Bestrahlung zu bevorzugen. Neuere Daten legen nahe, dass Patienten mit einer sehr guten Überlebensprognose sogar von einer Eskalation der Gesamtdosis über 30 Gy in 10 Fraktionen (Therapiedauer: 2 Wochen) hinaus profitieren [7].

Demzufolge ist also die Überlebensprognose der Patienten von wesentlicher Bedeutung für die Wahl des geeigneten Strahlentherapie-Regimes. Um die Prognose besser abschätzen zu können, wurde basierend auf einer retrospektiven Analyse von 1852 Patienten ein Überlebens-Score entwickelt und 2008 publiziert [8]. Allerdings konnte die Zuverlässigkeit dieses Scores nicht durch komparative Analysen bestätigt werden.

Ein wesentliches Ziel dieser Arbeit war demzufolge die Validierung des Überlebens-Scores anhand der prospektiv erhobenen Daten von 439 Patienten mit MSCC.

Angesichts der zunehmenden Personalisierung der Behandlung von Tumorpatienten stellt sich die Frage, ob ein Überlebens-Score für alle Patienten mit MSCC ausreicht, da sich die verschiedenen Primärtumoren hinsichtlich Prognose und biologischem Verhalten deutlich unterscheiden. Im zweiten Teil

der Arbeit wurde deshalb jeweils ein eigener Überlebens-Score für die fünf bei der MSCC häufigsten Primärtumoren entwickelt. Im Einzelnen handelt es sich dabei um das Mammakarzinom (~20%), das Prostatakarzinom (~20%), das nicht-kleinzellige Lungenkarzinom (~15%), das Plasmozytom (multiple Myelom) (~10%) und das so genannte CUP-Syndrom („Cancer of unknown primary“) (~10%) [1,2].

II. Validierung eines Überlebens-Scores nach Strahlentherapie der metastatisch bedingten Rückenmarkskompression (MSCC)

Rades D, Douglas S, Veninga T, et al. Validation and simplification of a score predicting survival in patients irradiated for metastatic spinal cord compression. Cancer 2010;116:3670-3673. [Impact Factor = 4,771]

Zur Validierung des im Jahr 2008 publizierten Scores für das Überleben von Patienten mit MSCC wurde eine Gruppe von 439 Patienten untersucht. Diese 439 Patienten setzten sich aus 265 Patienten, die aus einer vorherigen prospektiven Studie stammten [5], sowie aus 174 weiteren Patienten, welche seit Januar 2008 prospektiv verfolgt wurden, zusammen. Alle Patienten erhielten eine alleinige Strahlentherapie. Diese 439 Patienten wurden mit den 1852 Patienten aus der Studie von 2008 verglichen [8].

Der ursprüngliche Score aus dem Jahr 2008 basierte auf sechs unabhängigen Prognosefaktoren, welche in der entsprechenden multivarianten Analyse (Cox proportional hazards model) signifikant mit dem Gesamtüberleben assoziiert waren. Diese sechs Faktoren waren: Art des Primärtumors (Mammakarzinom versus Prostatakarzinom versus Myelom/Lymphom versus Lungenkarzinom versus andere Tumoren), das Intervall zwischen der Erstdiagnose der Tumorerkrankung und der Bestrahlung der MSCC (≤15 Monate versus >15 Monate), das Vorhandensein weiterer Knochenmetastasen bei Beginn der Strahlentherapie (nein versus ja), das Vorhandensein von Organmetastasen bei Beginn der Strahlentherapie (nein versus ja), die Gehfähigkeit vor Beginn der Strahlentherapie (gehfähig versus nicht gehfähig), und die Entwicklungszeit (Dynamik) der motorischen Defizite vor Beginn der Strahlentherapie (1-7 Tage versus 8-14 Tage versus >14 Tage).

Für jeden dieser Faktoren wurde ein Punktwert errechnet, welcher aus der 6-Monats-Überlebensrate in Prozent dividiert durch 10 bestand (Tabelle 1). Die sechs Punktwerte wurden zu einem Gesamtpunktwert addiert.

	Überlebensrate nach 6 Monaten (%)	Score (Punkte)
Art des Primärtumors		
Mammakarzinom	78	8
Prostatakarzinom	66	7
Myelom/Lymphom	85	9
Lungenkarzinom	25	3
Andere Tumoren	40	4
Weitere Knochenmetastasen		
nein	65	7
ja	48	5
Organmetastasen		
nein	80	8
ja	17	2
Intervall von Tumordiagnose bis RT		
≤ 15 Monate	41	4
> 15 Monate	71	7
Gehfähigkeit vor RT		
gehfähig	71	7
nicht gehfähig	31	3
Entwicklungszeit motorischer Defizite		
1-7 Tage	26	3
8-14 Tage	55	6
> 14 Tage	78	8

Tabelle 1. Die Überlebensraten nach 6 Monaten für die sechs unabhängigen Prognosefaktoren und die entsprechenden Punktwerte (Scores).

Die Gesamtpunktwerte lagen zwischen 20 und 45 Punkten. Unter Berücksichtigung der Gesamtpunktwerte wurden fünf Prognosegruppen (Gruppe A: 20-25 Punkte, Gruppe B: 26-30 Punkte, Gruppe C: 31-35 Punkte, Gruppe D: 36-40 Punkte, Gruppe E: 41-45 Punkte) gebildet. Die Gruppe mit dem geringsten Gesamtpunktwert wies die schlechteste Überlebensprognose auf. Die fünf Gruppen unterschieden sich signifikant hinsichtlich des Überlebens ($p<0,001$).

Mit den 439 Patienten des Validierungskollektivs wurde entsprechend verfahren. Unter Berücksichtigung der Gesamtpunktwerte wurden ebenfalls fünf verschiedene Prognosegruppen (A-E) gebildet (Abbildung 1). Im prospektiv untersuchten Kollektiv der Validierungsgruppe betrugen die Überlebensraten

nach 6 Monaten 11% (Gruppe A), 20% (Gruppe B), 48% (Gruppe C), 72% (Gruppe D) und 93% (Gruppe E). Die Überlebensraten in der vorherigen Studie mit 1852 Patienten betrugen 4%, 11%, 48%, 87% und 99%. Der Vergleich der fünf Prognosegruppen A-E beider Studien mit dem Chi-Quadrat-Test ergab keinen signifikanten Unterschied. In einem weiteren Schritt wurde der Überlebens-Score etwas vereinfacht, indem statt fünf Prognosegruppen nur drei Gruppen (Gruppe I: 20-30 Punkte, Gruppe II: 31-35 Punkte, Gruppe III: 36-45 Punkte) gebildet wurden (Abbildung 2). Die Überlebensraten nach 6 Monaten waren 16%, 48% und 81% (p<0,001). In der vorherigen Studie mit 1852 Patienten betrugen die Raten 9%, 48% und 93% (p<0,001). Auch der Vergleich dieser drei Prognosegruppen zwischen den beiden Studien zeigte keinen signifikanten Unterschied. Demzufolge kann der Überlebens-Score als valide und reproduzierbar angesehen werden.

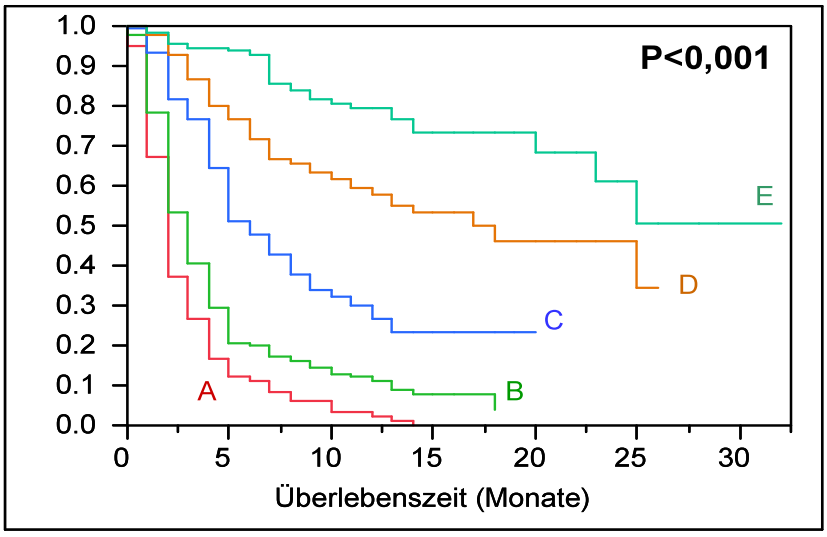


Abbildung 1. Kaplan-Meier Kurven für das Überleben der fünf Prognosegruppen A-E im Validierungskollektiv. Der Vergleich der Kurven erfolgte mit dem log-rank Test.

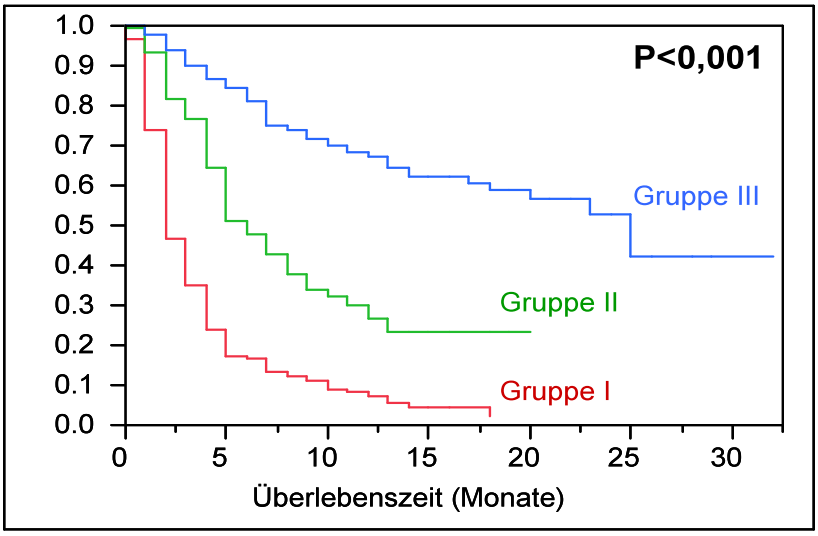


Abbildung 2. Kaplan-Meier Kurven für das Überleben der drei Prognosegruppen I-III im Validierungskollektiv. Der Vergleich der Kurven erfolgte mit dem log-rank Test.

III. Überlebens-Scores für die fünf bei der MSCC häufigsten Tumorentitäten

Rades D, Douglas S, Schild SE. A validated survival score for breast cancer patients with metastatic spinal cord compression. Strahlenther Onkol 2013;189:41-46. [Impact Factor = 3,561]

Rades D, Douglas S, Veninga T, et al. A survival score for patients with metastatic spinal cord compression from prostate cancer. Strahlenther Onkol 2012;188:802-806. [Impact Factor = 3,561]

Rades D, Douglas S, Veninga T, Schild SE. A validated survival score for patients with metastatic spinal cord compression from non-small cell lung cancer. BMC Cancer 2012;12:302. [Impact Factor = 3,011]

Douglas S, Schild SE, Rades D. A new score predicting the survival of patients with spinal cord compression from myeloma. BMC Cancer 2012;12:425. [Impact Factor = 3,011]

Douglas S, Schild SE, Rades D. Metastatic spinal cord compression in patients with cancer of unknown primary. Estimating the survival prognosis with a validated score. Strahlenther Onkol 2012;188:1048-1051. [Impact Factor = 3,561]

Die verschiedenen Tumorentitäten können hinsichtlich ihres biologischen Verhaltens deutliche Unterschiede aufweisen, was auch für die Überlebensprognose der Patienten von Bedeutung ist. Um das Behandlungskonzept möglichst individuell auf die Bedürfnisse der Patienten ausrichten zu können, wurden für die fünf bei der MSCC häufigsten Primärtumoren eigene Überlebens-Scores entwickelt. Diese fünf Tumorentitäten sind das Mammakarzinom, das Prostatakarzinom, das nicht-kleinzellige Lungenkarzinom, das Plasmozytom/Myelom und das CUP-Syndrom. Die Methodik bei der Entwicklung der Überlebens-Scores entsprach dem Vorgehen bei der Validierung des initialen Scores, bei dem alle Tumorentitäten eingeschlossen wurden (Tabelle 1).

Bei den fünf häufigsten Primärtumoren wurden die Patienten zu je 50% einer Testgruppe und einer Validierungsgruppe zugeordnet.

Für jeden der fünf Primärtumoren wurde eine separate multivariate Analyse durchgeführt, um die unabhängigen Prognosefaktoren für jede dieser Gruppen

zu identifizieren. Wiederum wurde für jeden unabhängigen Prognosefaktor ein Punktwert berechnet (Überlebensrate nach 6 Monaten in Prozent, dividiert durch 10) und die einzelnen Punktwerte wurden zu einem Gesamtpunktwert addiert. Nachfolgend werden die Überlebens-Scores für die einzelnen Tumorentitäten präsentiert.

IV. MSCC bei Patientinnen mit Mammakarzinom

Mit 510 Patientinnen war das Mammakarzinom der häufigste Primärtumor (22% des Gesamtkollektivs aller Patienten mit MSCC). Es wurden die folgenden acht möglichen prätherapeutischen Prognosefaktoren untersucht: Alter, Allgemeinzustand (ECOG), Zahl befallener Wirbelkörper, Vorhandensein weiterer Knochenmetastasen vor Strahlentherapie, Vorhandensein von Organmetastasen vor Strahlentherapie, Intervall von der Erstdiagnose des Mammakarzinoms bis zur Bestrahlung der MSCC, Gehfähigkeit vor Strahlentherapie und Entwicklungszeit motorischer Defizite vor der Strahlentherapie. In der multivarianten Analyse (Cox proportional hazards model) waren sechs Faktoren signifikant mit dem Überleben assoziiert. Diese Faktoren mit den Überlebensraten nach 6 Monaten und den entsprechenden Punktwerten sind in Tabelle 2 zusammengefasst.

	Überlebensrate nach 6 Monaten (%)	**Score (Punkte)**
Allgemeinzustand (ECOG)		
1-2	88	9
3-4	46	5
Gehfähigkeit vor RT		
gehfähig	43	4
nicht gehfähig	83	8
Weitere Knochenmetastasen		
nein	83	8
ja	66	7
Organmetastasen		
nein	90	9
ja	43	4
Intervall von Tumordiagnose bis RT		
≤ 15 Monate	55	6
> 15 Monate	79	8
Entwicklungszeit motorischer Defizite		
1-7 Tage	39	4
> 7 Tage	81	8

Tabelle 2. Die Überlebensraten nach 6 Monaten für die sechs unabhängigen Prognosefaktoren und die entsprechenden Punktwerte (Scores) beim Mammakarzinom.

Die Gesamtpunktwerte in der Testgruppe (N=255) lagen zwischen 30 und 50 Punkten. Es wurden vier Prognosegruppen gebildet (A: 30-35 Punkte, B: 36-40 Punkte, C: 41-45 Punkte, D: 46-50 Punkte; Abbildung 3), die sich signifikant unterschieden.

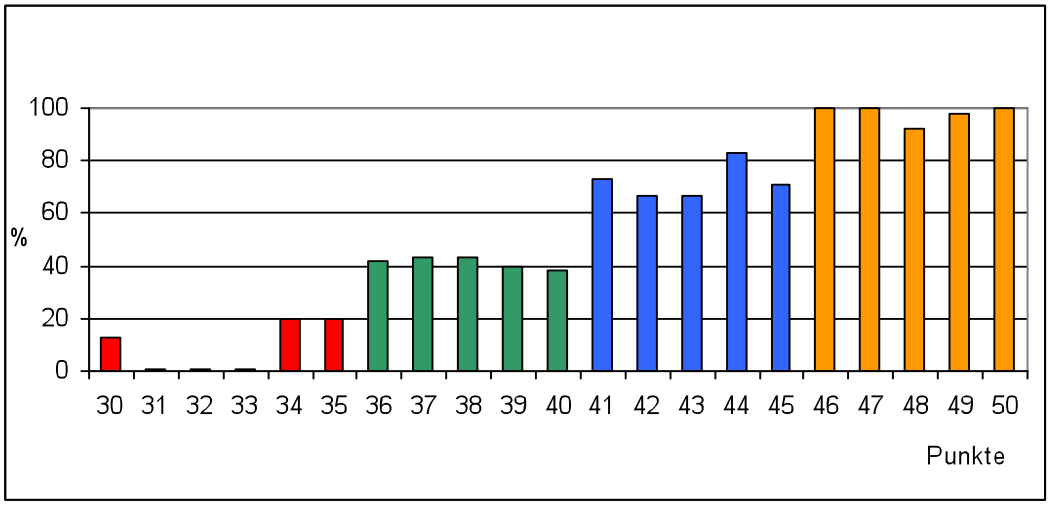
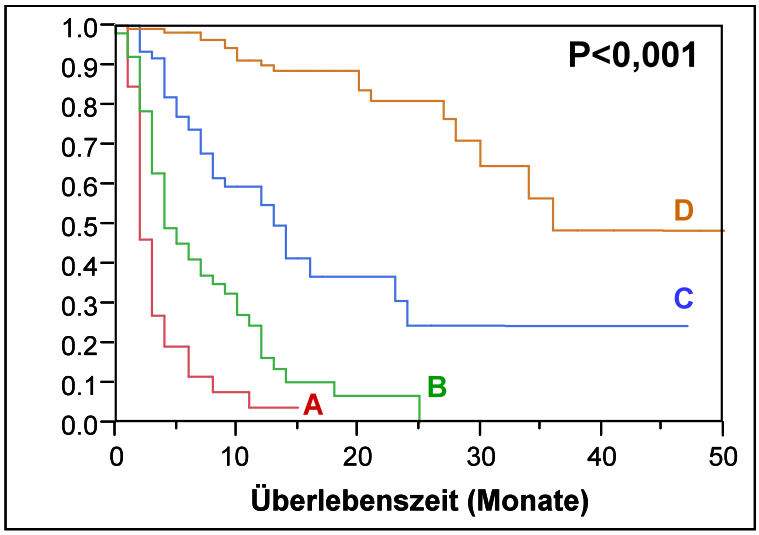


Abbildung 3. Die Gesamtpunktwerte (30-50 Punkte) und die entsprechenden Überlebensraten nach 6 Monaten beim Mammakarzinom.

Die Überlebensraten nach 6 Monaten in der Testgruppe betrugen 12% (Gruppe A), 41% (Gruppe B), 74% (Gruppe C) und 98% (Gruppe D) ($p<0,001$; Abbildung 4). Die Überlebensraten in der Validierungsgruppe (N=255) waren 14%, 46%, 77% und 99% ($p<0,001$; Abbildung 4). Die jeweiligen Vergleiche der fünf Prognosegruppen A-E beider Studien mit dem Chi-Quadrat-Test ergaben keinen signifikanten Unterschied. Somit kann dieser Überlebens-Score für die MSCC beim Mammakarzinom als valide und reproduzierbar betrachtet werden.



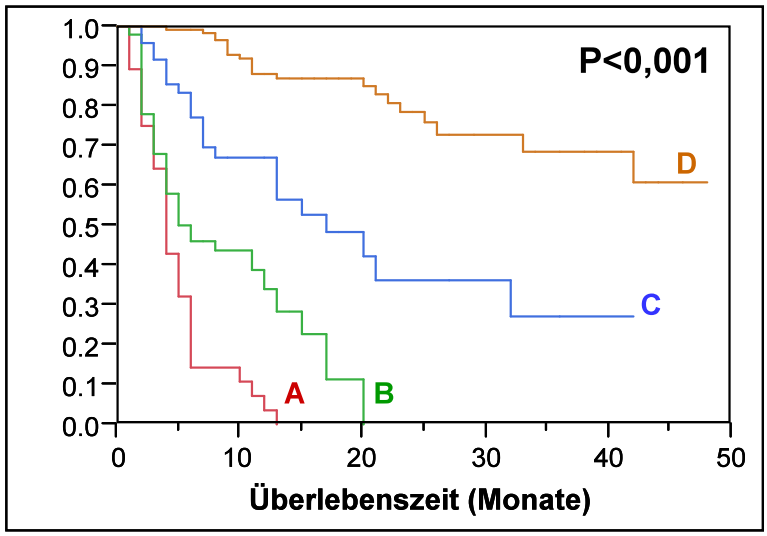


Abbildung 4. Kaplan-Meier Kurven für das Überleben in den Gruppen A-D in der Testgruppe (oben) und der Validierungsgruppe (unten) beim Mammakarzinom. Die P-Werte wurden mit Hilfe des log-rank Tests ermittelt.

