

Aus der Klinik für Strahlentherapie der Universität zu Lübeck

Lehrstuhlinhaber: Herr Prof. Dr. med. Dirk Rades

**Prognostische Faktoren und neue tumorspezifische Scores für das
Überleben von Patienten mit Bestrahlung von Knochenmetastasen**

Inauguraldissertation zur Erlangung der Doktorwürde der Universität zu Lübeck

- Aus der Sektion Medizin -

vorgelegt von Rapha Mareike Haus aus Datteln

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1. Berichterstatter: Priv.-Doz. Dr. med. Stefan Janssen

2. Berichterstatter/in: Prof. Dr. med. Benjamin Kienast

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Zur besseren Lesbarkeit werden in dieser Dissertation personenbezogene Bezeichnungen generell nur in der im Deutschen üblichen männlichen Form angeführt. Dies impliziert jedoch keine Benachteiligung des weiblichen Geschlechts, sondern soll im Sinne der sprachlichen Vereinfachung als geschlechtsneutral zu verstehen sein.

1. Abkürzungsverzeichnis

95%-KI	95%-Konfidenzintervall
ECOG Performance Status	Eastern Cooperative Oncology Group Performance Status
HR	Hazard Ratio
IMRT	Intensitätsmodulierte Strahlentherapie
MSCC	Metastatische Spinalkanalkompression
RR	Relatives Risiko
SBRT	Stereotactic Body Radiation Therapy
VMAT	Volumetric Modulated Arc Therapy

2. Auflistung der Publikationen der kumulativen Dissertation

1. Dirk Rades, **Rapha Haus**, Steven E. Schild, Stefan Janssen: Prognostic factors and a new scoring system for survival of patients irradiated for bone metastases. BMC Cancer 19, 1156 (2019)
2. Stefan Janssen, **Rapha Haus**, Steven E. Schild, Dirk Rades: A Simple Clinical Instrument to Predict the Survival Probability of Breast Cancer Patients Receiving Radiotherapy for Bone Metastases. Anticancer Research 40, 367-371 (2020)
3. **Rapha Haus**, Stefan Janssen, Steven E. Schild, Dirk Rades: A Disease-specific Score for Estimating Survival After Irradiation of Bone Metastases from Colorectal Cancer. Anticancer Research 40, 287-291 (2020)
4. **Rapha Haus**, Stefan Janssen, Steven E. Schild, Dirk Rades: Eastern Cooperative Oncology Group Performance Score is Associated with Survival after Radiotherapy of Bone Metastases from Prostate Cancer. In vivo 34, 679-682 (2020)
5. Dirk Rades, **Rapha Haus**, Stefan Janssen, Steven E. Schild: An easy-to-use scoring system to estimate the survival of patients irradiated for bone metastases from lung cancer. Translational Lung Cancer Research 9(4), 1067-1073 (2020)

3. Einleitung und Fragestellung

Bedingt durch Verbesserungen in Diagnostik und Therapie ist die Lebenserwartung von Krebspatienten in den letzten Jahren gestiegen, sodass entsprechend mehr Patienten bei längeren Krankheitsverläufen das Auftreten von Metastasen erleben (Siegel, 2019). Die zwei häufigsten Metastasierungsorte, die eine strahlentherapeutische Behandlung erfordern, sind das zentrale Nervensystem und das Skelettsystem. Knochenmetastasen treten bei bis zu 70% der Patienten mit Mamma- und Prostatakarzinom und bei bis zu 50% der Patienten mit Lungenkarzinom auf (Coleman, 2006). Viele dieser Patienten erhalten entweder eine alleinige Strahlentherapie der Knochenmetastasen oder, in Fällen von drohenden pathologischen Frakturen bzw. einer Kompression des Rückenmarks, eine vorherige stabilisierende Operation mit anschließender Strahlentherapie.