V. MSCC bei Patienten mit Prostatakarzinom

Im Gesamtkollektiv aller Patienten mit MSCC war das Prostatakarzinom mit einem Anteil von 19% der zweithäufigste Primärtumor. Bei Patienten mit einem Prostatakarzinom wurden acht prätherapeutische mögliche Prognosefaktoren untersucht. Diese waren, wie beim Mammakarzinom, Alter, Allgemeinzustand (ECOG), Zahl befallener Wirbelkörper, Vorhandensein weiterer Knochenmetastasen vor Strahlentherapie, Vorhandensein von Organmetastasen vor Strahlentherapie, Intervall von der Erstdiagnose des Prostatakarzinoms bis zur Bestrahlung der MSCC, Gehfähigkeit vor Strahlentherapie und Entwicklungszeit motorischer Defizite vor der Strahlentherapie. In der multivarianten Analyse (Cox proportional hazards model) blieben vier Faktoren signifikant (siehe Tabelle 3).

	Überlebensrate nach 6 Monaten (%)	**Score (Punkte)**
Allgemeinzustand (ECOG)		
1-2	87	9
3-4	38	4
Gehfähigkeit vor RT		
gehfähig	37	4
nicht gehfähig	82	8
Weitere Knochenmetastasen		
nein	74	7
ja	54	5
Organmetastasen		
nein	75	8
ja	18	2
Intervall von Tumordiagnose bis RT		
≤ 15 Monate	51	5
> 15 Monate	69	7

Tabelle 3. Die Überlebensraten nach 6 Monaten für die fünf unabhängigen Prognosefaktoren und die entsprechenden Punktwerte (Scores) beim Prostatakarzinom.

Die Gesamtpunktwerte in der Testgruppe (N=218) betrugen zwischen 20 und 39 Punkten. Unter Berücksichtigung der Gesamtpunktwerte wurden drei Prognosegruppen gebildet (A: 20-24 Punkte, B: 25-34 Punkte, C: 35-39

Punkte). Die Verteilung der Gesamtpunktwerte bei Patienten mit einem Prostatakarzinom zeigt Abbildung 5.

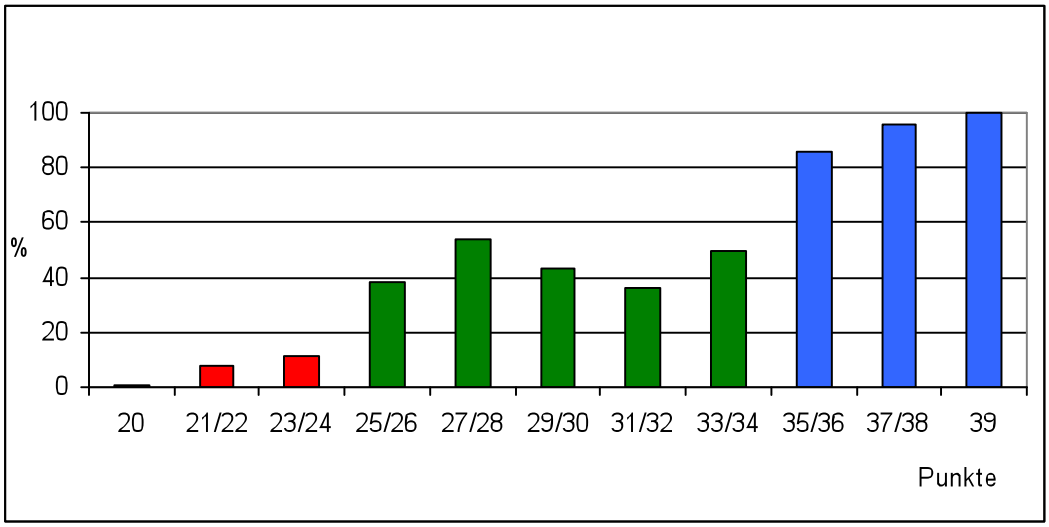
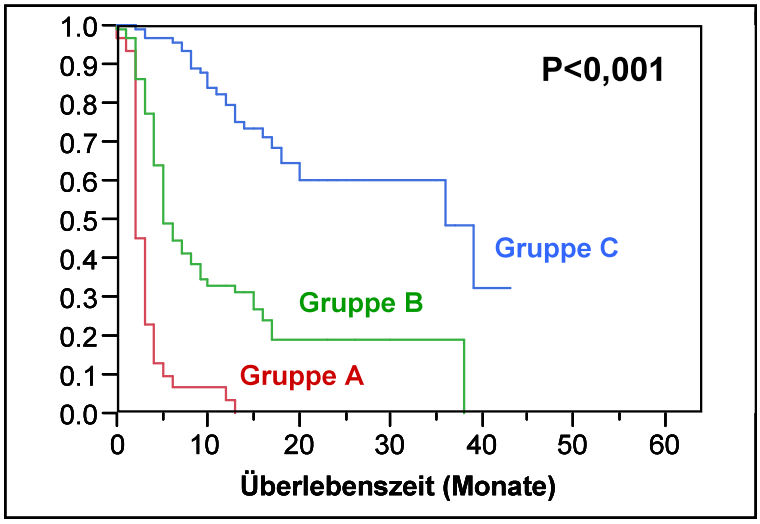


Abbildung 5. Die Gesamtpunktwerte (20-39 Punkte) und die entsprechenden Überlebensraten nach 6 Monaten beim Prostatakarzinom.

Die Überlebensraten nach 6 Monaten in der Testgruppe betrugen 7% (Gruppe A), 45% (Gruppe B) und 96% (Gruppe C) ($p<0,001$). Die Überlebensraten in der Validierungsgruppe (N=218) waren fast identisch und betrugen 7%, 45% und 95% ($p<0,001$). Diese Ergebnisse zeigen, dass dieser Überlebens-Score valide und gut reproduzierbar ist. Die Kaplan-Meier Kurven für das Überleben in den Prognosegruppen A-C in der Testgruppe und der Validierungsgruppe sind in Abbildung 6 dargestellt.



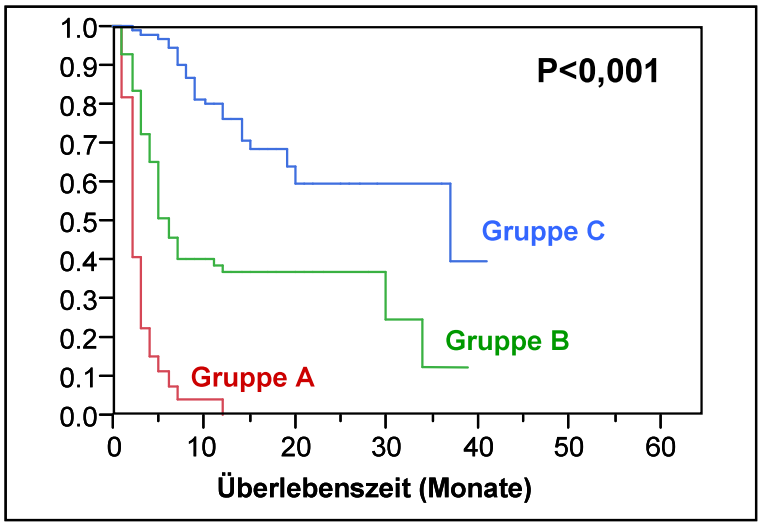


Abbildung 6. Kaplan-Meier Kurven für das Überleben in den Gruppen A-C in der Testgruppe (oben) und der Validierungsgruppe (unten) beim Prostatakarzinom. Die P-Werte wurden mit Hilfe des log-rank Tests ermittelt.

VI. MSCC bei Patienten mit nicht-kleinzelligem Lungenkarzinom

Von den insgesamt 2305 Patienten mit MSCC hatten 356 Patienten (15%) ein nicht-kleinzelliges Lungenkarzinom. Bei dieser Tumorentität wurden neun mögliche prätherapeutische Prognosefaktoren untersucht. Wie bereits bei Patientinnen mit einem Mammakarzinom und Patienten mit einem Prostatakarzinom beinhalteten diese Faktoren das Alter, den Allgemeinzustand (ECOG), die Anzahl befallener Wirbelkörper, das Vorhandensein weiterer Knochenmetastasen vor Strahlentherapie, das Vorhandensein von Organmetastasen vor Strahlentherapie, das Intervall von der Erstdiagnose des Lungenkarzinoms bis zur Bestrahlung der MSCC, die Gehfähigkeit vor Strahlentherapie und die Entwicklungszeit motorischer Defizite vor der Strahlentherapie. Hinzu kam beim nicht-kleinzelligen Lungenkarzinom das Geschlecht.

In der multivarianten Analyse (Cox proportional hazards model) waren vier Faktoren signifikant mit dem Überleben assoziiert (siehe Tabelle 4).

	Überlebensrate nach 6 Monaten (%)	**Score (Punkte)**
Allgemeinzustand (ECOG)		
1-2	51	5
3-4	15	2
Gehfähigkeit vor RT		
nicht gehfähig	12	1
gehfähig	44	4
Organmetastasen		
nein	56	6
ja	15	2
Entwicklungszeit motorischer Defizite		
1-7 Tage	12	1
> 7 Tage	40	4

Tabelle 4. Die Überlebensraten nach 6 Monaten für die vier unabhängigen Prognosefaktoren und die entsprechenden Punktwerte (Scores) beim nicht-kleinzelligen Lungenkarzinom.

Die Gesamtpunktwerte in der Testgruppe (N=178) bewegten sich zwischen 6 und 19 Punkten. Basierend auf diesen Gesamtpunktwerten wurden drei Prognosegruppen gebildet (A: 6-10 Punkte, B: 12-15 Punkte, C: 16-19 Punkte). Die Verteilung der Gesamtpunktwerte bei Patienten mit einem nicht-kleinzelligen Lungenkarzinom ist in Abbildung 7 dargestellt.

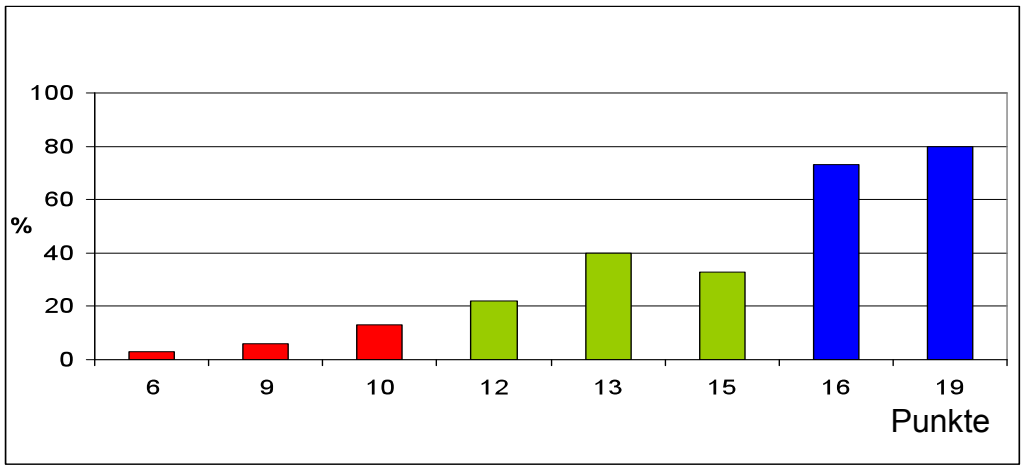
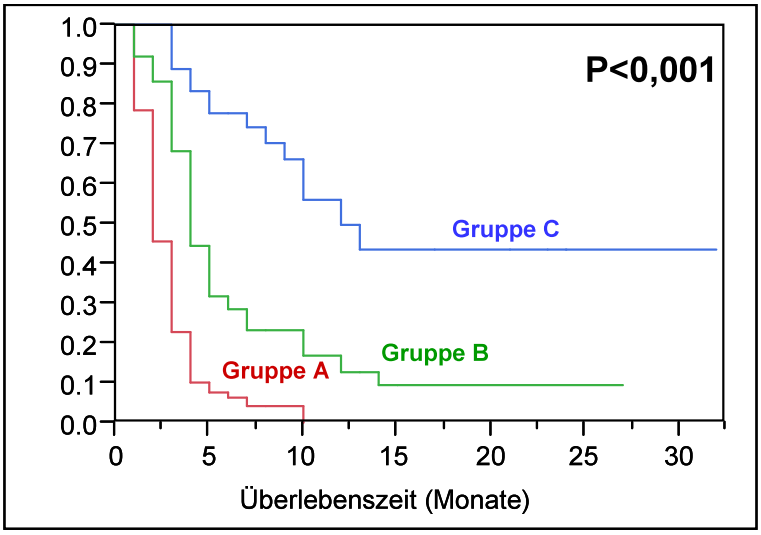


Abbildung 7. Die Gesamtpunktwerte (6-19 Punkte) und die entsprechenden Überlebensraten nach 6 Monaten beim nicht-kleinzelligen Lungenkarzinom.

Die Überlebensraten nach 6 Monaten in der Testgruppe betrugen 6% (Gruppe A), 29% (Gruppe B) und 78% (Gruppe C) ($p<0,001$). In der Validierungsgruppe (N=178) betrugen die Überlebensraten 4%, 24% und 76% ($p<0,001$). Die hohe Übereinstimmung der Überlebensraten in der Test- und der Validierungsgruppe sprechen für eine hohe Validität und Reproduzierbarkeit auch dieses Überlebens-Scores. Die entsprechenden Kaplan-Meier Kurven sind in Abbildung 8 dargestellt.



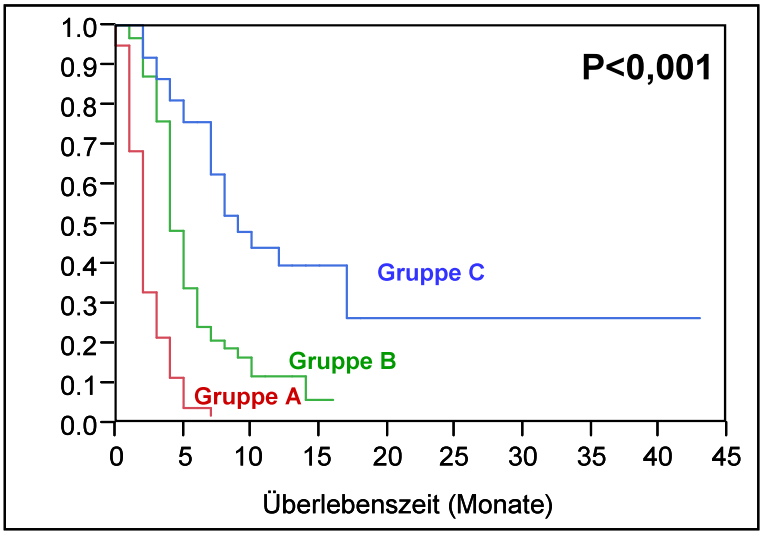


Abbildung 8. Kaplan-Meier Kurven für das Überleben in den Gruppen A-C in der Testgruppe (oben) und der Validierungsgruppe (unten) beim nicht-kleinzelligen Lungenkarzinom. Die P-Werte wurden mit Hilfe des log-rank Tests ermittelt.

VII. SCC bei Patienten mit Multiplem Myelom/Plasmozytom

Im Gesamtkollektiv hatten 126 Patienten (9%) ein multiples Myelom beziehungsweise Plasmozytom. Da es sich bei den Wirbelkörperbeteiligungen dieser Tumorentität nicht im eigentlichen Sinn um Metastasen handelt, spricht man statt von einer MSCC von einer SCC (spinal cord compression). Beim multiplen Myelom/Plasmozytom wurden die folgenden neun möglichen prätherapeutischen Prognosefaktoren untersucht: Alter, Allgemeinzustand (ECOG), Zahl befallener Wirbelkörper, Vorhandensein ossärer Läsionen vor Strahlentherapie, Vorhandensein von extraossären Manifestationen vor Strahlentherapie, Intervall von der Erstdiagnose der Erkrankung bis zur Bestrahlung der SCC, Gehfähigkeit vor Strahlentherapie und Entwicklungszeit motorischer Defizite vor der Strahlentherapie. Angesichts der, im Vergleich zu den anderen Primärtumoren, sehr guten Überlebensprognose wurde statt der Überlebensrate nach 6 Monaten die Überlebensrate nach 12 Monaten evaluiert. In der multivarianten Analyse (Cox proportional hazards model) waren lediglich drei Faktoren signifikant mit dem Überleben assoziiert (siehe Tabelle 5).

	Überlebensrate nach 12 Monaten (%)	**Score (Punkte)**
Allgemeinszustand (ECOG)		
1-2	81	8
3-4	60	6
Gehfähigkeit vor RT		
nicht gehfähig	56	6
gehfähig	81	8
Weitere ossäre Läsionen		
nein	84	8
ja	69	7

Tabelle 5. Die Überlebensraten nach 12 Monaten für die drei unabhängigen Prognosefaktoren und die entsprechenden Punktwerte (Scores) beim multiplen Myelom/Plasmozytom.

Die Gesamtpunktwerte in der Testgruppe (N=108) lagen zwischen 19 und 24 Punkten. Nach den Gesamtpunktwerten wurden beim multiplen Myelom/Plasmozytom drei Prognosegruppen gebildet (A: 19-20 Punkte, B: 21-23 Punkte, C: 24 Punkte). Die Verteilung der Gesamtpunktwerte zeigt Abbildung 9.

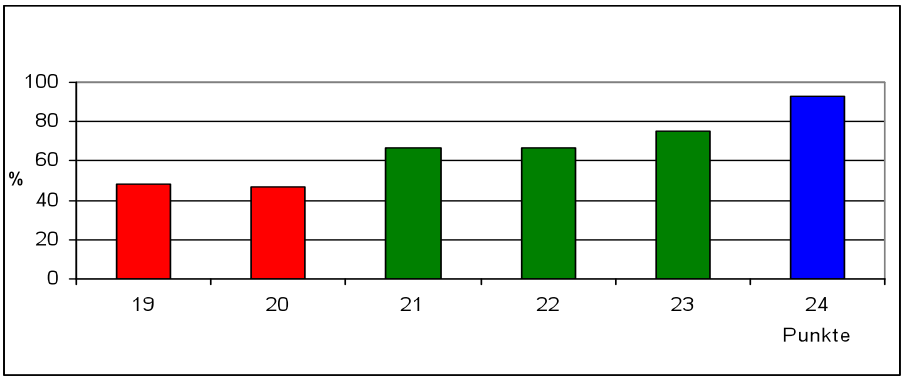
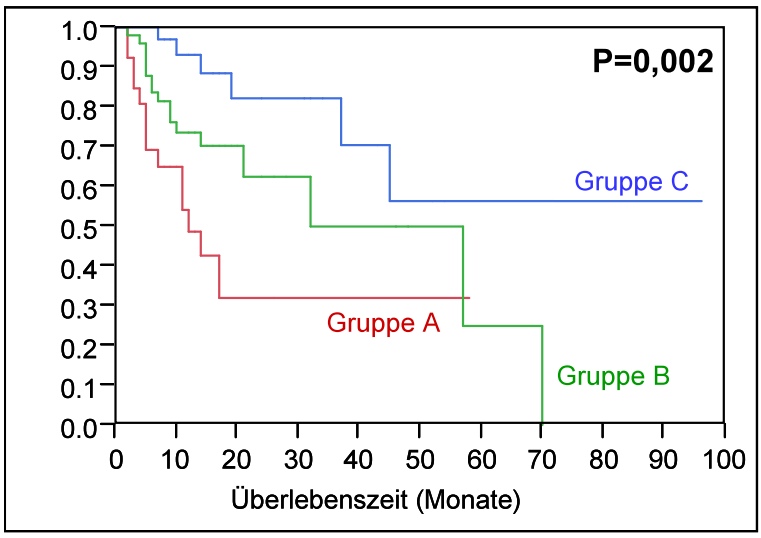


Abbildung 9. Die Gesamtpunktwerte (19-24 Punkte) und die entsprechenden Überlebensraten nach 12 Monaten beim multiplen Myelom/Plasmozytom.

Die Überlebensraten nach 12 Monaten in der Testgruppe betrugen 49% (Gruppe A), 74% (Gruppe B) und 93% (Gruppe C) (p=0,002). In der Validierungsgruppe (N=178) betrugen die Überlebensraten 51%, 80% und 90% (p<0,001). Die sehr ähnlichen Überlebensraten in den jeweiligen Gruppen A-C beim Vergleich von Test- und Validierungsgruppe können als Beleg für eine hohe Validität und Reproduzierbarkeit des Überlebens-Scores auch bei dieser Tumorentität gewertet werden. Die entsprechenden Kaplan-Meier Kurven sind in Abbildung 10 dargestellt.



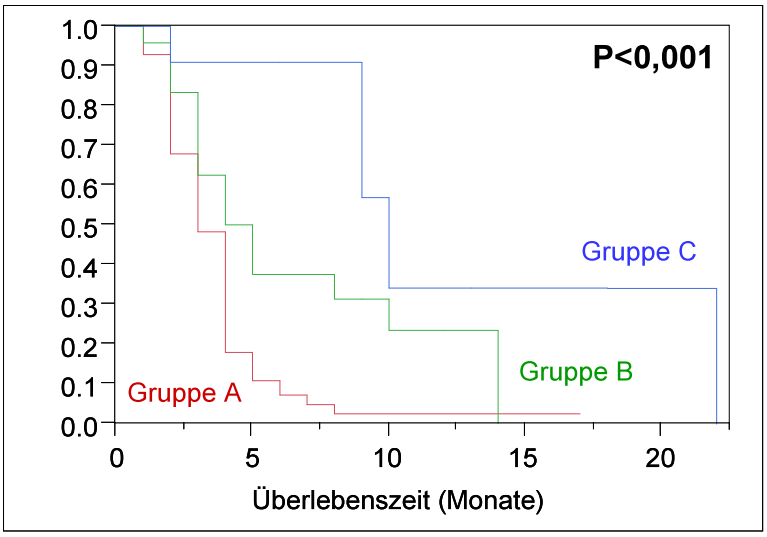


Abbildung 10. Kaplan-Meier Kurven für das Überleben in den Gruppen A-C in der Testgruppe (oben) und der Validierungsgruppe (unten) beim multiplen Myelom/Plasmozytom. Die P-Werte wurden mit Hilfe des log-rank Tests ermittelt.

VIII. MSCC bei Patienten mit unbekantem Primärtumor (CUP-Syndrom)

Bei 182 Patienten (8%) des Gesamtkollektivs war der Primärtumor zum Zeitpunkt der MSCC nicht bekannt. Man spricht in diesen Fällen von einem CUP-Syndrom. Bei diesen Patienten wurden acht mögliche prätherapeutische Prognosefaktoren untersucht. Diese waren Alter, Allgemeinzustand, Zahl befallener Wirbelkörper, Vorhandensein weiterer Knochenmetastasen vor Strahlentherapie, Vorhandensein von Organmetastasen vor Strahlentherapie, Gehfähigkeit vor Strahlentherapie und Entwicklungszeit motorischer Defizite vor der Strahlentherapie. Das Intervall von der Erstdiagnose der Tumorerkrankung bis zur Strahlentherapie der MSCC war naturgemäß kein sinnvoller Parameter, da beim CUP-Syndrom der Primärtumor nicht bekannt ist.

In der multivarianten Analyse (Cox proportional hazards model) waren vier Faktoren signifikant mit dem Überleben assoziiert. Diese Faktoren mit den Überlebensraten nach 6 Monaten und den entsprechenden Punktwerten sind in Tabelle 6 zusammengefasst.

	Überleben nach 6 Monaten (%)	**Score (Punkte)**
Allgemeinzustand (ECOG)		
1-2	56	6
3-4	16	2
Gehfähigkeit vor RT		
nicht gehfähig	17	2
gehfähig	39	4
Organmetastasen		
nein	50	5
ja	4	0
Entwicklungszeit motorischer Defizite		
1-7 Tage	10	1
> 7 Tage	47	5

Tabelle 6. Die Überlebensraten nach 6 Monaten für die vier unabhängigen Prognosefaktoren und die entsprechenden Punktwerte (Scores) beim CUP-Syndrom.

Die Gesamtpunktwerte in der Testgruppe (N=91) bewegten sich zwischen 5 und 20 Punkten. Unter Berücksichtigung der Gesamtpunktwerte wurden beim CUP-Syndrom drei Prognosegruppen gebildet (Gruppe A: 5-13 Punkte, Gruppe B: 14-16 Punkte, Gruppe C: 20 Punkte). Die Verteilung der Gesamtpunktwerte ist in Abbildung 11 dargestellt.

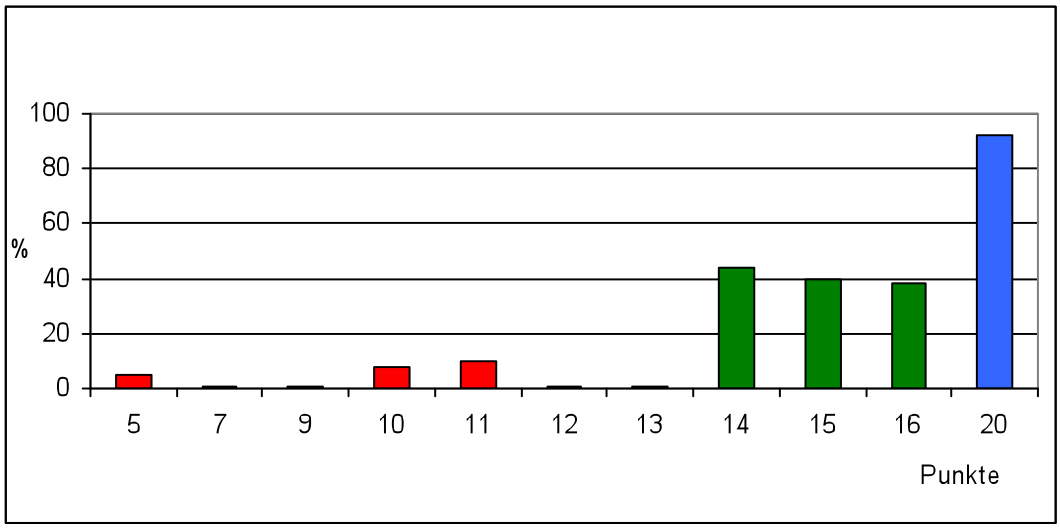
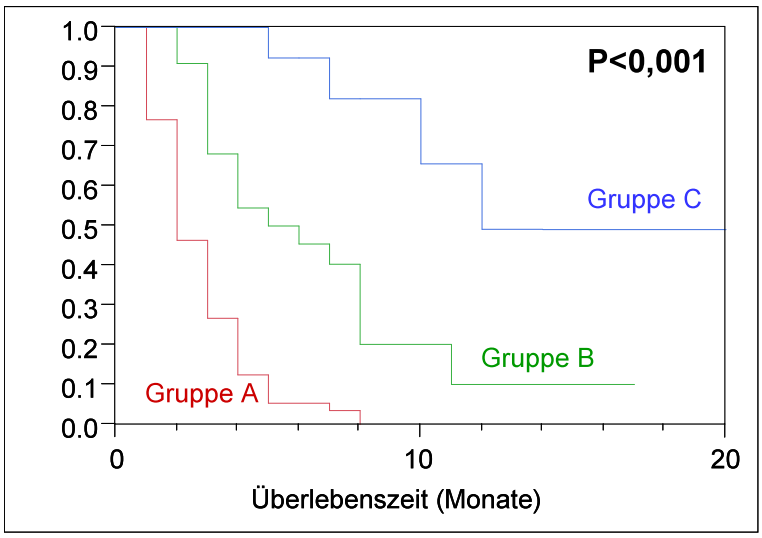


Abbildung 11. Die Gesamtpunktwerte (5-20 Punkte) und die entsprechenden Überlebensraten nach 6 Monaten beim CUP-Syndrom.

In der Testgruppe waren die Überlebensraten nach 6 Monaten 5% (Gruppe A), 41% (Gruppe B) und 92% (Gruppe C) ($p<0,001$). In der Validierungsgruppe (N=91) waren die Überlebensraten 7%, 38% und 91% ($p<0,001$). Da die Überlebensraten in den jeweiligen Gruppen A-C beim Vergleich von Test- und der Validierungsgruppe eine hohe Übereinstimmung aufwiesen, kann auch bei diesem Überlebens-Score von einer hohen Validität und einer sehr guten Reproduzierbarkeit ausgegangen werden. Die jeweiligen Kaplan-Meier Kurven zeigt Abbildung 12.



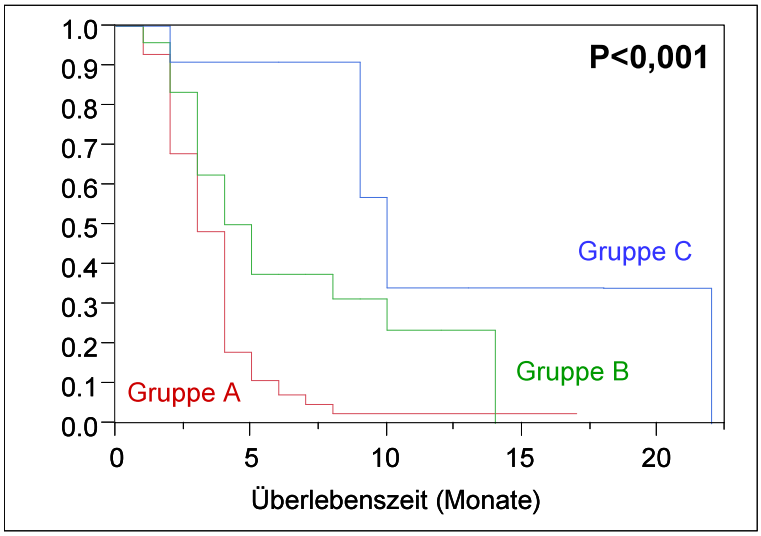


Abbildung 12. Kaplan-Meier Kurven für das Überleben in den Gruppen A-C in der Testgruppe (oben) und der Validierungsgruppe (unten) beim CUP-Syndrom. Die P-Werte wurden mit Hilfe des log-rank Tests ermittelt.

IX. Diskussion und Ausblick

Die MSCC stellt für die betroffenen Patienten eine sehr belastende onkologische Komplikation dar. In dieser palliativen Situation sind individuelle Behandlungskonzepte von großer Bedeutung. Diese Arbeit soll dazu beitragen, das Behandlungskonzept besser auf den einzelnen Patienten ausrichten zu können. Die meisten Patienten mit einer MSCC haben eine durchschnittliche Lebenserwartung von nur wenigen Monaten. Allerdings gibt es auch Patienten, welche noch längere Zeit, zum Teil sogar einige Jahre mit ihrer Erkrankung leben, woraus sich andere Therapiestrategien für die Patienten ergeben [1,2]

Bei Patienten mit schlechter Überlebensprognose besteht hingegen häufig der Wunsch, die wenige verbleibende Lebenszeit in der häuslichen Umgebung zu verbringen. Ein unnötig langer Krankenhausaufenthalt würde die Lebensqualität der Patienten sehr wahrscheinlich deutlich einschränken. Allerdings kann auch eine ambulante Strahlentherapie für die Patienten sehr anstrengend und belastend sein.

Die weltweit häufigste Therapie der MSCC ist die alleinige Strahlentherapie [1,2]. Die Gesamtbehandlungsdauer sollte bei der Wahl der adäquaten Therapiestrategie berücksichtigt werden. Anhand der derzeitigen Datenlage ist eine Kurzzeit-Strahlentherapie von bis zu einer Woche Dauer hinsichtlich des Effekts auf die motorische Funktion ähnlich wirksam wie eine Langzeit-Strahlentherapie von zwei bis vier Wochen Dauer [4,5]. Wenn man die mögliche Belastung für die oft schwer kranken Patienten durch die tägliche Bestrahlung betrachtet, so ist bei Patienten mit sehr schlechter Überlebensprognose eine Kurzzeit-Therapie zu bevorzugen. Allerdings kommt es nach einer Kurzzeit-Strahlentherapie häufiger zu einem Rezidiv einer MSCC in der bestrahlten Wirbelsäulenregion als nach einer Langzeit-Strahlentherapie [5,6]. Je länger ein Patient lebt, desto höher ist das Risiko, ein solches Rezidiv

zu erleiden. Somit profitieren Patienten mit besserer Überlebensprognose von einer Langzeit-Strahlentherapie.

Bei Patienten mit einer geschätzten Lebenserwartung von mindestens drei Monaten kann zusätzlich zur Strahlentherapie eine vorgeschaltete Operation sinnvoll sein. Der zunehmende Trend zu einer solchen Dekompression mit Stabilisierung der befallenen Wirbelkörper basiert auf einer randomisierten Studie von 101 Patienten [3]. In dieser Studie war die Kombination von Operation und Strahlentherapie der alleinigen Strahlentherapie hinsichtlich Gehfähigkeit nach Therapie und Überleben signifikant überlegen. Diese Studie wurde allerdings aufgrund methodischer Schwächen kritisiert. Das Patientenkollektiv war hoch selektioniert, denn in der Gruppe der alleinigen Strahlentherapie wurden mehr Patienten mit knöcherner Einengung des Spinalkanals (durch eine pathologische Fraktur), im Gegensatz zu einer Einengung durch eine epidurale Metastasenmanifestation eingeschlossen. Gefordert waren unter anderem ein guter bis sehr guter Allgemeinzustand und eine Überlebensprognose von mindestens drei Monaten. Patienten mit Plasmozytom oder Lymphom wurden nicht eingeschlossen [9,10]. Die Ergebnisse der Studie von Patchell et al. konnten in einer Matched-Pair-Analyse von 324 Patienten, deren Situation eher dem klinischen Alltag entsprach, nicht bestätigt werden [11]. Das Risiko für relevante Komplikationen nach einer Operation beträgt mehr als 10%, dennoch nimmt die Rate an Operationen bei MSCC in Deutschland zu [3,11,12]. Eine Intensivierung der Therapie durch eine zusätzliche Operation muss sorgsam abgewogen werden und in erster Linie bei Patienten mit besserer Überlebensprognose eingesetzt werden.

Diese Überlegungen hinsichtlich der verschiedenen Therapieoptionen zeigen, wie wichtig es ist, die Überlebensprognose von Patienten mit MSCC abschätzen zu können.

In der vorliegenden Arbeit konnte nun gezeigt werden, dass individuelle Charakteristika des jeweiligen Patienten und spezifische Eigenschaften der Tumorerkrankung einen Einfluss auf das Gesamtüberleben haben. Basierend auf den wichtigsten Eigenschaften, das heißt auf den in der multivarianten Analyse signifikanten Prognosefaktoren, wurde ein Überlebens-Score für Patienten mit MSCC entwickelt [8]. Der Score beinhaltet fünf prognostische Gruppen. Die Überlebensraten nach 6 Monaten betrugen 4% (Gruppe A), 11% (Gruppe B), 48% (Gruppe C), 87% (Gruppe D) und 99% (Gruppe E). Patienten der Gruppen A und B eignen sich eher für eine Kurzzeit-Strahlentherapie, während Patienten der Gruppen D und E eher Kandidaten für eine Langzeit-Strahlentherapie sind. Da fast die Hälfte der Patienten in Gruppe C nach 6 Monaten noch lebt und somit ein erhöhtes Risiko für ein Rezidiv hat, würde man diese Patienten eher mit einer Langzeit-Strahlentherapie behandeln.

Um eine noch genauere Einschätzung des jeweiligen Patienten und seiner Prognose vornehmen und die Therapie eventuell noch individueller gestalten zu können, wurde das Gesamtüberleben noch einmal gesondert für die bei der MSCC fünf häufigsten Tumorentitäten betrachtet. Es stellte sich heraus, dass auch die für diese fünf Entitäten erstellten Scores als valide zu betrachten sind und es für einzelne Tumorerkrankungen signifikante prognostische Faktoren gibt. Allerdings sind viele dieser Faktoren im initialen Score, welcher über 30 verschiedene Tumorerkrankungen einschließt, berücksichtigt [8]. Somit stellt sich weiterhin die Frage, ob wirklich für jede einzelne Tumorentität ein individueller Score benötigt wird, oder ob nicht ein einziger

entitätenübergreifender Score ausreicht. Weitere Untersuchungen zum Vergleich des entitätenübergreifenden Scores mit den tumorspezifischen Scores im Hinblick auf Validität und Genauigkeit sind geplant.

Insgesamt ist anzumerken, dass die in dieser Arbeit entwickelten Scores überwiegend auf retrospektiven Daten basieren. Ein Selektionsbias kann somit nicht ausgeschlossen werden. Dieser Aspekt muss bei der Anwendung der Scores berücksichtigt werden. Allerdings wird es schwierig sein, in naher Zukunft ausreichend viele Patienten aus prospektiven Studien für derartige Scores zur Verfügung zu haben.

Es ist von großer Wichtigkeit, den jeweiligen Patienten mit einer MSCC individuell unter Berücksichtigung seines Risikoprofils und seiner Überlebensprognose zu behandeln. Obwohl diese Studie auf retrospektiv erhobenen Daten basiert, lässt sich anhand dieser Daten schlussfolgern, dass eine valide Prognoseeinschätzung mit diesen Scores möglich ist, sofern die individuelle Erkrankung des Patienten und seine spezifischen Risikofaktoren ausreichend berücksichtigt werden.

Solche Scores Studien sollen dem Kliniker bei der Wahl der jeweils am besten geeigneten Therapie bei Patienten mit MSCC helfen. Für eine mögliche weitere Vereinfachung und Zusammenlegung der Scores sind noch weitere vergleichende Untersuchungen, welche eine fokussierte und individualisierte onkologische Therapie der jeweiligen Patienten möglich machen, erforderlich.

X. Literaturverzeichnis

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XI. Anhang

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A validated survival score for breast cancer patients with metastatic spinal cord compression

Of all primary tumor types leading to metastatic spinal cord compression (MSCC), breast cancer is the most common one accounting for more than 20% of cases [4, 7, 12, 14]. The optimal fractionation regimen of radiotherapy is still a matter of debate. It appears reasonable that the selection of the treatment for each patient must take into account the survival prognosis. Patients with an extraordinarily limited remaining life time of 2 months or less are certainly not candidates for decompressive surgery or longer-course radiotherapy, which may take up to 4 weeks. These patients with very poor prognosis may be considered for single-fraction radiotherapy or even best supportive care alone. Patients with an expected survival time of only a few months may be considered as candidates for short-course multifraction radiotherapy such as 5 fractions of 4 Gy given in 1 week. Patients with a relatively favorable survival prognosis are better treated with longer-course radiotherapy, usually 10 fractions of 3 Gy given in 2 weeks, as this regimen results in higher local control rates of MSCC than single-fraction and short-course multifraction regimens [9, 10]. Recent data have suggested that patients with an extraordinarily good survival prognosis may benefit from long-course radiotherapy with 20 fractions of 2 Gy in 4 weeks in terms of better local control of MSCC and survival when compared to 10 fractions of 3 Gy [11].

In order to choose the optimal regimen for each patient, it is very important to be able to estimate the patient's survival time. Each primary tumor type leading to MSCC is different with respect to its biological behavior and prognosis. Therefore, personalization of cancer treatment would be better facilitated if separate survival scores were available for the most common primary tumor types associated with MSCC. This accounts in particular for breast cancer, which is the most common primary tumor leading to MSCC [7]. This study was performed to design and validate a survival score specifically for patients with MSCC from breast cancer.

Patients and methods

A total of 510 unselected breast cancer patients treated with radiotherapy alone for MSCC between 1995 and 2011 were retrospectively evaluated. The data of 381 of these 510 patients had been included in a previous study generating a survival score for patients with more than 30 different primary tumor types [8]. Criteria for inclusion in the present analysis included motor deficits of the legs due to MSCC, no prior surgery or radiotherapy to the currently involved parts of the spinal cord, adequate diagnostic imaging including spinal computed tomography (CT) or spinal magnetic resonance imaging (MRI), and corticosteroid treatment during radiotherapy for at least 1 week. The data were collected from the patients, their treating physicians, and the patient files. The irradiated volumes encompassed one normal vertebra above and below the involved vertebrae.

From the database of the entire cohort of 510 patients, the patients were alternately assigned to the test group (uneven numbers, n=255) or the validation group (even numbers, n=255). Patient characteristics of both groups are given in **Tab. 1**. Short-course radiotherapy (1×8 Gy or 5×4 Gy) had been administered to 93 patients (36%) of the test group and 89 patients (35%) of the validation group, respectively, and longer-course radiotherapy (10×3 Gy, 15×2.5 Gy, or 20×2 Gy) had been administered to 162 patients (64%) and 166 patients (65%), respectively.