Weltweit kommen für die Bestrahlung von Knochenmetastasen verschiedene Dosis-Fraktionierungsregime zur Anwendung. Diese reichen von einer Einzeitbestrahlung (z.B. 1x8 Gy), über Kurzzeit-Regime über die Dauer von einer Woche (z.B. 5x4 Gy) bis zu Langzeit-Regimen über die Dauer von zwei bis vier Wochen (z.B. 10x3 Gy, 14-15x2,5 Gy und 18-20x2 Gy). Die wesentlichen Ziele bei der Strahlentherapie von Knochenmetastasen bestehen zum einem in der Symptomkontrolle, im Wesentlichen durch Schmerzlinderung, und zum anderen in der Prävention von Komplikationen wie dem Auftreten von pathologischen Frakturen oder einer Kompression des Spinalkanals. Gemäß mehrerer Meta-Analysen, welche Einzeitbestrahlungen mit fraktionierten Regimen verglichen, zeigten Einzeitbestrahlungen bei unkomplizierten schmerzhaften Knochenmetastasen (ohne Spinalkanalkompression, ohne extensive Weichteilkomponente und ohne (drohende) pathologische Fraktur) eine Äquieffektivität im Vergleich zu fraktionierten Bestrahlungsregimen (Wu, 2003; Chow, 2012; Sze, 2012). Allerdings kam es nach einer Einzeitbestrahlung signifikant häufiger als nach einer fraktionierten Strahlentherapie zu einer Re-Bestrahlung (Sze, 2012). Darüber hinaus war gemäß einer randomisierten Studie die Re-Kalzifizierungsrate von osteolytischen Läsionen nach fraktionierten Langzeit-Regimen signifikant stärker ausgeprägt als nach einzelfraktionierter Bestrahlung (Koswig, 1999). Da eine Re-Bestrahlung bei lokalem Rezidiv sowie eine Re-Kalzifizierung, die sich erst einige Monate nach Bestrahlungsende

bemerkbar macht, bei Patienten mit stark eingeschränkter Überlebensprognose in den Hintergrund rückt, ist hier ein möglichst kurzes und wenig beschwerliches Behandlungsregime wie eine Einzeitbestrahlung zu empfehlen. Für Patienten mit einer günstigeren Prognose sollten die lokale Langzeitkontrolle und die Prävention von therapieassoziierten Langzeitfolgen in größerem Maße berücksichtigt werden.

In der Onkologie nehmen personalisierte Therapieansätze, bei denen jeder Patient individuell betrachtet wird, einen immer größeren Stellenwert ein. Auch in der Strahlentherapie sollte, basierend auf den oben genannten Überlegungen, die verbleibende Lebenszeit des Patienten bei der Wahl des bestmöglichen, individuell angepassten Regimes Berücksichtigung finden. Bei der Abschätzung der individuellen Prognose des Patienten können Prognose-Scores für den behandelnden Arzt bei der Wahl des passenden Therapieregimes hilfreich sein.

Für Patienten mit Knochenmetastasen ist die Auswahl an Prognose-Scores bislang begrenzt. Einer der drei etablierten Scores bei Knochenmetastasen wurde anhand von Patienten, welche vor 1999 behandelt wurden, entwickelt und spiegelt daher nicht den Einfluss moderner Target-Therapien auf das Überleben von Tumorpatienten wider (Westhoff, 2014). Dieser Aspekt lässt sich zumindest partiell auch auf zwei weitere Scores übertragen, welche anhand von Patienten entwickelt wurden, die zwischen 2001 und 2010 bzw. zwischen 2000 und 2013 behandelt wurden (Bollen, 2014; Willeumier, 2018). In letzterer Studie wurden außerdem Patienten eingeschlossen, die orthopädische Operationen ohne anschließende Strahlentherapie erhielten, was zu einer behandlungsassoziierten Stichprobenverzerrung geführt haben könnte. Auch wurden Patienten mit metastatisch bedingter Myelonkompression (MSCC), deren Prognose als deutlich schlechter einzustufen ist, inkludiert, was ebenfalls zu einer Verzerrung geführt haben kann (Bollen, 2014).

Im Patientenkollektiv, auf der die vorliegende kumulative Dissertation basiert, erhielten alle Patienten eine Strahlentherapie; der Behandlungszeitraum zwischen 2009 und 2019 ist außerdem vergleichsweise aktuell und beinhaltet auch moderne Systemtherapien. Im Vergleich zu den oben genannten Studien wurden in den Untersuchungen, auf denen diese Dissertation beruht, verschiedene potenzielle Prognosefaktoren und unterschiedliche Dosis-Fraktionierungen miteinbezogen. Patienten, die eine MSCC aufwiesen, wurden in den Studien der kumulativen

Dissertation exkludiert. Da sich unterschiedliche Primärtumorentitäten in ihrer Prognose, ihrem Therapieansprechen und ihrem Metastasierungsverhalten voneinander unterscheiden, sollten sich Prognose-Scores idealerweise auf homogene Patientenkollektive mit nur einer Primärtumorentität beziehen.