In the test group, the following eight potential prognostic factors were investigated: age (≤61 vs. ≥62 years; median age: 61 years), Eastern Cooperative Oncology Group (ECOG) performance status (ECOG-PS 1–2 vs. 3–4), number of

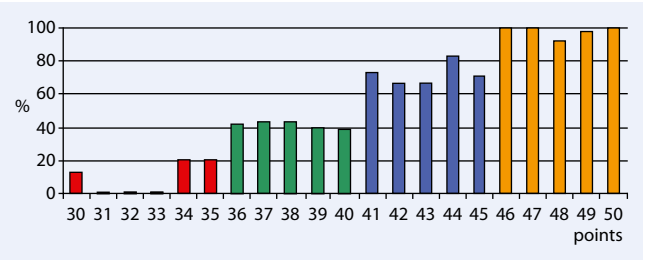

Fig. 1 ▲ Test group: total scores (30–50 points) in relation to the 6-month survival rate (in %). Four groups were formed: group A (30–35 points, *red columns*), group B (36–40 points, *green columns*), group C (41–45 points, *blue columns*), and group D (46–50 points, *orange columns*)

Tab. 1 Patient characteristics of the test group and the validation group

	Test group	Validation group	p value
	No. of patients (%)	No. of patients (%)	
Age			
≤61 years	130 (51)	138 (54)	
≥62 years	125 (49)	117 (46)	0.67
ECOG performance status			
1–2	163 (64)	162 (64)	
3–4	92 (36)	93 (36)	0.95
Number of involved vertebrae			
1–2	97 (38)	100 (39)	
≥3	158 (62)	155 (61)	0.89
Ambulatory status prior to RT			
Not ambulatory	65 (25)	59 (23)	
Ambulatory before RT	190 (75)	196 (77)	0.81
Other bone metastases			
No	101 (40)	102 (40)	
Yes	154 (60)	153 (60)	0.95
Visceral metastases			
No	160 (63)	166 (65)	
Yes	95 (37)	89 (35)	0.78
Interval from cancer diagnosis to radiotherapy of MSCC			
≤15 months	67 (26)	68 (27)	
>15 months	188 (74)	187 (73)	0.95
Time of developing motor deficits			
1–7 days	51 (20)	44 (17)	
>7 days	204 (80)	211 (83)	0.78
Radiation regimen			
Short-course radiotherapy	93 (36)	89 (35)	
Longer-course radiotherapy	162 (64)	166 (65)	0.89

involved vertebrae (1–2 vs. ≥3), ambulatory status before radiotherapy (no vs. yes), other bone metastases before radiotherapy (no vs. yes), visceral metastases before radiotherapy (no vs. yes), interval between first diagnosis of breast cancer and radiotherapy of MSCC (≤15 vs. >15 months), and time of developing motor deficits prior to radiotherapy (1–7 vs. >7 days). In addition to these pretreatment factors, the potential impact of the radiation regimen (short-course vs. longer-course radiotherapy) was investigated. Univariate analysis of survival was performed with the Kaplan-Meier method and the log-rank test [5]. In addition, the prognostic factors that were significant in the univariate analysis ($p<0.05$) were evaluated in a multivariate analysis with the Cox proportion hazards model. The prognostic factors that were significant in the multivariate analysis of the test group were included in the survival score as follows. The score for each significant prognostic factor was determined by dividing the 6-month survival rate (given in %) by ten. The total score represented the sum of the scores for each factor. To investigate the reproducibility of the score, the score groups of the test group were compared with the corresponding score groups of the validation group.

Results

In the univariate analysis of the test group, improved survival was associated with an ECOG performance status of 1–2 ($p<0.0001$), involvement of only 1–2 vertebrae ($p=0.008$), ambulatory status before radiotherapy ($p<0.0001$), no other bone metastases ($p=0.005$), no visceral metastases ($p<0.0001$), an interval from cancer diagnosis to radiotherapy of MSCC of more than 15 months ($p<0.0001$), slower development of motor deficits (>7 days) before radiotherapy ($p<0.0001$), and longer-course radiotherapy ($p=0.032$). The results of the univariate analysis of the test group are summarized in **Tab. 2**. In the multivariate analysis of the test group, ECOG performance status ($p=0.0006$), ambulatory status ($p=0.0002$), no other bone metastases ($p=0.015$), no visceral metastases ($p<0.0001$), interval from cancer diagnosis to radiotherapy of MSCC ($p=0.027$), and the time of developing motor deficits ($p=0.003$) remained significant and were included in the survival score. The radiation regimen was also significant ($p=0.021$). The results of the multivariate analysis of the test group are summarized in **Tab. 3**.

The 6-month survival rates and the corresponding score for each of the five significant prognostic factors are given in **Tab. 4**. The total scores ranged from 30 to 50 points (**Fig. 1**), and the patients were divided into four score groups: 30–35 points (group A, n=26), 36–40 points (group B, n=51), 41–45 points (group C, n=61), and 46–50 points (group D, n=117). The 6-month survival rates were 12% for group A, 41% for group B, 74% for group C, and 98% for group D ($p<0.0001$, **Fig. 2**). The survival rates of the four prognostic groups in the validation group were 14%, 46%, 77%, and 99%, respectively ($p<0.0001$, **Fig. 3**). Each of the score groups A to D of the test group was compared with each of the corresponding score groups A to D of the validation group with respect to the 6-month survival rates (results are given in **Tab. 5**). The survival rates of the validation group were similar to those of the test group.

Discussion

In many cases, MSCC carries a poor survival prognosis [7]. However, a considerable number of patients have a more favorable prognosis and may live for years. This is particularly true for patients with MSCC from breast cancer. Despite the fact that treatment standards are widespread, one emerging strategy in oncology is the personalization of cancer treatment. Just such an individualized treatment approach accounts for the patient's life expectancy. Therefore, survival scores are important, as they allow an

estimate of the survival prognosis of each patient. Four years ago, we published a survival score for patients with MSCC including patients with more than 30 different primary tumors [8]. However, because the various tumors behave differently, it is important to have separate scores for the different tumor entities, especially the most common ones. Breast cancer is the most common primary tumor in patients with MSCC [7]. In the present study, six independent pretreatment prognostic factors were identified: ECOG performance status, ambulatory status before radiotherapy, other bone metastases, visceral metastases, interval from cancer diagnosis to radiotherapy of MSCC, and the time of developing motor deficits. The radiation regimen was also significantly associated with survival in both the univariate and the multivariate analysis. Although the radiation regimen was not a pretreatment prognostic factor, it was included in the multivariate analysis in order avoid a potential bias caused by this additional prognostic treatment factor. The risk of a hidden bias could not be completely excluded owing to the retrospective nature of the data included in this survival score.

In comparison to other solid tumors, breast cancer patients with MSCC have a more favorable survival prognosis [7]. This aspect is reflected by the fact that almost half of the patients belonged to prognostic group D, which had the best survival prognosis. The fact that breast cancer patients have such a favorable prognosis may explain the finding that longer-course radiotherapy with higher total doses resulted in significantly better survival than short-course radiotherapy with lower total doses. A recent matched-pair analysis has suggested that patients with a very good survival prognosis benefit from an escalation of the total radiation dose [11].

Based on the six independent pretreatment prognostic factors, the survival score was designed resulting in the designation of four prognostic groups. Group A patients had a very poor survival prognosis and may be considered for best supportive care including corticosteroids, analgesic drugs, and physiotherapeutic measures or single-fraction

Abstract · Zusammenfassung

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D. Rades · S. Douglas · S.E. Schild

A validated survival score for breast cancer patients with metastatic spinal cord compression

Abstract

Background. To create a validated scoring system predicting survival of breast cancer patients with metastatic spinal cord compression (MSCC).

Patients and methods. Of 510 patients, one half were assigned to either the test or the validation group. In the test group, eight pretreatment factors (age, performance status, number of involved vertebrae, ambulatory status, other bone metastases, visceral metastases, interval from cancer diagnosis to radiotherapy of MSCC, time of developing motor deficits) plus the radiation regimen were retrospectively investigated. Factors significantly associated with survival in the multivariate analysis were included in the scoring system. The score for each factor was determined by dividing the 6-month survival rate (%) by ten. The total score was the sum of the scores for each factor.

Results. In the multivariate analysis of the test group, performance status, ambulatory status, other bone metastases, visceral metastases, interval from cancer diagnosis to radiotherapy of MSCC, and time of developing motor deficits were significant for survival and included in the score. Total scores ranged from 30 to 50 points. In the test group, the 6-month survival rates were 12% for 30–35 points, 41% for 36–40 points, 74% for 41–45 points, and 98% for 46–50 points ($p<0.0001$). In the validation group, the 6-month survival rates were 14%, 46%, 77%, and 99%, respectively ($p<0.0001$).

Conclusion. The survival rates of the validation group were similar to the test group. Therefore, this score was reproducible and can help when selecting the appropriate radiotherapy regimen for each patient taking into account her survival prognosis.

Keywords

Breast cancer · Metastatic spinal cord compression · Prognosis · Survival score · Radiation regimen

Ein validierter Überlebensscore für Brustkrebspatientinnen mit metastatisch bedingter Rückenmarkskompression

Zusammenfassung

Hintergrund. Ziel dieser Arbeit war es, einen validierten Score zu entwickeln, mit dem das Überleben von Brustkrebspatientinnen mit metastatisch bedingter Rückenmarkskompression („metastatic spinal cord compression", MSCC) vorausgesagt werden kann.

Patienten und Methode. Von insgesamt 510 Patientinnen wurde jeweils die Hälfte der Testgruppe oder der Validierungsgruppe zugeteilt. In der Testgruppe wurden acht prätherapeutische Faktoren (Alter, Allgemeinzustand, Zahl befallener Wirbelkörper, Gehfähigkeit, andere Knochenmetastasen, Organmetastasen, Intervall von der Erstdiagnose der Tumorerkrankung bis zur Strahlentherapie der MSCC, Entwicklungszeit motorischer Defizite) und das Fraktionierungsschema retrospektiv untersucht. Die Faktoren, die in der Multivarianzanalyse signifikant mit dem Überleben assoziiert waren, gingen in den Score ein. Der Score für jeden Faktor wurde ermittelt, indem die 6-Monats-Überlebensrate (%) durch zehn geteilt wurde. Der Prognosescore entsprach der Summe der Scores der einzelnen Faktoren.

Ergebnisse. In der multivariaten Analyse der Testgruppe waren der Allgemeinzustand, Gehfähigkeit, andere Knochenmetastasen, Organmetastasen, das Intervall von der Erstdiagnose der Tumorerkrankung bis zur Strahlentherapie der MSCC und die Entwicklungszeit motorischer Defizite signifikant mit dem Überleben assoziiert. Die Scores lagen zwischen 30 und 50 Punkten. In der Testgruppe betrugen die 6-Monats-Überlebensraten 12% bei 30–35 Punkten, 41% bei 36–40 Punkten, 74% bei 41–45 Punkten und 98% bei 46–50 Punkten ($p<0,0001$). In der Validierungsgruppe betrugen die entsprechenden 6-Monats-Überlebensraten 14%, 46%, 77%, und 99% ($p<0,0001$).

Schlussfolgerungen. Die Überlebensraten in der Validierungsgruppe ähnelten den Überlebensraten in der Testgruppe. Demzufolge kann der Score als reproduzierbar angesehen werden. Der Score kann dabei helfen, das am besten geeignete Bestrahlungsregime für die einzelne Patientin unter Berücksichtigung ihrer Überlebensprognose auszuwählen.

Schlüsselwörter

Brustkrebs · Metastatisch bedingter Rückenmarkskompression · Prognose · Überlebensscore · Bestrahlungsregime

Tab. 2 Test group: univariate analysis of survival

	Survival at 6 months (%)	Survival at 12 months (%)	p value
Age			
≤61 years	74	59	
≥62 years	71	57	0.20
ECOG performance status			
1–2	88	75	
3–4	46	28	<0.0001
Number of involved vertebrae			
1–2	79	67	
≥3	68	53	0.008
Ambulatory status before radiotherapy			
Not ambulatory	43	28	
Ambulatory before RT	83	68	<0.0001
Other bone metastases			
No	83	66	
Yes	66	53	0.005
Visceral metastases			
No	90	82	
Yes	43	18	<0.0001
Interval from cancer diagnosis to radiotherapy of MSCC			
≤15 months	55	36	
>15 months	79	66	<0.0001
Time of developing motor deficits			
1–7 days	39	24	
>7 days	81	67	<0.0001
Radiation regimen			
Short-course radiotherapy	70	51	
Longer-course radiotherapy	74	62	0.032

Tab. 3 Test group: multivariate analysis of survival

	Risk ratio	95% confidence interval	p value
ECOG performance status	2.00	1.34–3.00	0.0006
Number of involved vertebrae	1.37	0.98–1.95	0.07
Ambulatory status before radiotherapy	2.13	1.44–3.13	0.0002
Other bone metastases	2.51	1.19–5.26	0.015
Visceral metastases	11.04	6.81–18.43	<0.0001
Interval from cancer diagnosis to radiotherapy of MSCC	1.29	1.03–1.61	0.027
Time of developing motor deficits	1.45	1.14–1.85	0.003
Radiation regimen	1.25	1.03–1.51	0.021

radiotherapy (8 Gy/1 fraction). Group B patients had a 6-month survival probability of less than 50% and can be considered good candidates for treatment with short-course multifraction radiotherapy such as 20 Gy in 5 fractions over 1 week. It has been shown that short-course radiotherapy is as effective as longer programs with respect to posttreatment motor function and ambulatory status. Group B patients are not likely to live long enough to experience a local recurrence of MSCC, which is less common after longer-course than after short-course radiotherapy [9, 10]. Thus, patients with a more favorable survival prognosis such as group C and group D patients are the ones most likely to benefit from longer-course programs in terms of better local control of MSCC. Ten fractions of 3 Gy in 2 weeks is the most frequently used longer-course program for MSCC worldwide, which we would recommend for group C patients. Group D patients have a very favorable survival prognosis, with a 1-year survival rate of 90% in the test group and 88% in the validation group. A recent matched-pair analysis has suggested that patients with such a favorable survival prognosis benefit from an escalation of the radiation dose beyond 10 fractions of 3 Gy. After 20 fractions of 2 Gy or 15 fractions of 2.5 Gy, the local control rate at 2 years was 92% compared to 71% after 10 fractions of 3 Gy (p=0.013), and the survival rate at 2 years was 68% compared to 53% (p=0.032). Furthermore, a lower dose per fraction is generally associated with a lower risk of radiation-related late toxicity. Therefore, group D patients may be best treated with 20 fractions of 2 Gy over 4 weeks. In patients of score groups B, C, and D, the option of upfront decompressive surgery in addition to radiotherapy may be indicated, since in a small randomized trial of 101 patients, additional upfront decompressive surgery resulted in better ambulatory function and survival than radiotherapy alone [6]. However, in accordance with this randomized trial, decompressive surgery should be limited to patients with a good performance status, involvement of only one spinal segment, and paraplegia not lasting longer than 48 h.

In contrast to other scoring systems that have been developed for patients with vertebral metastasis or palliative situations and that have included many different primary tumor types, the present survival score focused on patients with motor deficits due to MSCC from breast cancer [1, 2, 3, 8, 13, 15]. Therefore, this new score takes into account the patient's individual situation more than previous scoring systems, which likely contributes to a better personalization of the treatment regimen for these patients.

To validate the scoring system, the four prognostic groups A to D of the test group were compared with the corresponding prognostic groups A to D of the validation group. The 6-month survival rates in the validation group were very similar to the 6-month survival rates in the test group. The difference in 6-month survival between the

Tab. 4 Test group: 6-month survival rates and corresponding scores

	Survival at 6 months (%)	Score (points)
ECOG performance status		
1–2	88	9
3–4	46	5
Ambulatory status before radiotherapy		
Not ambulatory	43	4
Ambulatory before RT	83	8
Other bone metastases		
No	83	8
Yes	66	7
Visceral metastases		
No	90	9
Yes	43	4
Interval from cancer diagnosis to radiotherapy of MSCC		
≤15 months	55	6
>15 months	79	8
Time of developing motor deficits		
1–7 days	39	4
>7 days	81	8

Tab. 5 Comparison of groups A–D of the test group with the corresponding groups A–D of the validation group with respect to the 6-month survival rates

	Survival at 6 months (%)	Survival at 12 months (%)	p value at 6 months
Score group A			
Test group (n=26)	12	4	
Validation group (n=28)	14	4	0.96
Score group B			
Test group (n=51)	41	16	
Validation group (n=50)	46	34	0.84
Score group C			
Test group (n=61)	74	55	
Validation group (n=48)	77	67	0.91
Score group D			
Test group (n=117)	98	90	
Validation group (n=129)	99	88	0.94

corresponding prognostic groups of the test group and the validation group was quite small, ranging between 1% and 5% This demonstrated that this new score for MSCC from breast cancer can be considered valid and reproducible.

Conclusion

In summary, the new survival score was developed and validated in 510 patients with MSCC from breast cancer, and is the largest reported series of such patients. The score included six independent prognostic factors and four prognostic groups (A to D). Group A patients had a very poor survival prognosis and may be candidates for best supportive care or single-fraction radiotherapy. Group B patients may be considered for short-course multifraction radiotherapy such as 5 fractions of 4 Gy given over 1 week. Group C and group D patients have a favorable survival prognosis and should, therefore, receive longer-course radiotherapy. Group C patients may be treated with 10 fractions of 3 Gy in 2 weeks, whereas group D patients may benefit from longer-course programs with higher total doses and lower doses per fraction than 10 fractions of 3 Gy, for example, with 20 fractions of 2 Gy in 4 weeks.

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Conflict of interest. On behalf of all authors, the corresponding author states the following: Dirk Rades has received speaker's honoraria from Amgen and Novartis Omcology.

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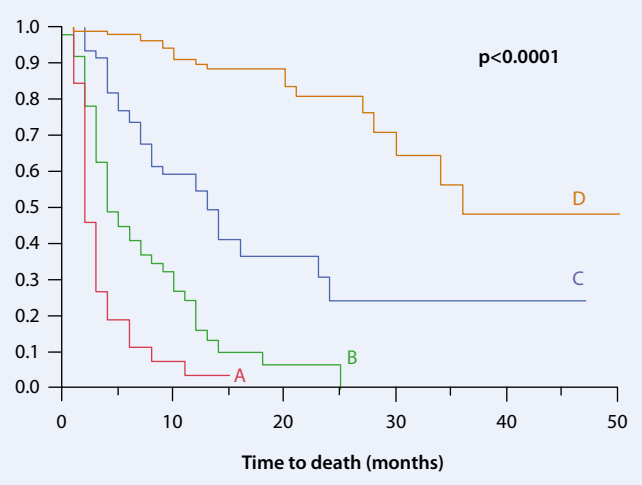

Fig. 2 ▲ Kaplan-Meier curves for survival of the four prognostic groups, A (30–35 points), B (36–40 points), C (41–45 points), and D (46–50 points), from the test group

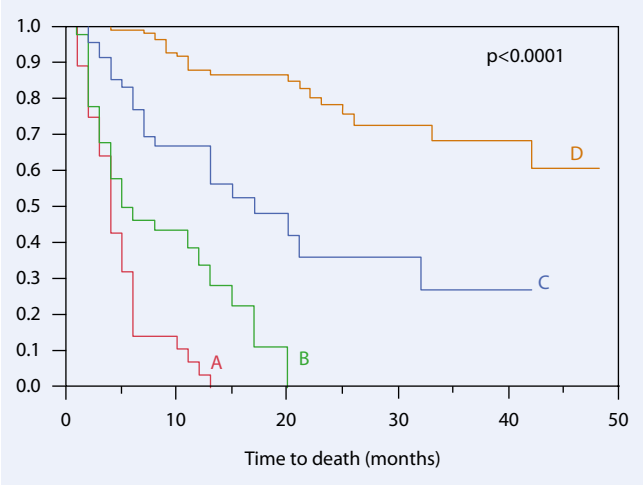

Fig. 3 ▲ Kaplan-Meier curves for survival of the four score groups, A (30–35 points), B (36–40 points), C (41–45 points), and D (46–50 points), from the validation group

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S. Douglas · S.E. Schild · D. Rades

Metastatisch bedingte Rückenmarkskompression bei Patienten mit unbekanntem Primärtumor

Abschätzung der Überlebensprognose mithilfe eines validierten Scores

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Metastatic spinal cord compression in patients with cancer of unknown primary

Estimating the survival prognosis with a validated score

Cancer of unknown primary (CUP) accounts for about 10% of the tumor types in patients developing metastatic spinal cord compression (MSCC) [1, 2, 5, 9, 10]. Personalization of cancer treatment has become more important in oncology in recent years. However, selection of the optimal treatment for the individual patient must take into account the patient's survival prognosis. In patients with a very poor survival prognosis, treatment approaches including spinal surgery or longer-course radiotherapy of several weeks should be avoided. These patients appear better treated with single-fraction radiotherapy or, in selected cases, even with best supportive care alone. In contrast, patients with a more favorable survival prognosis may benefit from decompressive surgery and longer-course radiotherapy programs, which may lead to better outcomes than single-fraction or short-course irradiation [4, 7, 8]. The survival prognosis of patients with MSCC may be predicted with the help of survival scores. When attempting to personalize the treatment for patients with MSCC, it would be desirable to have particular scores for the different primary tumors, because different tumors vary with respect to their biological behavior. In this study, we created and validate a survival score specifically for patients with MSCC from CUP.

Tab. 1 Patient characteristics of the test group and the validation group. The p-values were obtained from the chi-square test

	Test group no. of patients (%)	Validation group no. of patients (%)	p-value
Age			
≤65 years	43 (47)	46 (51)	
≥66 years	48 (53)	45 (49)	0.84
Gender			
Female	28 (31)	27 (30)	
Male	63 (69)	64 (70)	0.96
ECOG performance status			
1–2	27 (30)	25 (27)	
3–4	64 (70)	66 (73)	0.91
Number of involved vertebrae			
1–2	29 (32)	30 (33)	
≥3	62 (68)	61 (67)	0.96
Ambulatory status prior to radiotherapy			
Not ambulatory	47 (52)	44 (48)	
Ambulatory before radiotherapy	44 (48)	47 (52)	0.84
Other bone metastases			
No	35 (38)	32 (35)	
Yes	56 (62)	59 (65)	0.84
Visceral metastases			
No	46 (51)	43 (47)	
Yes	45 (49)	48 (53)	0.84
Time of developing motor deficits			
1–7 days	48 (53)	43 (47)	
>7 days	43 (47)	48 (53)	0.67
Radiation regimen			
Short-course radiotherapy	46 (51)	47 (52)	
Longer-course radiotherapy	45 (49)	44 (48)	0.95

Tab. 2 Test group: univariate analysis of survival

	Survival at 6 months (%)	Survival at 12 months (%)	p-value
Age			
≤65 years	35	8	
≥66 years	21	10	0.14
Gender			
Female	25	14	
Male	29	7	0.40
ECOG performance status			
1–2	56	23	
3–4	16	2	**<0.001**
Number of involved vertebrae			
1–2	34	8	
≥3	24	9	0.22
Ambulatory status prior to radiotherapy			
Not ambulatory	17	2	
Ambulatory	39	16	**0.002**
Other bone metastases			
No	40	12	
Yes	20	7	**0.023**
Visceral metastases			
No	50	16	
Yes	4	Not available	**<0.001**
Time of developing motor deficits			
1–7 days	10	0	
>7 days	47	22	**<0.001**
Radiation regimen			
Short-course radiotherapy	26	8	
Longer-course radiotherapy	29	9	0.52

Tab. 3 Test group: multivariate analysis of survival

	Risk ratio	95% confidence interval	p-value
ECOG performance status	2.61	1.48–4.82	**<0.001**
Ambulatory status prior to radiotherapy	1.63	1.02–2.64	**0.042**
Other bone metastases	1.38	0.85–2.27	0.19
Visceral metastases	2.77	1.70–4.59	**<0.001**
Time of developing motor deficits	1.40	1.09–1.82	**0.008**

Tab. 4 Test group: 6-month survival rates and corresponding scores

	Survival at 6 months (%)	Score (points)
ECOG performance status		
1–2	56	6
3–4	16	2
Ambulatory status before radiotherapy		
Not ambulatory	17	2
Ambulatory before radiotherapy	39	4
Visceral metastases		
No	50	5
Yes	4	0
Time of developing motor deficits		
1–7 days	10	1
>7 days	47	5

Patients and methods

The data of 182 unselected patients irradiated for MSCC from CUP were retrospectively analyzed. A requirement was that the patients had MSCC-related motor deficits of the legs. Patients who had prior surgery or radiotherapy to the currently involved parts of the spinal cord were excluded from the analyses. Adequate diagnostic imaging including spinal computed tomography (CT) or spinal magnetic resonance imaging (MRI) was requested as well as corticosteroid treatment during radiotherapy. The data were collected from the patients, their physicians, and patient files. Radiotherapy was performed with 6–10-MeV photon beams from a linear accelerator. The treatment volumes generally encompassed one normal vertebra above and below the involved vertebrae. Ninety-three patients had received short-course radiotherapy (1 fraction of 8 Gy or 5 fractions of 4 Gy in 1 week) and 89 patients longer-course radiotherapy (10 fractions of 3 Gy in 2 weeks, 14–15 fractions of 2.5 Gy in 3 weeks, or 20 fractions of 2 Gy in 4 weeks).

The 182 patients were alternately assigned to the test group (n=91) or the validation group (n=91). The characteristics of both groups are shown in **Tab. 1**. In the test group, eight pretreatment factors were investigated including age (≤65 vs. ≥66 years; median age: 64 years), gender, Eastern Cooperative Oncology Group performance status (ECOG-PS 1–2 vs. 3–4), number of involved vertebrae (1–2 vs. ≥3), preradiotherapy ambulatory status (not ambulatory vs. ambulatory), other bone metastases prior to radiotherapy (no vs. yes), visceral metastases prior to radiotherapy (no vs. yes), and time of developing motor deficits prior to radiotherapy (faster, 1–7 days vs. slower, >7 days). In addition to these pretreatment factors, the impact of the radiation regimen (short-course vs. longer-course radiotherapy) was investigated. The univariate analysis of survival was performed with the Kaplan–Meier method and the log-rank test [3]. The significant prognostic factors ($p<0.05$) were additionally evaluated in a multivariate analysis performed with the Cox proportion

hazards model. The prognostic factors that were significant in the multivariate analysis of the test group were included in the scoring system. The score for each significant 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 factor.

Results

In the univariate analysis of the test group, survival was associated with ECOG-PS (p<0.001), preradiotherapy ambulatory status (p=0.002), other bone metastases (p=0.023), visceral metastases (p<0.001), and the time of developing motor deficits (p<0.001). The results of this univariate analysis are summarized in **Tab. 2**. In the multivariate analysis of the test group, ECOG-PS (p<0.001), ambulatory status (p=0.042), visceral metastases (p<0.001), and the time of developing motor deficits (p=0.008) maintained significance and were included in the survival score (**Tab. 3**). The scores for each of the four significant prognostic factors obtained from the 6-months survival rate are shown in **Tab. 4**.

The addition of the four scores for each factor resulted in total scores of 5, 7, 9, 10, 11, 12, 13, 14, 15, 16, or 20 points (**Fig. 1**). According to the total scores, the patients of the test group were divided into three prognostic groups: <14 points (group A, *n*=56), 14–16 points (group B, *n*=22), and >16 points (group C, *n*=13). The 6-month survival rates were 5% for group A, 41% for group B, and 92% for group C (p<0.001). The 6-month survival rates of the three prognostic groups A (n=56), B (n=24), and C (n=11) of the validation group were 7%, 38%, and 91%, respectively (p<0.001).

Discussion

Survival scores help estimate the survival prognosis of each patient and contribute to the personalization of cancer care. This is particularly important for a palliative situation such as MSCC. For example, overtreatment should be avoided in patients with a very limited remaining lifespan. Personalization of the treatment

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S. Douglas · S.E. Schild · D. Rades

Metastatic spinal cord compression in patients with cancer of unknown primary. Estimating the survival prognosis with a validated score

Abstract

Background. This study aimed to create and validate a survival score for patients with metastatic spinal cord compression (MSCC) from cancer of unknown primary.

Patients and methods. The entire cohort (n=182) was divided into a test group (n=91) and a validation group (n=91). In the test group, eight pretreatment factors including age, gender, Eastern Cooperative Oncology Group performance status (ECOG-PS), number of involved vertebrae, ambulatory status, other bone metastases, visceral metastases, and time of developing motor deficits were retrospectively analyzed.

Results. The score included the prognostic factors that were significant for survival in the multivariate analysis (ECOG-PS, ambulatory status, visceral metastases, time of developing motor deficits). The score for each factor was determined by dividing the 6-month survival rate by 10. Prognostic scores represented the sum of the scores for the four factors and ranged from 5 to 20 points. The 6-month survival rates were 5% for <14 points, 41% for 14–16 points, and 92% for >16 points (p<0.001). In the validation group, the 6-month survival rates were 7%, 38%, and 91% (p<0.001).

Conclusion. This survival score can be considered valid and reproducible, since the survival rates of the validation group were comparable to those of the test group. This score can help when selecting the individual treatment and when counseling patients and relatives.

Keywords

Metastatic spinal cord compression · Cancer of unknown primary · Radiotherapy · Prognosis · Survival score

Metastatisch bedingte Rückenmarkskompression bei Patienten mit unbekanntem Primärtumor. Abschätzung der Überlebensprognose mithilfe eines validierten Scores

Zusammenfassung

Hintergrund. Ziel dieser Studie war es, einen Überlebensscore für Patienten mit metastatisch bedingter Rückenmarkskompression (MSCC) bei unbekanntem Primärtumor zu entwickeln und zu validieren.

Patienten und Methode. Das Gesamtkollektiv (*n*=182) wurde in eine Testgruppe (*n*=91) und eine Validierungsgruppe (*n*=91) aufgeteilt. In der Testgruppe wurden acht prätherapeutische Prognosefaktoren [Alter, Geschlecht, Allgemeinzustand („Eastern Cooperative Oncology Group performance status", ECOG-PS), Zahl befallener Wirbelkörper, Gehfähigkeit, andere Knochenmetastasen, Organmetastasen, Entwicklungszeit motorischer Defizite] retrospektiv untersucht.

Ergebnisse. Der Score beinhaltete die Faktoren, die in der Multivarianzanalyse signifikant für das Überleben waren (ECOG-PS, Gehfähigkeit, Organmetastasen, Entwicklungszeit motorischer Defizite). Der Score für jeden Faktor wurde ermittelt, indem die 6-Monats-Überlebensrate durch 10 geteilt wurde. Die Prognosescores entsprachen der Summe der Scores der 4 Faktoren und lagen zwischen 5 und 20 Punkten. Die 6-Monats-Überlebensraten betrugen 5% bei <14 Punkten, 41% bei 14–16 Punkten und 92% bei >16 Punkten (*p*<0,001). In der Validierungsgruppe betrugen die 6-Monats-Überlebensraten 7%, 38% bzw. 91% (*p*<0,001).

Schlussfolgerungen. Dieser Überlebensscore kann als valide und reproduzierbar betrachtet werden, da die Überlebensraten der Validierungsgruppe denen der Testgruppe vergleichbar waren. Der Score kann bei der Wahl des individuellen Behandlungsregimes und bei der Beratung von Patienten und Angehörigen hilfreich sein.

Schlüsselwörter

Metastatisch bedingte Rückenmarkskompression · Unbekannter Primärtumor · Strahlentherapie · Prognose · Überlebensscore

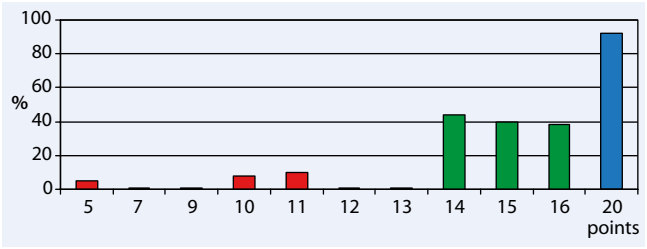

Fig. 1 ◀ Test group: the scores and the corresponding 6-month survival rates (in %)

approach can be better achieved if separate survival scores are available for specific tumor entities that may vary with respect to biological behavior and prognosis [5]. This study aimed to create a survival score particularly designed for patients with MSCC from CUP. ECOG-PS, preradiotherapy ambulatory status, visceral metastases, and the time of developing motor deficits were identified as independent prognostic factors for survival. ECOG-PS and ambulatory status were new prognostic factors and were not identified in our previous analysis of patients with MSCC from CUP [6].

When compared with MSCC from other solid tumors such as breast cancer and prostate cancer, patients with MSCC from CUP have an unfavorable prognosis [5]. In the present study, this finding is supported by the fact that in the entire cohort, 112 of 182 patients (62%) belonged to group A, the worst prognostic group. In group A, only 5% of patients in the test group and 7% in the validation group survived 6 months or longer. These patients may be considered for single-fraction radiotherapy or, in selected cases, for best supportive care alone. The 6-month survival rates of group B patients were 41% and 38%, respectively. These patients may receive short-course radiotherapy such as 5 fractions of 4 Gy in 1 week, because 5 fractions of 4 Gy is as effective as longer programs (10 fractions of 3 Gy in 2 weeks or 20 fractions of 2 Gy in 4 weeks) with respect to improvement of motor function [7]. By contrast, longer-course radiotherapy results in better local control of MSCC, which becomes more of an issue in patients with a more favorable survival prognosis (group C). In selected patients of the prognostic groups B and C, spinal surgery may be considered prior to radiotherapy. A randomized trial of 101 patients had suggested that in MSCC patients with a good performance status and involvement of only one spinal segment, additional decompressive surgery could improve both ambulatory function and survival when compared to radiotherapy alone [4].

Because the 6-month survival rates in the validation group were comparable to the corresponding survival rates in the test group, this new score appears valid and reproducible. However, the retrospective nature of the data included in this score must be taken into account when interpreting the results. Retrospective data always bear the risk of a hidden selection bias. However, since a prospective study on MSCC from CUP cannot be expected in the near future, this score can be considered the most appropriate instrument currently available to predict the survival of such patients.

Conclusion

In summary, this survival score including four independent prognostic factors and three prognostic groups score can be considered valid and reproducible, since the survival rates of the validation group were comparable to those of the test group. This survival score can contribute to the selection of the most appropriate treatment for the individual patient. Furthermore, it can help the physician when counseling the patients and their relatives.

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Conflict of interest. On behalf of all authors, the corresponding author states the following: D.R. has received speaker's honoraria from Amgen, Merck Serono, Novartis Oncology, and Astra Zeneca.

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BMC Cancer

RESEARCH ARTICLE Open Access

A new score predicting the survival of patients with spinal cord compression from myeloma

Sarah Douglas[1], Steven E Schild[2] and Dirk Rades[1*]

Abstract

Background: This study was performed to create and validate a scoring system for the survival of patients with malignant spinal cord compression (SCC) from myeloma.

Methods: Of the entire cohort (N = 216), 108 patients were assigned to a test group and 108 patients to a validation group. In the test group, nine pre-treatment factors including age, gender, Eastern Cooperative Oncology Group performance status (ECOG-PS), number of involved vertebrae, ambulatory status prior to radiotherapy, other bone lesions, extraosseous lesions, interval from first diagnosis of myeloma to radiotherapy of SCC, and the time developing motor deficits were retrospectively analyzed.

Results: On univariate analysis, improved survival was associated with ECOG-PS 1–2 ($p = 0.006$), being ambulatory ($p = 0.005$), and absence of other bone lesions ($p = 0.019$). On multivariate analysis, ECOG-PS ($p = 0.036$) and ambulatory status ($p = 0.037$) were significant; other bone lesions showed a strong trend ($p = 0.06$). These factors were included in the score. The score for each factor was determined by dividing the 12-month survival rate (in%) by 10. The total risk score was the sum of the three factor scores and ranged from 19 to 24 points. Three prognostic groups were designed with the following 12-month survival rates: 49% for 19–20 points, 74% for 21–23 points, and 93% for 24 points ($p = 0.002$). In the validation group, the 12-month survival rates were 51%, 80%, and 90%, respectively ($p < 0.001$).

Conclusions: This score appears reproducible, because the 12-month survival rates of both the test and the validation group were very similar. This new survival score can help personalize the treatment of patients with SCC from myeloma and can be of benefit when counseling patients.

Keywords: Myeloma, Metastatic spinal cord compression, Radiotherapy, Survival prognosis, Scoring system

Background

Myeloma is one of the most common malignant diseases leading to malignant spinal cord compression (SCC) [1,2]. In contrast to patients with SCC from a solid tumor, myeloma patients with SCC are usually not candidates for spinal surgery, because myeloma is an extraordinarily radiosensitive lesion [2]. Thus, patients with SCC from myeloma were exluded from the randomized trial of Patchell et al. that compared radiotherapy alone to radiotherapy plus upfront decompressive surgery in patients with SCC [3]. Therefore, radiotherapy alone is generally considered the standard treatment for SCC from myeloma [2]. Personalizing cancer care is one of the most important trends in oncology. In order to administer the best treatment regimen to the individual patient, it is mandatory to consider the patient's survival prognosis. Long term local control of SCC is dose dependent. As such, patients with a more favorable prognosis can benefit from longer-course radiotherapy (mostly 30 Gy in 10 fractions over 2 weeks) in terms of better local control, whereas patients with an unfavorable prognosis may only need to receive short-course radiotherapy with an overall treatment time of one week or less [4]. On the other hand, patients with an extraordinarily good survival prognosis appear to benefit from an escalation of the radiation dose beyond 30 Gy in 10 fractions [5]. These patients live long enough that local failure can be an issue. Therefore, it is important to be able to estimate the patient's survival prognosis. This

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could be achieved with the use of survival scores. Because different primary tumors have different biological behavior, it is important to have a specific survival score for each tumor entity associated with SCC [1,2]. Patients with SCC from myeloma must be considered unique, as they have the best survival prognosis of all patients developing SCC from a malignant disease [6]. In the study presented here, we create and validate a survival score for this group of patients.

Results

In the test group, survival was associated with the Eastern Cooperative Oncology Group performance status (ECOG-PS) (p = 0.006), ambulatory status prior to radiotherapy (p = 0.005), and other bone lesions (p = 0.019) on univariate analysis (Table 1). In the corresponding multivariate analysis, ECOG-PS (p = 0.036) and ambulatory status prior to radiotherapy (p = 0.037) maintained significance (Table 2). The presence of other bone lesions showed a strong trend (p = 0.06). All three prognostic factors were included in the scoring system. The scores for each of these factors obtained from the 12-month survival rate are shown in Table 3.

The addition of the three scores for each factor resulted in total scores from 19 to 24 points (Figure 1). According to the total scores, the patients of the test group were divided into three prognostic groups, 19–20 points (group A, n = 26), 21–23 points (group B, n = 49),

Table 1 Test group: Univariate analysis of pre-treatment factors and the radiation regimen for survival

	Survival at 6 months (%)	Survival at 12 months (%)	Median survival time (months)	p-value
Age				
≤ 63 years	82	76	45	
≥ 64 years	88	73	57	0.92
Gender				
i Female	76	61	37	
Male	90	83	45	0.29
ECOG Performance status				
1-2	91	81	57	
3-4	73	60	14	**0.006**
Number of involved vertebrae				
1-2	83	73	70	
≥ 3	87	77	37	0.95
Ambulatory status prior to radiotherapy				
Not Ambulatory	70	56	14	
Ambulatory before RT	90	81	57	**0.005**
Other bone lesions				
No	98	84	not reached	
Yes	76	69	32	**0.019**
Extraosseous lesions				
No	86	75	45	
Yes	67	not available	not available	0.35
Interval from cancer diagnosis to radiotherapy of MSCC				
≤ 15 months	90	77	45	
> 15 months	80	73	32	0.19
Time developing motor deficits				
1-14 days	80	66	19	
> 14 days	89	81	57	0.27
Radiation regimen				
Short-course radiotherapy	81	72	45	
Longer-course radiotherapy	87	76	57	0.97

Table 2 Test group: Multivariate analysis of pre-treatment factors and the radiation regimen for survival

	Risk ratio	95%-confidence interval	p-value
ECOG Performance status	2.09	1.05 – 4.12	**0.036**
Ambulatory status prior to radiotherapy	2.14	1.05 – 4.24	**0.037**
Other bone lesions	1.97	0.96 – 4.37	0.06

and 24 points (group C, n = 33) (Figure 1). The 12-month survival rates were 49% for group A, 74% for group B, and 93% for group C (p = 0.002, Figure 2). The 12-month survival rates of the three prognostic groups A, B and C in the validation group were 51%, 80%, and 90%, respectively (p < 0.001, Figure 2). Thus, the corresponding survival rates of the test group and the validation group were very similar.

Discussion

Personalization of cancer treatment has been increasingly emphasized in the literature. This is especially obvious when one reviews the new targeted agents that affect specific biochemical reactions and often have activity specific to certain mutations of a biologically active target molecule. Such an individualized approach should take into account the patient's survival time, particularly in a palliative situation such as malignant SCC. Therefore, survival scores that help the physician to tailor the treatment to the individual patients are important. Since the various tumors behave differently, it would be helpful to have a particular survival score for each tumor entity, at least for the most common diseases associated with SCC such as breast cancer, prostate cancer, non-small cell lung cancer, and myeloma [1,2]. In the present study, a survival score was designed particularly for patients with SCC from myeloma. The score included three prognostic factors, ECOG-PS, ambulatory status prior to radiotherapy, and other bone lesions. These factors found to be significantly associated with survival were also reported in our previous report on prognostic factors for SCC from myeloma [7]. In contrast to the test group of the present study, our previous report determined that extraosseous lesions were also significantly associated with survival. However, we decided to include only those prognostic factors found to be independent in the multivariate analysis of the test group in the present scoring system, because we felt that this would make the score more robust. This approach was supported by the fact that the 12-month survival rates of the validation group were similar to those of the test group.