Zielsetzung dieser kumulativen Dissertation war es, Prognosefaktoren für das Überleben von Patienten nach Bestrahlung von Knochenmetastasen zu identifizieren. Darauf basierend sollten neue Prognose-Scores für unterschiedliche Primärtumorentitäten erstellt werden, die im klinischen Alltag eine einfach zu handhabende Hilfestellung bieten und konsequent zu einer Therapieindividualisierung führen.

4. Methoden und Ergebnisse

4.1 Publikation 1: Prognosefaktoren und ein neuer Überlebens-Score für Patienten mit Bestrahlung von Knochenmetastasen

Es wurden die Daten von 445 Patienten, welche an zwei deutschen strahlentherapeutischen Institutionen zwischen 2009 und 2017 mit fraktionierter Strahlentherapie bei symptomatischen (schmerzhaften) Knochenmetastasen ohne Spinalkanalkompression bei soliden Primärtumoren behandelt wurden, retrospektiv analysiert. Die Studie wurde von der Ethikkommission der Universität Lübeck bewilligt. Patienten nach Einzeitbestrahlung wurden in der Studie nicht berücksichtigt, um das Risiko einer möglichen Verzerrung zu minimieren. Die Fraktionierungsregime (Kurzzeit-Strahlentherapie mit 5-6x4 Gy gegenüber Langzeit-Strahlentherapie mit 30-40 Gy in 10-20 Fraktionen) sowie 13 weitere Faktoren wurden im Hinblick auf mögliche Assoziationen mit dem Überleben analysiert (Tabelle 1 in Publikation 1).

Mit Hilfe der Kaplan-Meier-Methode wurden die Überlebensraten und anschließend in einer univariaten Analyse die Unterschiede zwischen den verschiedenen Kaplan-Meier-Kurven mit Hilfe des Log-Rank-Tests berechnet. Jene Faktoren, welche in der univariaten Analyse Signifikanz erreichten ($p < 0,05$) oder einen Trend zeigten ($p < 0,055$), wurden in die multivariate Analyse (Cox-Regression) eingeschlossen. Die in der multivariaten Analyse signifikanten ($p < 0,05$) oder grenzwertig signifikanten Faktoren ($p < 0,055$) wurden für die Entwicklung des Scores verwendet.

In der univariaten Analyse war ein verbessertes Überleben signifikant mit dem weiblichen Geschlecht ($p < 0,001$), einem Karnofsky-Index von 80-100 ($p < 0,001$), bestimmten Primärtumortypen (Mammakarzinom, Prostatakarzinom, Nierenzellkarzinom) ($p < 0,001$), einem längeren Intervall (≥ 9 Monate) zwischen Tumordiagnose und der Strahlentherapie von Knochenmetastasen ($p = 0,044$), der Abwesenheit von viszerale Metastasen ($p = 0,002$), der Abwesenheit von pathologischen Frakturen ($p = 0,049$) und einem Langzeit-Strahlentherapie-Regime ($p = 0,022$) assoziiert.

In der multivariaten Analyse war ein verbessertes Überleben signifikant mit dem Karnofsky-Index (HR: 1,91, 95%-KI: 1,51-2,41, $p<0,001$) und dem Primärtumortyp (HR: 1,12, 95%-KI: 1,07-1,17, $p<0,001$) assoziiert. Der Faktor Alter erreichte eine grenzwertige Signifikanz (HR: 1,14, 95%-KI: 1,00-1,30, $p=0,054$). Daher wurden diese drei Faktoren für den Score verwendet. Da der Karnofsky-Index bei 43 Patienten (9,7%) nicht bekannt war, wurde der Score mit den Daten von 402 Patienten entwickelt. Die 12-Monats-Überlebensrate von jedem signifikanten Faktor (in Prozent) wurde durch 10 geteilt, um den entsprechenden Faktor-Score zu erhalten (Tabelle 4.1.1). Die einzelnen Faktor-Scores wurden für jeden Patienten addiert, sodass entsprechende Patienten-Scores zwischen 8 und 17 Punkten erreicht wurden. Basierend auf den Patienten-Scores wurden drei prognostische Gruppen erstellt: Gruppe A (8-9 Punkte), Gruppe B (10-14 Punkte) und Gruppe C (15-17 Punkte). Die 12-Monats-Überlebensraten dieser Gruppen betrugen 9%, 38% und 72% (Abbildung 4.1.1, $p<0,001$). Die 6-Monats-Überlebensraten betrugen 30%, 54% und 85%; die mediane Überlebenszeit betrug 3 Monate, 8 Monate und 24 Monate ($p<0,001$).