Patients with SCC from myeloma have a better survival prognosis than patients with SCC from a solid tumor [1,2]. This is reflected by the fact that the worst prognostic group, group A, was the smallest group in this study. Patients of group C had a very good prognosis with 12-month survival rates of 93% in the test group and 90% in the validation group. According to a retrospective study, these patients appear to benefit from an escalation of the radiation dose beyond the world wide commonest regimen 30 Gy in 10 fractions in terms of better treatment outcomes [5]. This may also apply to patients of group B, whose 12-months survival rates were 74% and 80%, respectively. In contrast, group A patients who had the worst prognosis of the three groups, may be candidates for 30 Gy in 10 fractions or even a short-course regimen such as 20 Gy in 5 fractions. These suggestions should be interpreted with caution, because the data included in this survival score were retrospective in nature. Retrospective data always bear the risk of including hidden selection biases. However, it would be difficult and take many years to perform a prospective trial with an adequate number of patients with SCC from myeloma. The authors know of no plans to perform just such a prospective trial.

Table 3 Test group: 12-month survival rates and corresponding scores

	Survival at 12 months (%)	Score (points)
ECOG Performance status		
1–2	81	8
3-4	60	6
Ambulatory status prior to radiotherapy		
Not Ambulatory	56	6
Ambulatory	81	8
Other bone lesions		
No	84	8
Yes	69	7

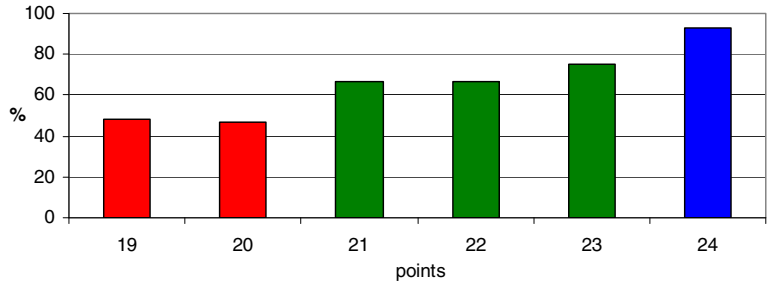

Figure 1 Test group: The total scores in relation to the 12-month survival rate (in%).

Conclusions

This new survival score for patients with SCC from myeloma included three prognostic factors, ECOG-PS, ambulatory status prior to radiotherapy, and other bone lesions. Three prognostic groups were identified based on risk scores ranging from 19 to 24 points. The 12-month survival rates of each of the three prognostic groups in the validation group were similar to those of the test group. Therefore, this score can be considered reproducible. This information can contribute to personalization of the treatment for SCC from myeloma. Furthermore, the score can be helpful when counseling patients and relatives regarding prognosis and therapy.

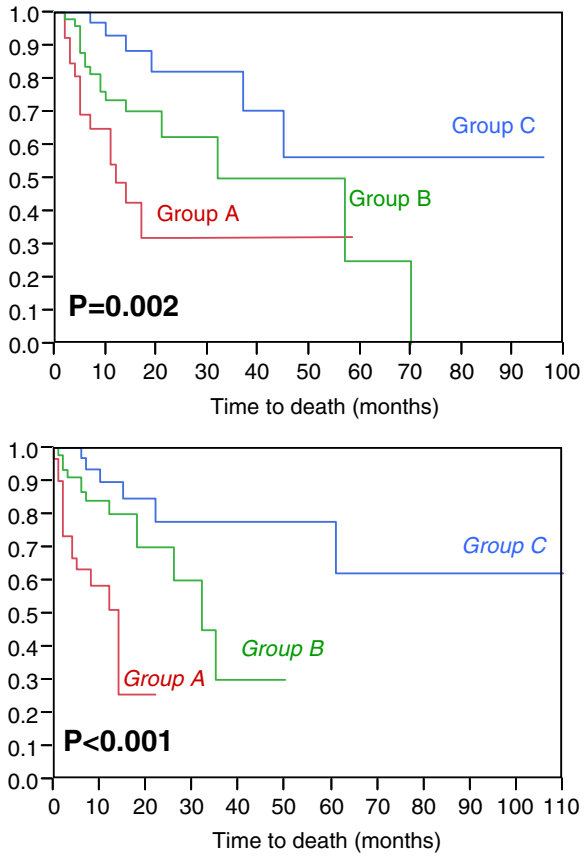

Figure 2 Kaplan-Meier curves for survival of the three score groups A (19–20 points), B (21–23 points), and C (24 points) from the test group (top) and from the validation group (bottom).

Methods

In this study, the data of 216 unselected patients being irradiated for SCC from myeloma between 1992 and 2011 were retrospectively analyzed. Because this study did not report on a clinical trial, and because the data were retrospective in nature and analyzed anonymously, approval by an ethic committee and informed consent from the patienst were not necessary. Patients included in this study received radiotherapy alone for SCC-related motor deficits of the lower extremities, did not have prior surgery or radiotherapy to the currently involved parts of the spinal cord, did have adequate diagnostic imaging with spinal CT or MRI was requested, and had received corticosteroid treatment during radiotherapy. Since the vast majority of the patients were already known as myeloma patients, a biopsy of the spinal lesions was not performed in most patients included in this study. The data were collected from the patients themselves, from their treating physicians, and from their files. Radiotherapy was performed with 6–10 MeV photon beams from a linear accelerator. The treatment volumes generally encompassed one normal vertebra above and below the involved parts of the spinal cord.

The 216 patients were alternately assigned to the test group (N = 108, uneven numbers) or the validation group (N = 108, even numbers). Patient characteristics of these groups are given in Table 4. In the test group, nine pre-treatment factors were investigated including age (≤63 vs. ≥64 years; median age: 63 years), gender, ECOG-PS (1–2 vs. 3–4), number of involved vertebrae (1–2 vs. ≥3), pre-radiotherapy ambulatory status (not ambulatory vs. ambulatory), other bone lesions prior to radiotherapy (no vs. yes), extraosseous lesions prior to radiotherapy (no vs. yes), interval between first diagnosis of myeloma and radiotherapy of SCC (≤15 vs. >15 months), and time of developing motor deficits prior to radiotherapy (1–7 vs. >7 days). In the entire

Table 4 Patient characteristics of the test group and the validation group. The p-values were obtained from the Chi-square test

	Test group	Validation group	p-value
	n patients (%)	n patients (%)	
Age			
≤ 63 years	57 (53)	54 (50)	
≥ 64 years	51 (47)	54 (50)	0.84
Gender			
Female	38 (35)	42 (39)	
Male	70 (65)	66 (71)	0.81
ECOG Performance status			
1-2	75 (69)	70 (65)	
3-4	33 (31)	38 (35)	0.73
Number of involved vertebrae			
1-2	48 (44)	50 (46)	
≥ 3	60 (56)	58 (54)	0.91
Ambulatory status prior to radiotherapy			
Not Ambulatory	27 (25)	32 (30)	
Ambulatory before RT	81 (75)	76 (70)	0.75
Other bone lesions			
No	45 (42)	43 (40)	
Yes	63 (58)	65 (60)	0.92
Extraosseous lesions			
No	105 (97)	102 (94)	
Yes	3 (3)	6 (6)	0.89
Interval from cancer diagnosis to radiotherapy of MSCC			
≤ 15 months	58 (54)	59 (55)	
> 15 months	50 (46)	49 (45)	0.95
Time developing motor deficits			
1-14 days	46 (43)	50 (46)	
> 14 days	62 (57)	58 (54)	0.78
Radiation regimen			
Short-course radiotherapy	37 (34)	38 (35)	
Longer-course radiotherapy	71 (66)	70 (65)	0.96

cohort, the 12-month survival rate was 83% in patients who could walk without aid prior to radiotherapy and 80% in those patients who could walk with aid ($p = 0.92$). Because the 12-month survival rates were very similar, these two groups were combined to the group "ambulatory".

In addition to the pre-treatment factors, the potential impact of the radiation regimen (short-course radiotherapy with 1x8 Gy or 5x4 Gy over 1 week vs. longer-course radiotherapy with 10x3 Gy over 2 weeks, 14-15x2.5 Gy over 3 weeks, or 20x2 Gy over 4 weeks) has been investigated. Since other prognostic factors of multiple myeloma such as beta-2 myoglobulin and serum creatinine were not available in most patients being treated for SCC, an oncologic emergency situation, these factors were not included in the present study.

The univariate analysis was performed with the Kaplan-Meier-method and the log-rank test [8]. The significant prognostic factors ($p < 0.05$) were included in a multivariate analysis performed with the Cox proportion hazards model. The prognostic factors that were significant in the multivariate analysis of the test group ($p < 0.05$) or showed a strong trend ($p \leq 0.06$) were included in the survival score. The score for each significant prognostic factor was determined by dividing the 12-month survival rate (in%) by 10 according to our previous survival score

that included many different primary tumor types [9]. The total score represented the sum of the scores for each factor.

Abbreviations

ECOG-PS, Eastern Cooperative Oncology Group performance score; Gy, Gray; MeV, Mega electron volts; SCC, Spinal cord compression.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

SD, SES and DR participated in the design of the study. SES performed the statistical analyses. SD and DR provided study material. All authors were involved in manuscript writing. They read and approved the final manuscript.

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RESEARCH ARTICLE Open Access

A validated survival score for patients with metastatic spinal cord compression from non-small cell lung cancer

Dirk Rades[1,4*], Sarah Douglas[1], Theo Veninga[2] and Steven E Schild[3]

Abstract

Background: This multicenter study aimed to create and validate a scoring system for survival of patients with metastatic spinal cord compression (MSCC) from non-small cell lung cancer (NSCLC).

Methods: The entire cohort of 356 patients was divided in a test group (N = 178) and a validation group (N = 178). In the test group, nine pre-treatment factors including age, gender, Eastern Cooperative Oncology Group performance status (ECOG-PS), number of involved vertebrae, pre-radiotherapy ambulatory status, other bone metastases, visceral metastases, interval from cancer diagnosis to radiotherapy of MSCC, and the time developing motor were retrospectively analyzed.

Results: On multivariate analysis, survival was significantly associated with ECOG-PS, pre-radiotherapy ambulatory status, visceral metastases, and the time developing motor deficits. These 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 risk score represented the sum of the scores for each factor. According to the risk scores, which ranged from 6 to 19 points, three prognostic groups were designed. The 6-month survival rates were 6% for 6–10 points, 29% for 11–15 points, and 78% for 16–19 points ($p < 0.001$). In the validation group, the 6-month survival rates were 4%, 24%, and 76%, respectively ($p < 0.001$).

Conclusions: Since the survival rates of the validation group were similar to those of the test group, this score can be considered reproducible. The scoring system can help when selecting the individual treatment for patients with MSCC from NSCLC. A prospective confirmatory study is warranted.

Keywords: Non-small cell lung cancer, Metastatic spinal cord compression, Radiotherapy, Survival prognosis, Scoring system

Background

Non-small lung cancer (NSCLC) accounts for about 15% of all primary tumor types leading to metastatic spinal cord compression (MSCC) [1]. Treatment options for this oncologic emergency include different types and programs of radiotherapy alone or, for selected patients, upfront decompressive surgery followed by radiotherapy [2]. Selection of the optimal treatment approach for the individual patient should take into account the patient's estimated survival time. Patients with a very poor survival prognosis are generally not candidates for a burdensome treatment including decompressive surgery or longer-course radiotherapy of two to four weeks. They appear better treated with single-fraction radiotherapy which means less discomfort for these debilitated patients. In contrast, patients with a more favorable survival prognosis may benefit from decompressive surgery or from longer-course radiotherapy programs, which lead to better local control of MSCC than single-fraction or short-course irradiation [3,4].

For optimal personalization of the treatment for each patient with MSCC, it is critical to regard patients with MSCC from a particular primary tumor type as a separate group of patients, because primary tumors vary with

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respect to their biological behavior. Therefore, the present study aimed to create and validate a survival score particularly for patients with MSCC from NSCLC, one of the most common primary tumor types in patients presenting with this oncologic complication.

Results

The median survival time in the entire cohort was 4 months. The patients whose data were included in this study had been treated between 1992 and 2010. The 6-months survival rates were 25% for patients treated until 2005 (n = 262) and 34% for patients treated after 2005 (n = 94) (p = 0.39).

In the univariate analysis of the test group, survival was associated with the Eastern Cooperative Oncology Group performance status (ECOG-PS), number of involved vertebrae, pre-radiotherapy ambulatory status, other bone metastases, visceral metastases, and the time developing motor deficits. The results of this univariate analysis are given in Table 1. In the multivariate analysis of the test group, ECOG-PS, pre-radiotherapy ambulatory status, visceral metastases, and the time developing motor deficits maintained significance and were included in our scoring system. The results of the multivariate analysis are shown in Table 2. The scores for each of the four significant prognostic factors obtained from the 6-months survival rate are given in Table 3. The addition of the four scores for each factor resulted in total scores of 6, 9, 10, 12, 13, 15, 16, or 19 points (Figure 1). According to the total scores, the patients of the test group were divided into three risk groups: 6–10 points (group A, n = 79), 11–15 points (group B, n = 63), and 16–19 points (group C, n = 36). The 6-month survival rates were 6% for group A, 29% for group B, and 78% for group C ($p < 0.001$, Figure 2). The 6-months survival rates of the three risk groups of the validation group were 4%, 24%, and 76%, respectively ($p < 0.001$, Figure 3).

Discussion

Personalization of cancer treatment, which has become more important in oncology during recent years, must take into account the patient's life expectancy. This accounts in particular for a palliative situation such as MSCC. Survival scores help estimate the survival prognosis of each patient. Several scores created to estimate the survival of patients with bone metastases already exist. A few prognostic scores have been developed in particular for patients with bone metastases in the vertebral column.

The majority of these scores were designed by to help surgeons decide whether spinal surgery may be indicated or not. In 1990, Tokuhashi et al. presented a score based on the data of 64 patients with a metastatic spine tumor who underwent spinal surgery [5]. Their score has been revised 15 years later in a series of 246 patients [6]. Bauer et al. reported a scoring system including scoring for pathological fracture based on the data of 88 patients with spinal metastasis plus 153 patients with bone metastasis of the extremities in 1995 [7]. Leithner et al., who compared different scoring systems in their series of 69 patients in 2008, suggested a modified Bauer score without scoring for pathological fracture [8]. The Tomita score presented in 2001 included the data of 67 patients [9]. Except the revised Tokuhashi score [6], these scoring systems may have a limited validity due to the relatively small number of patients included. Furthermore, these scores were designed for patients with spinal metastasis in general, and not particularly for patients with motor deficits due to MSCC.

In 2005, Van der Linden et al. presented a score in a larger series of patients (n = 342) with painful spinal metastases who had received radiotherapy alone and no surgery [10]. In that study, patients with neurologic impairment were not included. All these previous scoring systems included patients with spinal metastasis from many different primary tumors. However, because various primary tumor types behave differently, it is important to have separate scores for the different tumor entities, in particular for the most common ones such as breast cancer, prostate cancer, and NSCLC [1].

In the present study, four independent prognostic factors were found to be significantly associated with survival in patients with MSCC from NSCLC in a comparably large series of patients. These significant factors included the ECOG-PS, pre-radiotherapy ambulatory status, visceral metastases, and the time developing motor deficits. In our previous report on prognostic factors for different outcomes in the entire cohort of 356 patients, gender, other bone metastases, and the interval from the first diagnosis of NSCLC to radiotherapy of MSCC were also significantly associated with survival [11]. However, we included only those prognostic factors found to be independent in the multivariate analysis of the test group in the present score, because we felt that this would make the score more robust.

When compared to MSCC from other solid tumors, patients with MSCC from NSCLC have a less favorable estimated survival [1]. This is reflected by the fact that the worst prognostic group, group A, was the largest group in the present study. Based on the 6-months survival times related to the four independent prognostic factors, three prognostic groups were formed. Group A patients had the worst prognosis, only 6% of patients in the test group and 4% in the validation group survived at least 6 months following irradiation. These patients may be considered candidates for single-fraction radiotherapy or even best supportive care alone. Group B

Table 1 Test group: Univariate analysis of pre-treatment factors and the radiation regimen for survival

	Survival at 6 months (%)	Survival at 12 months (%)	Median survival time (months)	p-value
Age				
≤ 64 years	28	15	3	
≥ 65 years	30	15	4	0.50
Gender				
Female	32	29	4	
Male	27	10	4	0.13
ECOG Performance status				
1-2	51	26	6	
3-4	15	7	3	**<0.001**
Number of involved vertebrae				
1-2	44	28	4	
≥ 3	19	4	3	**<0.001**
Ambulatory status prior to RT				
Not Ambulatory	12	7	2	
Ambulatory before RT	44	21	5	**<0.001**
Other bone metastases				
No	45	30	4	
Yes	19	4	3	**<0.001**
Visceral metastases				
No	56	38	9	
Yes	15	3	3	**<0.001**
Interval from cancer diagnosis to radiotherapy of MSCC				
≤ 15 months	26	13	3	
> 15 months	40	23	5	0.16
Time developing motor deficits				
1-7 days	12	4	2	
> 7 days	40	22	5	**<0.001**
Radiation regimen				
Short-course radiotherapy	24	10	3	
Longer-course radiotherapy	32	18	4	0.12

patients had 6-months survival rates of 29% and 24%, respectively and may be treated with short-course multifraction radiotherapy such as 20 Gy in 5 fractions over one week. Short-course radiotherapy is as effective as longer programs with respect to post-radiotherapy motor function [12]. In contrast, local control of MSCC is better with longer-course than with short-course radiotherapy [3,4]. However, local control of MSCC

Table 2 Test group: Multivariate analysis of pre-treatment factors and the radiation regimen for survival

	Risk ratio	95%-confidence interval	p-value
ECOG Performance status	1.98	1.36 – 2.91	**<0.001**
Number of involved vertebrae	1.17	0.89 – 1.56	0.27
Ambulatory status before radiotherapy	1.65	1.05 – 2.63	**0.029**
Other bone metastases	1.16	0.63 – 2.10	0.63
Visceral metastases	2.44	1.66 – 3.68	**<0.001**
Time developing motor deficits	1.33	1.12 – 1.57	**0.001**

Table 3 Test group: 6-month survival rates and corresponding scores

	Survival at 6 months (%)	Score (points)
ECOG Performance status		
1-2	51	5
3-4	15	2
Ambulatory status before radiotherapy		
Not Ambulatory	12	1
Ambulatory before RT	44	4
Visceral metastases		
No	56	6
Yes	15	2
Time developing motor deficits		
1-7 days	12	1
> 7 days	40	4

appears of minor importance in group B patients, because most of these patients will not live long enough to experience a local recurrence of MSCC. In contrast, group C patients who achieved 6-months survival rates of 78% and 76%, respectively, are at a higher risk of developing a local recurrence of MSCC and, therefore, are likely to benefit from longer-course radiotherapy such as 10x3 Gy in 2 weeks or 20x2 Gy in 4 weeks. In group B and group C patients, upfront decompressive surgery in addition to radiotherapy may be reasonable for selected patients with a good performance status and involvement of only one spinal segment. This accounts in particular for patients who are unlikely to be able to walk after radiotherapy alone. In a randomized trial of 101 patients, decompressive surgery followed by radiotherapy led to better pre-radiotherapy ambulatory function and survival than radiotherapy alone in such patients [2].

The present score focused on a single tumor entity. In contrast, previous prognostic indices for patients with vertebral metastases or other palliative situations included many different tumor types [5-10,13-17]. Therefore, the present scoring system takes more into account the patient's individual situation. In order to validate our score, the risk groups A, B and C of the test group were compared to the corresponding groups A, B and C of the validation group. The 6-months survival rates of the three groups in the validation group proved to be similar to the corresponding 6-months survival rates in the test group. Thus, this new score for MSCC from NSCLC appears valid and reproducible. However, the score is based on retrospective data. Furthermore, data on systemic treatment following treatment was not available in most patients. These two aspects may have led to a hidden selection bias. Therefore, the results of the present study need to be confirmed in a prospective series of patients.