4.2 Publikation 2: Ein einfaches klinisches Instrument zur Vorhersage der Überlebenswahrscheinlichkeit bei Brustkrebs-Patientinnen mit Bestrahlung von Knochenmetastasen

In einer Kohorte von 126 Mammakarzinom-Patientinnen, die eine fraktionierte Langzeitbestrahlungstherapie bei Knochenmetastasen erhielten, wurden 11 potenziell prognostische Faktoren (Tabelle 1 in Publikation 2) retrospektiv im Hinblick auf eine mögliche Assoziation mit dem Überleben analysiert. Folgende Bestrahlungsregime kamen zur Anwendung: 10x3 Gy über 2 Wochen ($n=77$), 12-13x3 Gy über 2,5 Wochen ($n=4$), 14-15x2,5 Gy über 3 Wochen ($n=26$), 15x2 Gy über 3 Wochen ($n=5$) und 18-20x2 Gy über 3,5-4 Wochen ($n=14$). Patientinnen mit metastatisch bedingter Spinalkanalkompression wurden exkludiert.

Die statistischen Analysen wurden mit der Kaplan-Meier-Methode und dem Log-Rank-Test durchgeführt (univariate Analyse). Jene Faktoren, welche sich als signifikant herausstellten ($p < 0,05$) oder einen starken Trend für eine Assoziation mit dem Überleben zeigten ($p < 0,06$), wurden zusätzlich multivariat mit Hilfe der Cox-Regression analysiert. In den Score wurden schließlich die Faktoren miteinbezogen, die in der multivariaten Analyse unabhängig mit dem Überleben assoziiert waren.

Die mediane Nachbeobachtungszeit in der gesamten Kohorte betrug 16,5 Monate (Spannweite: 1-129 Monate) sowie 22 Monate (Spannweite: 2-102 Monate) bei den Patientinnen, die zum Zeitpunkt der letzten Kontaktaufnahme noch lebten. Für die gesamte Kohorte betrug das mediane Überleben 27 Monate. Zum Zeitpunkt von 6, 12, 18 und 24 Monaten betrugen die entsprechenden Überlebensraten 80%, 66%, 57% und 51%. In der univariaten Analyse waren ein ECOG Performance Status von 0-1 ($p = 0,003$) und die Abwesenheit von viszerale Metastasen ($p = 0,005$) signifikant positiv mit dem Überleben assoziiert. Zusätzlich zeigte die Abwesenheit von pathologischen Frakturen einen starken Trend zur Assoziation mit einem verbesserten Überleben ($p = 0,058$).

In der Cox-Regressionsanalyse behielten die Faktoren ECOG Performance Status (RR: 1,70, 95%-KI: 1,05-2,72, $p = 0,032$) und die Abwesenheit von viszerale Metastasen (RR: 1,75, 95%-KI: 1,11-2,79, $p = 0,017$) Signifikanz. Der Faktor pathologische Frakturen erreichte indessen keine Signifikanz (RR: 1,40, 95%-KI: 0,86-2,23, $p = 0,17$).

Es wurden somit nur die beiden unabhängigen prognostischen Faktoren ECOG Performance Status und Vorkommen von viszerale Metastasen in den Score miteinbezogen. Unter Berücksichtigung der korrespondierenden Überlebensraten wurden für einen ECOG Performance Status von ≥ 2 und ein Vorkommen von viszerale Metastasen 0 Punkte sowie für einen ECOG Performance Status von 0-1 und eine Abwesenheit von viszerale Metastasen 1 Punkt vergeben. Auf diesen Punkten basierend wurden drei Gruppen erstellt, mit entsprechend 0 Punkten, 1 Punkt und 2 Punkten. Die Überlebensraten dieser Gruppen zum Zeitpunkt von 6, 12, 18 und 24 Monaten sind in Tabelle 4.2.1 zusammengefasst. Die korrespondierenden Kaplan-Meier-Kurven zeigt Abbildung 4.2.1.

4.3 Publikation 3: Ein Diagnose-spezifischer Score zur Abschätzung des Überlebens nach der Bestrahlung von Knochenmetastasen bei Patienten mit kolorektalem Karzinom

In diese Studie wurden 25 Patienten mit kolorektalem Karzinom, die an Knochenmetastasen ohne Spinalkanalkompression bestrahlt wurden, eingeschlossen. In der retrospektiven Analyse wurden 11 verschiedene prognostische Faktoren auf ihren potenziellen Einfluss auf das Überleben analysiert (Tabelle 1 in Publikation 3) und ein Prognose-Score entwickelt. Die Strahlentherapie wurde fraktioniert mit 6x4 Gy (n=1), 10x3 Gy (n=5), 12x3 Gy (n=1), 14-15x2,5 Gy (n=16), 15x2 Gy (n=1) oder 20x2 Gy (n=1) durchgeführt.

Es wurde eine univariate Analyse mithilfe der Kaplan-Meier-Methode und dem Log-Rank-Test durchgeführt. Faktoren, die sich in der univariaten Analyse als signifikant herausstellten ($p < 0,05$) oder einen Trend zeigten ($p < 0,10$), wurden in eine multivariate Analyse eingeschlossen (Cox-Regression). Jene Faktoren, welche in der multivariaten Analyse eine Signifikanz zeigten, wurden für die Entwicklung des prognostischen Scores verwendet.

Die mediane Nachbeobachtungszeit in der gesamten Kohorte betrug 4 Monate (Spannweite: 0-65 Monate). Die Überlebensraten zum Zeitpunkt von 3, 6, 9 und 12 Monaten betrugen entsprechend 56%, 44%, 32% und 23%. In der univariaten Analyse war ein günstiger (0-1) ECOG Performance Status ($p = 0,005$) sowie die Abwesenheit von weiteren Knochenmetastasen ($p = 0,001$) und eine niedrige Anzahl (n=1) an bestrahlten metastatischen Lokalisationen ($p = 0,049$) signifikant mit einer günstigen Überlebensprognose assoziiert. Zusätzlich zeigte das Fehlen einer systemischen Therapie vor Bestrahlung einen Trend für ein günstigeres Überleben ($p = 0,067$).

In der multivariaten Analyse blieben die Faktoren ECOG Performance Status (HR: 6,97, 95%-KI: 1,75-36,34, $p = 0,005$) und systemische Therapie vor Bestrahlung (HR: 7,50, 95%-KI: 1,64-60,17, $p = 0,007$) signifikant. Die Faktoren weitere Knochenmetastasen (HR: 2,05, 95%-KI: 0,51-9,74, $p = 0,32$) und Anzahl an bestrahlten Lokalisationen der Knochenmetastasen (HR: 1,25, 95%-KI: 0,35-4,54, $p = 0,73$) erreichten keine Signifikanz.

Daher wurden ausschließlich die Faktoren ECOG Performance Status und systemische Therapie vor Bestrahlung für die Entwicklung eines Scores verwendet. Basierend auf dem Überleben, wurde den Patienten 1 Punkt (günstige Prognose: ECOG Performance Status von 0-1 oder keine vorangegangene systemische Therapie) oder 0 Punkte (ungünstige Prognose: ECOG Performance Status von ≥ 2 oder vorangegangene systemische Therapie) zugewiesen, woraus drei prognostischen Gruppen mit entweder 0 Punkten (n=7), 1 Punkt (n=11) oder 2 Punkten (n=2) resultieren. Die Überlebensraten dieser drei Gruppen werden in Tabelle 4.3.1 und Abbildung 4.3.1 gezeigt.

4.4 Publikation 4: Der ECOG Performance Status ist mit dem Überleben von Prostatakarzinom-Patienten nach Bestrahlung von Knochenmetastasen assoziiert

Die Daten von 74 an Knochenmetastasen bestrahlten Prostatakarzinom-Patienten wurden retrospektiv ausgewertet. Alle Patienten erhielten eine fraktionierte Langzeitbestrahlung mit entweder 10x3 Gy über 2 Wochen (n=31), 12x3 Gy über 2,5 Wochen (n=1), 14-15x2,5 Gy über 3 Wochen (n=32), 15x2 Gy über 3 Wochen (n=3) oder 18-20x2 Gy über 3,5-4 Wochen (n=7). 10 Faktoren wurden in Hinblick auf das Überleben untersucht (Tabelle 1 in Publikation 4).