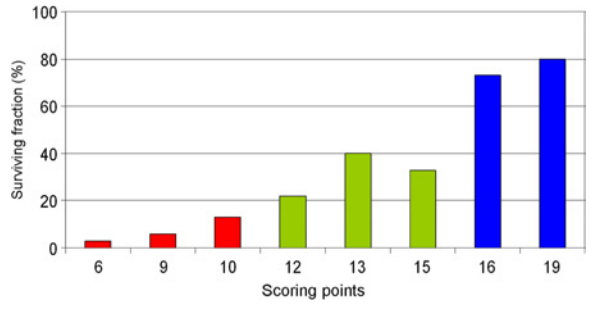

Figure 1 Test group: The total scores in relation to the 6-months survival rate (in %).

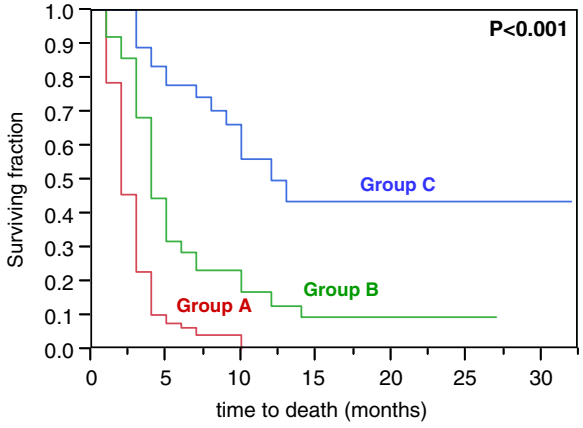

Figure 2 Kaplan-Meier curves for survival of the three score groups A (6–10 points), B (11–15 points), and C (16–19 points) from the test group.

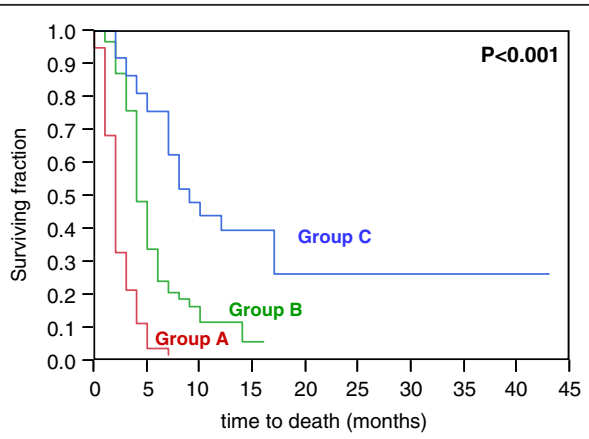

Figure 3 Kaplan-Meier curves for survival of the three score groups A (6–10 points), B (11–15 points), and C (16–19 points) from the validation group.

Conclusions

The present survival score for patients with MSCC from NSCLC was based on four independent prognostic factors and included three prognostic groups. Patients of group A have the worst prognosis and may be candidates for single-fraction radiotherapy or even best supportive care alone. Patients of group B may be treated with short-course multi-fraction radiotherapy, and patients of group C, who have the most favorable prognosis, appear best treated with longer-course radiotherapy. For selected patients of groups B and C, upfront decompressive surgery in addition to radiotherapy may be considered. The decision for or against decompressive surgery requires an additional scoring system taking into accout the functional outcome following radiotherapy alone. Regarding the score presented here, a prospective confirmatory study is warranted.

Methods

Three-hundred-and-fifty-six unselected patients with treated with MSCC from NSCLC were retrospectively analyzed in this multicenter study. The patients had received radiotherapy alone for MSCC-related motor deficits of the legs. Patients who had prior surgery or radiotherapy to the currently involved parts of the spinal cord were not included. The majority of the patients

Table 4 Patient characteristics of the test group and the validation group. The p-values were obtained from the Chi-square test

	Test group	Validation group	p-value
	n patients (%)	n patients (%)	
Age			
≤ 64 years	97 (54)	94 (53)	
≥ 65 years	81 (46)	84 (47)	0.89
Gender			
Female	47 (26)	45 (25)	
Male	131 (74)	133 (75)	0.92
ECOG Performance status			
1-2	67 (38)	66 (37)	
3-4	111 (62)	112 (63)	0.96
Number of involved vertebrae			
1-2	71 (40)	77 (43)	
≥ 3	107 (60)	101 (57)	0.73
Ambulatory status prior to RT			
Not Ambulatory	84 (47)	78 (44)	
Ambulatory before RT	94 (53)	100 (56)	0.73
Other bone metastases			
No	67 (38)	76 (43)	
Yes	111 (62)	102 (57)	0.58
Visceral metastases			
No	61 (34)	56 (31)	
Yes	117 (66)	122 (69)	0.81
Interval from cancer diagnosis to radiotherapy of MSCC			
≤ 15 months	148 (83)	150 (84)	
> 15 months	30 (17)	28 (16)	0.92
Time developing motor deficits			
1-7 days	74 (42)	73 (41)	
> 7 days	104 (58)	105 (59)	0.95
Radiation regimen			
Short-course radiotherapy	71 (40)	72 (40)	
Longer-course radiotherapy	107 (60)	106 (60)	0.97

(n = 262) were treated unitl 2005, i.e. before the randomized study of Patchell et al. comparing radiotherapy alone to decompressice surgery followed by radiotherapy was published [2]. Of the 94 patients treated between 2006 and 2010, only 16 patients (4% of the entire cohort) would have met the inclusion criteria of the Patchell study. Thus, the risk of a selection bias due to excluding patients receiving surgery appears relatively low.

Adequate diagnostic imaging including spinal CT or spinal MRI was requested, as well as corticosteroid treatment during radiotherapy. Patients were presented to a surgeon prior to radiotherapy to discuss the option of upfront decompressive surgery when indicated. The data were collected from the patients, their treating physicians, and the patient files. Because this study did not report on a clinical trial, and because the data were retrospective in nature and analyzed anonymously, approval by an ethic committee was not necessary. Radiotherapy was performed with 6–10 MeV photon beams from a linear accelerator. The treatment volumes generally encompassed one normal vertebra above and below the involved vertebrae. One-hundred-and-forty-three patients had received short-course radiotherapy (1x8 Gy or 5x4 Gy in 1 week), and 213 patients were treated with longer-course radiotherapy (10x3 Gy in 2 weeks, 14-15x2.5 Gy in 3 weeks, or 20x2 Gy in 4 weeks).

The 356 patients were alternately assigned to the test group (N = 178) or the validation group (N = 178). The characteristics of both patient groups are given in Table 4. In the test group, nine pre-treatment factors were investigated including age (≤64 vs. ≥65 years; median age: 64 years), gender, ECOG-PS (1–2 vs. 3–4), number of involved vertebrae (1–2 vs. ≥3), pre-radiotherapy ambulatory status (not ambulatory vs. ambulatory), other bone metastases prior to radiotherapy (no vs. yes), visceral metastases prior to radiotherapy (no vs. yes), interval between first diagnosis of NSCLC and radiotherapy of MSCC (≤15 vs. >15 months, in accordance with previous studies), and time of developing motor deficits prior to radiotherapy (1–7 vs. >7 days, in accordance with previous studies). Because 69 patients of the 194 patients (36%) who were ambulatory prior to radiotherapy in the entire cohort had a poor ECOG-PS of 3–4, both performance status and pre-radiotherapy ambulatory status were investigated. In addition to these pre-treatment factors, the potential impact of the radiation regimen (short-course vs. longer-course radiotherapy) has been investigated. The univariate analysis of survival was performed with the Kaplan-Meier-method and the log-rank test [18]. The significant prognostic factors ($p < 0.05$) were additionally evaluated in a multivariate analysis performed with the Cox proportion hazards model. The prognostic factors that were significant in the multivariate analysis of the test group were included in the scoring system. The score for each significant 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 factor.

Abbreviations

ECOG: Eastern Cooperative Oncology Group; ECOG-PS: Eastern Cooperative Oncology Group performance score; Gy: Gray; MeV: Mega electron volts; MSCC: Metastatic spinal cord compression; RT: Radiotherapy.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

DR and SES participated in the design of the study. SES performed the statistical analyses. SD, TV, and DR provided study materials. All authors were involved in manuscript writing; they read and approved the final manuscript.

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A survival score for patients with metastatic spinal cord compression from prostate cancer

Prostate cancer patients account for 20% of all patients developing metastatic spinal cord compression (MSCC) [5]. Most patients with MSCC receive radiotherapy (RT) alone [1, 2, 9, 10]. The appropriate treatment regimen for the individual should take into account the patient's survival prognosis. Patients with a very poor estimated survival may be candidates for best supportive care or for short-course radiotherapy with up to five fractions given in 1 week, whereas patients with a favorable survival prognosis appear better treated with longer-course RT programs resulting in higher local control rates of MSCC. Therefore, it would be of great value for selecting the best treatment for each patient if one were able to estimate the patient's survival time. Four years ago, a score predicting survival in patients with MSCC was presented and included more than 30 different primary tumor types [6]. Because each primary tumor leading to MSCC shows different biological behavior and is associated with a different prognosis, it appears reasonable to develop separate survival scores for the different primary tumors. Prostate cancer is of particular importance, because it is one of the three most common primary tumors leading to MSCC. The present study aimed to create and to validate a survival score particularly designed for MSCC from prostate cancer. Such a score would allow physicians to better tailor the treatment to the individual patient.

Patients and methods

A total of 436 unselected patients treated with RT alone for MSCC from prostate cancer between 1992 and 2010 were retrospectively evaluated. The data of 351 of these 436 patients were already included in the previous survival score including more than 30 different types of primary tumor [7]. Criteria for inclusion in this analysis included weakness of the legs due to MSCC, no prior surgery or RT to the involved parts of the spinal cord, adequate imaging (spinal CT or MRI), and corticosteroid treatment during RT for at least 1 week. The data were collected from the patients, treating physicians, and the patient files. The irradiated volumes encom-

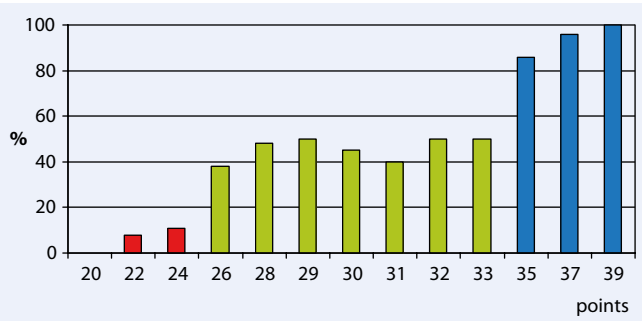

Fig. 1 ▲ Test group: the total scores in relation to the 6-month survival rate (given in %)

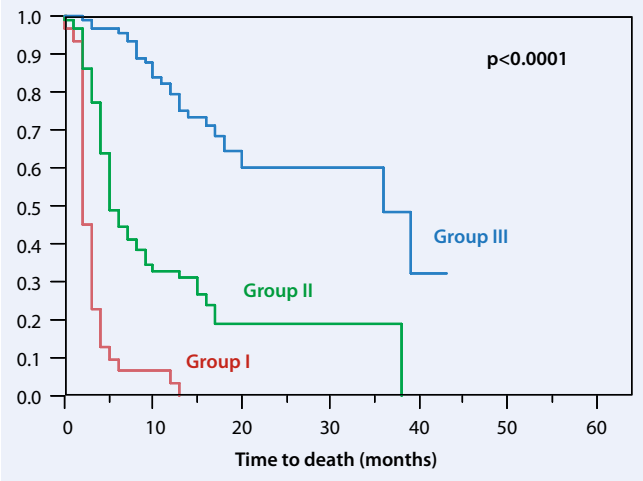

Fig. 2 ▶ Kaplan–Meier curves for survival of the three score groups I (20–24 points), II (25–34 points), and III (35–39 points) of the test group

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Tab. 1 Patients' characteristics of the test group and the validation group

	Test group n (%)	Validation group n (%)
Age ≤ 70 years > 70 years	105 (48) 113 (57)	111 (51) 107 (49)
ECOG performance status 1–2 3–4	107 (49) 111 (51)	113 (52) 105 (48)
Number of involved vertebrae 1–2 ≥ 3	86 (39) 132 (61)	92 (42) 126 (58)
Ambulatory status prior to RT Not ambulatory Ambulatory before RT	97 (44) 121 (56)	89 (41) 129 (59)
Other bone metastases No Yes	91 (42) 127 (58)	93 (43) 125 (57)
Visceral metastases No Yes	169 (78) 49 (22)	167 (77) 51 (23)
Interval from cancer diagnosis to RT ≤ 15 months > 15 months	87 (40) 131 (60)	90 (41) 128 (59)
Time developing motor deficits 1–7 days > 7 days	62 (28) 156 (72)	60 (28) 158 (72)
Radiation schedule Short-course RT Longer-course RT	122 (56) 96 (44)	121 (56) 97 (44)

RT radiotherapy.

passed one normal vertebra above and below the involved vertebrae.

The patients were alternately assigned to the test group (uneven numbers, n = 218) or the validation group (even numbers, n = 218). The patient characteristics of both groups are summarized in **Tab. 1** In the test group, eight potential prognostic factors including age (≤70 vs. > 70 years), ECOG performance status (ECOG-PS 1–2 vs. 3–4), number of involved vertebrae (1–2 vs. ≥3), ambulatory status before RT (no vs. yes), other bone metastases before RT (no vs. yes), visceral metastases before RT (no vs. yes), interval between first diagnosis of prostate cancer, and RT of MSCC (≤15 vs. > 15 months), and time of developing motor deficits prior to RT (1–7 vs. > 7 days) plus the fractionation regimen (short-course RT with 1 × 8 Gy or 5 × 4 Gy vs. longer-course RT with 10 × 3 Gy, 15 × 2.5 Gy, or 20 × 2 Gy) were investigated for potential associations with survival. The univariate analysis of survival was performed with the Kaplan–Meier method and the log-rank test [3]. The prognostic factors that were significant or almost significant in the univariate analysis ($p < 0.06$) were additionally evaluated with the Cox proportion hazards model.

The survival score included the prognostic factors found significant in the multivariate analysis of the test group. The score for each significant prognostic factor was determined by dividing the 6-month survival rate (given in %) by 10. The total score represented the sum of the scores for each factor. The score groups of the test group were compared to the corresponding score groups of the validation group.

Results

In the univariate analysis of the test group, improved survival was associated with ECOG performance status 1–2 ($p < 0.0001$), ambulatory status before RT ($p < 0.0001$), no other bone metastases ($p = 0.001$), no visceral metastases ($p < 0.0001$), an interval from cancer diagnosis to RT of MSCC of > 15 months ($p = 0.015$), and slower development of motor deficits (> 7 days) before RT ($p < 0.0001$). Age ≤ 70 years showed a strong trend ($p = 0.055$). The results of the univariate analysis of the test group are summarized in **Tab. 2** In the multivariate analysis, ECOG performance status (risk ratio (RR) 2.67; 95% confidence interval (CI) 1.76–4.12; $p < 0.0001$), ambulatory status (RR 3.17; 95% CI 2.16–4.69; $p < 0.0001$), no other bone metastases (RR 1.53; 95% CI 1.04–2.28; $p = 0.030$), no visceral metastases (RR 4.15; 95% CI 2.76–6.15; $p < 0.0001$), and the interval from cancer diagnosis to RT of MSCC (RR 1.27; 95% CI 1.05–1.53; $p = 0.014$) remained significant. Age (RR 1.28; 95% CI 0.89–1.85; $p = 0.19$) and development of motor deficits (RR 1.42; 95% CI 0.95–2.09; $p = 0.08$) were not significant.

The 6-month survival rates and the corresponding score for each of the five significant prognostic factors are given in **Tab. 3** The addition of the five scores for each factor resulted in total scores of 20, 21, 22, 24, 26, 28, 29, 30, 31, 32, 33, 35, 37, or 39 points (**Fig. 1**). According to the total scores, the patients were assigned to three score groups, 20–24 points (group I, n = 31), 26–33 points (group II, n = 92), and 35–39 points (group III, n = 95). The actuarial 6-month survival rates were 6.5% for group I patients, 44.6% for group II patients, and 95.8% for group III patients ($p < 0.0001$, **Fig. 2**). The corresponding survival rates in the validation group were 7.4%, 45.4%, and 94.7%, respectively ($p < 0.0001$, **Fig. 3**). The comparison of each of the score groups I, II and III of the test group to each corresponding score group of the validation group with respect to the 6-month survival rates are given in **Tab. 4** The survival scores for the test and the validation group were not statistically significant.

Discussion

Life expectancy of patients with MSCC from solid tumors ranges from a few months to several years [5]. A personalized therapeutic approach should take into account each patient's prognosis. In cases with a more favorable expected survival, longer term local control becomes

more important. Local control rates in patients with MSCC from prostate cancer have been reported to be higher after longer-course RT than after short-course RT [8]. Therefore, a prognostic score that allows survival to be predicted can have a significant impact on the individual therapeutic approach. The patients who are likely to have a relatively long survival time are good candidates for longer-course RT with 10 × 3 Gy or 20 × 2 Gy (given in 2 or 4 weeks, respectively) instead of short-course RT. The present study aimed to create and to validate a survival score particularly for patients with MSCC from prostate cancer. In the multivariate analysis of the present study, improved survival was significantly associated with ECOG performance status 1–2, being ambulatory prior to RT, lack of other bone or visceral metastases, and with a longer interval between the first diagnosis of prostate cancer and RT of MSCC. Because survival was not investigated in our previous study of 281 patients, all five independent prognostic factors identified in the present study can be considered new for prostate cancer patients [8].

In the present study, a scoring system that predicts survival of these patients has been developed based on the five significant prognostic factors. The scoring system includes three prognostic groups that were significantly different from each other. Patients of score group I had a 6-month survival probability of less than 10% and may, therefore, be considered candidates for best supportive care or single-fraction RT with 1 × 8 Gy. Single-fraction RT appears to be a good option in order to avoid that these patients spend as least time as possible of their very limited life span with anti-cancer treatment. Patients of score group II had a 6-month survival probability of less than 50% and may be considered candidates for short-course RT such as 5 × 4 Gy in 1 week. Patients of score group III had a more favorable survival prognosis and may live long enough to experience a local recurrence of MSCC. Because a previous study of MSCC from prostate cancer has suggested that local control of MSCC is significantly better with longer-course RT such as 10 × 3 Gy in 2 weeks or 20 × 2 Gy in 4 weeks, these patients appear best treated with longer-

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A survival score for patients with metastatic spinal cord compression from prostate cancer

Abstract

Background. This study aimed to develop and validate a survival scoring system for patients with metastatic spinal cord compression (MSCC) from prostate cancer.

Patients and methods. Of 436 patients, 218 patients were assigned to the test group and 218 patients to the validation group. Eight potential prognostic factors (age, performance status, number of involved vertebrae, ambulatory status, other bone metastases, visceral metastases, interval from cancer diagnosis to radiotherapy of MSCC, time developing motor deficits) plus the fractionation regimen were retrospectively investigated for associations with survival. Factors significant in the multivariate analysis were included in the survival score. The score for each significant prognostic factor was determined by dividing the 6-month survival rate (%) by 10. The total score represented the sum of the scores for each factor. The prognostic groups of the test group were compared to the validation group.

Results. In the multivariate analysis of the test group, performance status, ambulatory status, other bone metastases, visceral metastases, and interval from cancer diagnosis to radiotherapy were significantly associated with survival. Total scores including these factors were 20, 21, 22, 24, 26, 28, 29, 30, 31, 32, 33, 35, 37, or 39 points. In the test group, the 6-month survival rates were 6.5% for 20–24 points, 44.6% for 26–33 points, and 95.8% for 35–39 points ($p < 0.0001$). In the validation group, the 6-month survival rates were 7.4%, 45.4%, and 94.7%, respectively ($p < 0.0001$).

Conclusions. Because the survival rates of the validation group were almost identical to the test group, this score can be considered valid and reproducible.

Keywords

Metastatic spinal cord compression · Prostate cancer · Radiation therapy · Survival · Prognostic score

Ein Überlebens-Score für Patienten mit metastatisch bedingter Rückenmarkskompression beim Prostatakarzinom

Zusammenfassung

Hintergrund. Ziel dieser Studie war es, einen Überlebens-Score für Patienten mit metastatisch bedingter Rückenmarkskompression („metastatic spinal cord compression", MSCC) beim Prostatakarzinom zu entwickeln und zu validieren.