Für die univariate Analyse wurde die Kaplan-Meier-Methode und der Log-Rank-Test angewendet. Signifikante Faktoren ($p < 0,05$) oder Faktoren, die in der univariaten Analyse einen Trend zeigten ($p < 0,10$), wurden zusätzlich in einer multivariaten Cox-Regression im Hinblick auf ihre Unabhängigkeit ausgewertet.

Die mediane Überlebenszeit in der gesamten Kohorte betrug 12 Monate. Die entsprechenden Überlebensraten zum Zeitpunkt von 3, 6, 9 und 12 Monaten betrugen 84%, 73%, 56% und 47%. In der univariaten Analyse war ein ECOG Performance Status von 0-1 signifikant mit einem verbesserten Überleben assoziiert (Abbildung 4.4.1, $p < 0,001$). Bei Abwesenheit von viszerale Metastasen

($p=0,099$) und nur einer bestrahlten Metastasen-Lokalisation ($p=0,099$) zeigte sich ein Trend zu einem längeren Überleben ($p=0,099$).

In der Cox-Regression erreichte der Faktor ECOG Performance Status Signifikanz (RR: 3,43, 95%-KI: 1,67-7,12), während die Faktoren Abwesenheit von viszerale Metastasen (RR: 1,07, 95%-KI: 0,54-2,05) und nur eine bestrahlte Metastasen-Lokalisation (RR: 1,12, 95%-KI: 0,59-2,11) keine Signifikanz zeigten.

4.5 Publikation 5: Ein einfacher Score zur Abschätzung des Überlebens von Lungenkrebspatienten mit Bestrahlung von Knochenmetastasen

In diese retrospektive Studie wurden 153 Patienten mit einem Lungenkarzinom, die eine fraktionierte Bestrahlung von Knochenmetastasen ohne Spinalkanalkompression erhielten, eingeschlossen. 12 Faktoren (Tabelle 1 in Publikation 5) wurden im Hinblick auf ihren potenziellen Einfluss auf das Überleben ausgewertet.

Um das Risiko einer durch unterschiedliche Dosisfraktionierungen bedingten Stichprobenverzerrung zu reduzieren, wurden nur Patienten mit fraktionierterer Langzeitbestrahlung eingeschlossen. Folgende Fraktionierungsregime kamen zur Anwendung: 10x3 Gy über 2 Wochen ($n=76$), 12-13x3 Gy über 2,5 Wochen ($n=4$), 14-15x2 Gy über 3 Wochen ($n=12$), 14-15x2,5 Gy über 3 Wochen ($n=49$) oder 18-20x2 Gy über 2,5-3 Wochen ($n=12$).

Mit Hilfe der Kaplan-Meier-Methode und dem Log-Rank-Test wurde eine univariate Analyse des Überlebens durchgeführt. Die potenziellen prognostischen Faktoren, die in der univariaten Analyse signifikant mit dem Überleben assoziiert waren ($p<0,05$), wurden in der Folge in eine Cox-Regression eingeschlossen (multivariate Analyse). Anschließend wurden die Faktoren, die in der Cox-Regression signifikant waren ($p<0,05$) oder einen Trend zeigten ($p\leq 0,01$), für die Erstellung eines Scores zur Abschätzung des Überlebens herangezogen.

Die mediane Nachbeobachtungszeit betrug in der gesamten Kohorte 5 Monate (Spannbreite: 0-155 Monate) sowie 13 Monate (Spannbreite: 4-155 Monate) bei den Patienten, die zum Zeitpunkt der letzten Kontrolle noch lebten. Die Überlebensraten in der gesamten Kohorte betrugen zum Zeitpunkt nach 3, 6, 9 und 12 Monaten 59%, 46%, 36% und 30%. In der univariaten Analyse waren die Faktoren Alter ≤ 65 Jahre ($p=0,017$) und ein ECOG Performance Status von 0-1 ($p<0,001$) signifikant mit dem Überleben assoziiert. In der multivariaten Cox-Regression blieb der ECOG Performance Status signifikant (RR: 2,77, 95%-KI: 1,93-4,00, $p<0,001$); der Faktor Alter zeigte einen Trend (RR: 1,34, 95%-KI: 0,94-1,89, $p=0,10$).