Patienten und Methoden. Von insgesamt 436 Patienten wurden jeweils 218 Patienten der Test- oder der Validierungsgruppe zugeordnet. Acht mögliche Prognosefaktoren (Alter, Allgemeinzustand, Anzahl befallener Wirbelkörper, Vorhandensein weiterer Knochenmetastasen, Vorhandensein von Organmetastasen, Gehfähigkeit vor Therapie, Intervall von der Diagnose der Tumorerkrankung bis zur Strahlentherapie der MSCC, Entwicklungszeit motorischer Defizite vor Strahlentherapie) sowie das Strahlentherapieregime wurden retrospektiv hinsichtlich ihres Einflusses auf das Überleben untersucht. Die Faktoren, die in der multivariaten Analyse signifikant waren, gingen in den Score ein. Der Score wurde für jeden einzelnen Faktor ermittelt, indem die Überlebensrate (in %) nach 6 Monaten durch 10 dividiert wurde. Der Gesamt-Score entsprach der Summe der Scores der einzelnen Faktoren. Die Prognosegruppen der Testgruppe wurden mit denen der Validierungssgruppe verglichen.

Ergebnisse. In der multivariaten Analyse der Testgruppe waren Allgemeinzustand, Gehfähigkeit, weitere Knochenmetastasen, Organmetastasen und das Intervall von der Diagnose der Tumorerkrankung bis zur Strahlentherapie signifikant mit dem Überleben assoziiert. Die Gesamt-Scores betrugen 20, 21, 22, 24, 26, 28, 29, 30, 31, 32, 33, 35, 37, oder 39 Punkte. In der Testgruppe betrugen die Überlebensraten nach 6 Monaten 6,5% bei 20–24 Punkten, 44,6% bei 26–33 Punkten sowie 95,8% bei 35–39 Punkten ($p < 0,0001$). In der Validierungsgruppe waren die Überlebensraten nach 6 Monaten 7,4%, 45,4%, und 94,7% ($p < 0,0001$).

Schlussfolgerung. Da die Überlebensraten in der Validierungsgruppe nahzeu identisch mit den Überlebensraten in der Testgruppe waren, kann dieser Score als valide und reproduzierbar betrachtet werden.

Schlüsselwörter

Metastatisch bedingte Rückenmarkskompression · Prostatakarzinom · Strahlentherapie · Überleben · Prognose-Score

Tab. 2 Test group: univariate analysis of survival (Kaplan–Meier analysis; log-rank test)

	Survival at 6 months (%)	Survival at 12 months (%)	p
Age			0.055
≤ 70 years (n = 105)	70	53	
> 70 years (n = 113)	55	45	
ECOG performance status			< 0.0001*
1–2 (n = 107)	87	73	
3–4 (n = 111)	38	26	
Number of involved vertebrae			0.13
1–2 (n = 86)	67	51	
≥ 3 (n = 132)	58	47	
Ambulatory status prior to RT			< 0.0001*
Not ambulatory (n = 97)	37	23	
Ambulatory before RT (n = 121)	82	69	
Other bone metastases			0.001*
No (n = 91)	74	59	
Yes (n = 127)	54	41	
Visceral metastases			< 0.0001*
No (n = 189)	75	59	
Yes (n = 49)	18	14	
Interval from cancer diagnosis to RT			0.015*
≤ 15 months (n = 87)	51	39	
> 15 months (n = 131)	69	55	
Time developing motor deficits			< 0.0001*
1–7 days (n = 62)	40	31	
> 7 days (n = 156)	71	56	
Radiation schedule			0.84
Short-course RT	63	51	
Longer-course RT	60	46	
Entire cohort	62	49	

*Value considered significant.

Tab. 3 Test group: 6-month survival rates (Kaplan–Meier analysis) and corresponding scores

	Survival at 6 months (%)	Score (points)
ECOG performance status		
1–2	87	9
3–4	38	4
Ambulatory status prior to RT		
Not ambulatory	37	4
Ambulatory before RT	82	8
Other bone metastases		
No	74	7
Yes	54	5
Visceral metastases		
No	75	8
Yes	18	2
Interval from cancer diagnosis to RT		
≤ 15 months	51	5
> 15 months	69	7

Tab. 4 Comparison of each of the score groups I, II, and III of the test group to each corresponding score group of the validation group with respect to the 6-month survival rates (Kaplan–Meier analysis; χ^2 test)

	Survival at 6 months (%)	p
Score group I		0.98
Test group (n = 31)	6.5	
Validation group (n = 27)	7.4	
Score group II		0.96
Test group (n = 92)	44.6	
Validation group (n = 97)	45.4	
Score group III		0.95
Test group (n = 95)	95.8	
Validation group (n = 94)	94.7	

course RT [8]. Patients of score groups II and III should be presented to a neurosurgeon to discuss the option of decompressive surgery prior to RT. In a randomized trial, the addition of decompressive surgery resulted in improved functional outcome and survival when compared to RT alone [4]. However, surgery is generally limited to selected patients with a good performance status, involvement of only one spinal segment, and paraplegia lasting for no longer than 48 h.

In order to validate the scoring system, each of the three score groups of the test group were compared to the corresponding score groups of the validation group with respect to the 6-month survival rate. The survival rates in the validation group were almost identical to the survival rates in the test group, which demonstrated a high validity and reproducibility of this new survival score. The score groups were more similar than in our previous survival score developed in a series of patients with many different primary tumors [6, 7]. The poorer results with differences of up to 14% between the test group and a validation group were most likely due to the heterogeneity regarding the types of primary tumor in the previous study. This demonstrates the importance of creating separate survival scores for the different primary tumors, as performed in the present study. However, the retrospective nature of the study must be taken into account when interpreting the results. Retrospective studies always bear the risk of hidden selection biases.

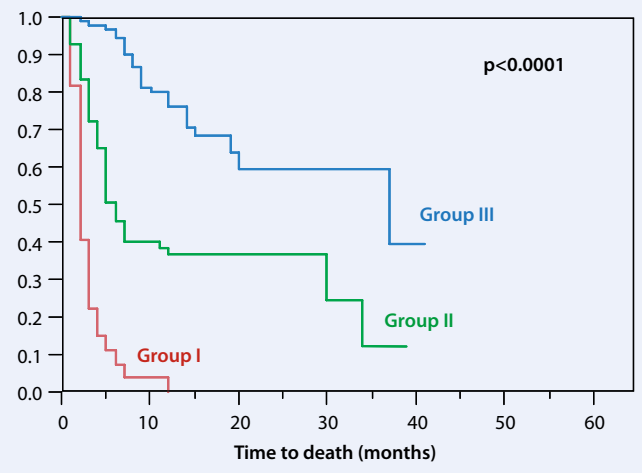

Fig. 3 ◀ Kaplan–Meier curves for survival of the three score groups I (20–24 points), II (25–34 points), and III (35–39 points) of the validation group

Conclusion

In this study of 436 patients with MSCC from prostate cancer, a new survival score was developed and validated. Based on five independent prognostic factors, three prognostic groups were created. Group I patients (20–24 points) had a very poor survival prognosis and may be considered for best supportive care or single-fraction RT. Group II patients (25–34 points) may be considered candidates for short-course RT. Group III patients (35–39 points) have a favorable survival prognosis and appear, therefore, better treated with longer course RT. This prognostic score can be used for proper stratification in randomized trials of prostate cancer patients presenting with MSCC. Furthermore, it may be important when counseling patients and their relatives.

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Conflict of interest. The corresponding author states the following: D. Rades received speakers honoraria from Amgen and Novartis Oncology.

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Original Article

Validation and Simplification of a Score Predicting Survival in Patients Irradiated for Metastatic Spinal Cord Compression

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BACKGROUND: Based on an analysis of 1852 retrospectively evaluated patients with metastatic spinal cord compression (MSCC), a scoring system was developed to predict survival. This study was performed to validate the scoring system in a new data set. **METHODS:** The score included 6 prognostic factors: tumor type, interval between tumor diagnosis and MSCC, other bone or visceral metastases, ambulatory status, and duration of motor deficits. Scores ranged between 20 and 45 points, and patients were initially divided into 5 groups: those with 20 to 25 points, those with 26 to 30 points, those with 31 to 35 points, those with 36 to 40 points, and those with 41 to 45 points. To facilitate the clinical use of the score, the patients were regrouped into 3 groups: those with 20 to 30 points, those with 31 to 35 points, and those with 36 to 45 points. In this study, data of 439 new patients were included who were divided into the same prognostic groups as in the preceding study. **RESULTS:** In this study, the 6-month survival rates were 7% (for those with 20-25 points), 19% (for those with 26-30 points), 56% (for those with 31-35 points), 73% (for those with 36-40 points), and 90% (for those with 41-45 points), respectively ($P < .0001$). After regrouping, the 6-month survival rates were 14% (for those with 20-30 points), 56% (for those with 31-35 points), and 80% (for those with 36-45 points), respectively, in this study ($P < .0001$). **CONCLUSIONS:** In the current study, the difference in 6-month survival between the prognostic groups was found to be as significant as in the preceding study. Thus, this scoring system was considered valid to estimate survival of MSCC patients. The system could have been simplified by including only 3 instead of 5 prognostic groups. ***Cancer* 2010;116;3670–3.** © *2010 American Cancer Society.*

KEYWORDS: metastatic spinal cord compression, survival, prognostic factors, scoring system, validation.

Approximately 5% to 10% of all cancer patients develop metastatic spinal cord compression (MSCC) during their lifetime.[1] The majority of MSCC patients are treated with radiotherapy alone. Each treatment session may be associated with discomfort for these debilitated patients during transportation to the radiation oncology department and patient positioning on the treatment couch. Thus, a short-course of radiotherapy with no more than 5 radiation sessions would be the best option, in particular for patients with a short survival time. However, a considerable proportion of MSCC patients live longer than a few months and may live long enough to experience a recurrence of MSCC in the irradiated spinal region. The rate of such in-field recurrences is significantly higher after short-course radiotherapy than after longer radiation programs such as 10×3 grays (Gy) in 2 weeks or 20×2 Gy in 4 weeks.[2,3] A scoring system that allows one to estimate the survival of MSCC patients would help the physician select the appropriate radiation regimen for the individual patient (ie, single-fraction radiotherapy, multifraction short-course radiotherapy, or longer course radiotherapy). We have developed just such a scoring system based on a multivariate analysis of survival in 1852 MSCC patients.[4] The scoring system included the 6 prognostic factors that were found to be significant for survival on the multivariate analysis. These factors were tumor type, interval between tumor diagnosis and MSCC, other bone metastases at the time of radiotherapy, visceral metastases at the time of radiotherapy, ambulatory status before radiotherapy, and duration of motor

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deficits before radiotherapy. The total score ranged between 20 and 45 points, and the patients were divided into 5 groups according to their score. The difference between the 5 groups was highly significant. However, this scoring system was not validated until this report. Furthermore, 5 groups appear too many to allow a quick use of the score during clinical routine, in particular if radiotherapy has to be administered urgently outside the regular working time.

The current study included 439 patients and aimed to validate our scoring system. Furthermore, a simplification of the previous scoring system has been performed by reducing the number of prognostic groups from 5 to 3.

MATERIALS AND METHODS

In the current study, 439 patients (265 patients from a previous prospective study[3] plus 174 additional patients who have been prospectively followed since January 2008) were included. The patients had been treated with radiotherapy alone.

These 439 patients represent the validation group for the scoring system that has been previously developed to estimate the survival of MSCC patients.[4] The scoring system to be validated was based on the retrospective analysis of 1852 patients. It included the following 6 prognostic factors that were found to be significantly associated with survival on the multivariate analysis of those 1852 patients: type of primary tumor (breast cancer vs prostate cancer vs myeloma/lymphoma vs lung cancer vs other tumors), interval between tumor diagnosis and MSCC ($\leq$15 months vs $>$15 months), presence of other bone metastases at the time of radiotherapy, presence of visceral metastases at the time of radiotherapy, pretreatment ambulatory status (ambulatory vs nonambulatory), and time of developing motor deficits before radiotherapy (1-7 days vs 8-14 days vs $>$14 days) (Table 1). For each of these 6 prognostic factors, a separate score was calculated by dividing the 6-month survival rate by 10. The total score included in the scoring system represents the sum of all the scores (rounded values) from the 6 prognostic factors. The total scores ranged between 20 and 45 points. Five groups were formed according to the total score based on the 6-month survival rates for each score: 20 to 25 points (Group A), 26 to 30 points (Group B), 31 to 35 points (Group C), 36 to 40 points (Group D), and 41 to 45 points (Group E). The 5 groups were compared for survival using the Kaplan-Meier method.[5] The Kaplan-Meier curves were compared using the log-rank test. The difference was significant with a $P < .0001$.

Table 1. Significant Prognostic Factors and Corresponding Scores

Prognostic Factor	Score
Type of primary tumor	
Breast cancer	8
Prostate cancer	7
Myeloma/lymphoma	9
Lung cancer	3
Other tumors	4
Other bone metastases at the time of RT	
Yes	5
No	7
Visceral metastases at the time of RT	
Yes	2
No	8
Interval from tumor diagnosis to MSCC, mo	
≤15	4
>15	7
Ambulatory status before RT	
Ambulatory	7
Nonambulatory	3
Time of developing motor deficits before RT, d	
1-7	3
8-14	6
>14	8

RT indicates radiotherapy; MSCC, metastatic spinal cord compression.

The scoring system, which was developed on the basis of the retrospective analysis of 1852 patients, was applied in the same way to the 439 patients in the current series. Five prognostic groups were formed in accordance with the previously developed scoring system.

To simplify the scoring system, the 5 prognostic groups were replaced by 3 groups: 20 to 30 points (Group I), 31 to 35 points (Group II), and 36 to 45 points (Group III). The results for both the preceding cohort and the present cohort were generated with the 3-group system to confirm its utility.

RESULTS

In the current study, the 6-month survival rates were 11% for the 97 patients with a total score of 20 to 25 points, 20% for those 140 patients with a score of 26 to 30 points, 48% for those 162 patients with a score of 31 to 35 points, 72% for those 141 patients with a score of 36 to 40 points, and 93% for those 112 patients with a score of 41 to 45 points (P lt;.0001) (Fig. 1). The 6-month survival rates in the preceding series of 1852

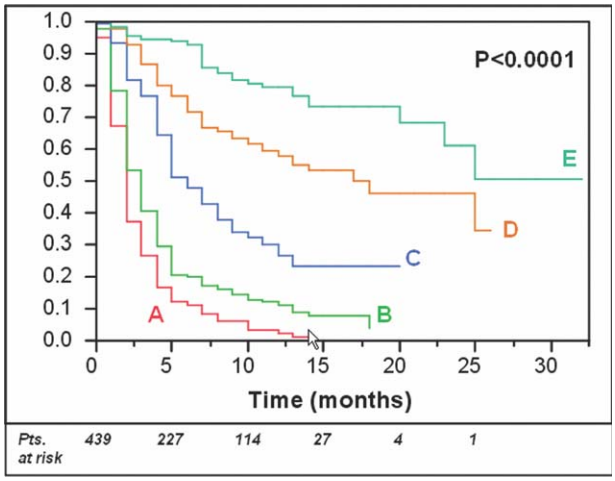

Figure 1. Kaplan-Meier curves of the 5 groups from the current study are shown with respect to survival (Group A: 20-25 points; Group B: 26-30 points; Group C: 31-35 points; Group D: 36-40 points; and Group E: 41-45 points). Pts indicates patients.

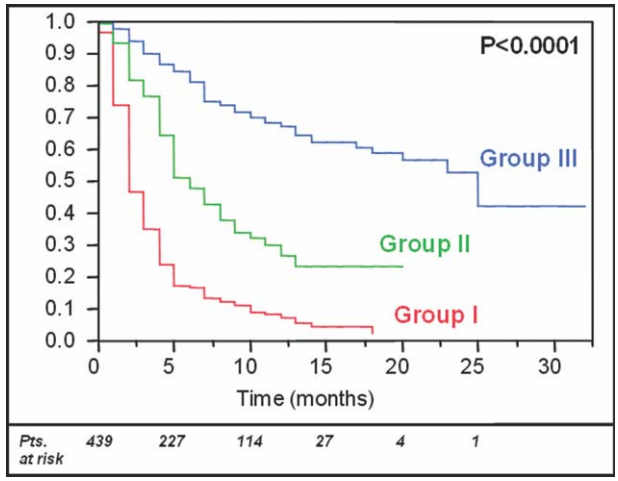

Figure 2. Kaplan-Meier curves of the 3 newly designed groups of patients (Pts) in the current study are shown with respect to survival (Group I: 20-30 points; Group II: 31-35 points; and Group III: 36-45 points).

patients who formed the basis for developing the survival score were 4%, 11%, 48%, 87%, and 99%, respectively ($P < .0001$). The comparisons of each of the different prognostic groups (Groups A to E) of this prospective series with the prognostic groups (Groups A to E) of the preceding retrospective study did not reveal a significant difference. The *P* values were .45 for the comparison of both Groups A, .10 for the comparison of Groups B, .40 for the comparison of Groups C, .24 for the comparison of Groups D, and .57 for the comparison of Groups E, respectively.

After reduction of the number of prognostic groups in the current study, the 6-month survival rates of the 3 prognostic groups [20-30 points [Group I; N = 237], 31-35 points [Group II; N = 162], and 36-45 points [Group III; N = 253]) were 16%, 48% and 81%, respectively ($P < .0001$) (Fig. 2). The corresponding 6-month survival rates in the preceding study were 9%, 48%, and 93%, respectively ($P < .0001$). Again, the comparison of each of the different prognostic groups of both series did not reveal a significant difference. The *P* values were .16 for the comparison of both Groups I, .40 for the comparison of Groups II, and .15 for the comparison of Groups III.

DISCUSSION

The duration of survival for patients with MSCC varies considerably. The majority of the patients have a short survival of only a few months, whereas other MSCC patients may live for years.[2,6] It is important in oncology to individualize cancer care to the needs of each patient. For MSCC patients with a poor survival prognosis, short-course radiotherapy with 1 to 5 fractions administered in a week or less is considered appropriate. Short-course radiotherapy is associated with less discomfort for the patients than longer course radiotherapy programs because of fewer trips to the radiation oncology department and fewer, mostly painful, positionings on the treatment couch. Furthermore, a shorter radiation regimen uses less of a patient's limited lifespan and reduces the cost of therapy.[7] MSCC patients with a relatively favorable survival prognosis often live long enough to develop a recurrence of MSCC in the previously irradiated spinal region. Because longer course radiotherapy has been reported to be associated with fewer recurrences than short-course radiotherapy, longer course radiotherapy appears to be the better option for this subset of patients.[2,3] In addition, more prolonged, higher dose radiotherapy regimens were associated with significantly longer survival in patients with favorable prognostic factors (scores of $\geq$36 in our retrospective analysis).[4] It is still not clear whether longer course radiotherapy with a radiation dose >30 Gy in 10 fractions or 40 Gy in 20 fractions may improve the patient's ambulatory function. Thus, randomized trials are required that investigate a potential benefit of such a dose escalation. Furthermore, randomized trials should be performed to define the role of high-precision radiotherapy techniques for the treatment of MSCC.

A scoring system that allows one to estimate the survival of MSCC patients can help to select the most appropriate radiation regimen for the individual patient. Such a scoring system including 5 prognostic groups has been developed on a large retrospective series of 1852 patients.[4] However, that score has not yet been validated. The current study included 439 new MSCC patients. The 6-month survival rates in the current series were not found to be significantly different from those of the preceding study. This finding demonstrates the validity of the previously developed score. However, one may consider 5 prognostic groups too complicated for daily routine, in particular if the patient is presented to the radiation oncologist outside the regular working hours (ie, at night or on weekends). Therefore, we decided to simplify the scoring system by reducing the number of prognostic groups from 5 to 3. The 6-month survival rates of these groups have been determined in both series (ie, in the primary series of 1852 patients and in the current series of 439 patients). Again, the survival rates of the 3 prognostic groups were not found to be significantly different in both series, which demonstrated the validity also of the scoring system with the new grouping.

In conclusion, the previously developed scoring system proved valid in another series of patients. It appears simpler for daily clinical routine to use 3 instead of 5 prognostic groups. Patients in the prognostic Groups I (20-30 points) should be treated with short-course radiotherapy because their 6-month survival rates are low. Patients in the prognostic Group III (36-45 points) should receive longer course radiotherapy because they are at a higher risk to develop a recurrence of MSCC in the previously irradiated spinal region because they live significantly longer. In patients in the prognostic Group II, the treatment decision should be left to the treating physician who is able to assess other less tangible factors such as Karnofsky performance status and comorbidity. Because this score has been developed and validated in patients treated with radiotherapy alone, it should be used only in patients not receiving decompressive surgery.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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XII. Danksagung

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XIII.Curriculum vitae

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Publikationen:

1. Douglas S, Huttenlocher S, Bajrovic A, Rudat V, Schild SE, Rades D. Prognostic factors for different outcomes in patients with metastatic spinal cord compression from cancer of unknown primary. BMC Cancer. 2012 Jun 21;12:261. doi: 10.1186/1471-2407-12-261.

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