Beide Faktoren wurden anschließend für die Entwicklung eines Scores zur Abschätzung des Überlebens genutzt. Es wurden die folgenden Scoring-Punkte zugewiesen: Alter ≤ 65 Jahre = 1 Punkt, Alter ≥ 66 Jahre = 0 Punkte, ECOG Performance Status von 0-1 = 1 Punkt und ECOG Performance Status von ≥ 2 = 0 Punkte. Auf diese Weise wurden drei prognostische Gruppen mit entsprechend 0 Punkten ($n=38$), 1 Punkt ($n=71$) und 2 Punkten ($n=44$) erstellt. Die Überlebensraten dieser drei Gruppen zum Zeitpunkt von 3, 6, 9 und 12 Monaten sind in Tabelle 4.5.1 zusammengefasst; die zugehörigen Kaplan-Meier-Kurven zeigt Abbildung 4.5.1.

5. Diskussion, Zusammenfassung und Ausblick

Knochenmetastasen sind häufige Manifestationen bei Patienten mit fortgeschrittenem Tumorleiden. Die Strahlentherapie, entweder alleinig oder nach einer stabilisierenden Operation, ist zur Symptomkontrolle z.B. bei Schmerzen oder bei drohenden Komplikationen wie einer Myelonkompression ein wesentlicher Bestandteil des Therapiekonzeptes. Für die bestmögliche Behandlung von Tumorpatienten mit Knochenmetastasen, die optimal auf die individuelle Situation des Patienten zugeschnitten ist, ist es wichtig, die verbleibende Lebenszeit, die zwischen wenigen Wochen und mehreren Jahren variieren kann, so präzise wie möglich abzuschätzen. Hierbei können Prognose-Scores eine große Hilfe sein. Obwohl bereits einige Scores verfügbar sind, welche spezifisch für Patienten mit Bestrahlung von Knochenmetastasen entwickelt wurden, sind diese Scores veraltet und berücksichtigen nicht den Einfluss moderner Target-Therapien auf das Überleben der Patienten (Bollen, 2014; Willeumir, 2018).

2005 wurde in der Dutch Bone Metastasis Study Group ein Score aus den Daten von 342 Patienten entwickelt, welche zwischen 1996 und 1998 mit 1x8 Gy oder 6x4 Gy bei spinalen Knochenmetastasen ohne wesentliche neurologische Ausfälle bestrahlt wurden (van der Linden, 2005). Basierend auf den drei unabhängig signifikanten Prädiktoren Karnofsky-Index ($p < 0,001$), Primärtumortyp ($p < 0,001$) und viszerale Metastasen ($p = 0,02$) wurden drei prognostische Gruppen mit einer mittleren Überlebenszeit von 3,0, 9,0 und 18,7 Monaten erstellt. Für den Zeitraum von mehreren Jahren war dies der einzige anerkannte Überlebensscore für Patienten, die an Knochenmetastasen bestrahlt wurden. Im Gegensatz zu den Arbeiten dieser kumulativen Dissertation war der Score jedoch ausschließlich auf spinale Metastasen limitiert und berücksichtigte keine anderen metastatischen Lokalisationen wie Becken, Rippen, Extremitäten oder Schädelkalotte. Daher sind die prognostischen Gruppen, die in dieser Studie erstellt wurden, möglicherweise nicht auf Patienten mit anderen metastatischen Lokalisationen als der Wirbelsäule anwendbar.

2014 wurden zwei weitere Überlebens-Scores für Patienten mit einer Strahlentherapie von Knochenmetastasen präsentiert. Einer dieser Scores wurde ebenfalls innerhalb der Dutch Bone Metastasis Study Group entwickelt, in diesem Fall aus Daten von 1157 Patienten, die mit 1x8 Gy oder 6x4 Gy bestrahlt wurden

(Westhoff, 2014). Es wurden verschiedene unabhängige Faktoren, einschließlich des Geschlechts, des Primärtumortyps, des Karnofsky-Index, des Vorkommen von viszerale Metastasen sowie zweier Selbstbewertungs-Scores, welche die allgemeine Gesundheit und Lebenseinschätzung der Patienten betrafen, identifiziert. Da dieses Modell schlussendlich jedoch sehr komplex erschien, entwickelten die Autoren einen vereinfachten Score, welcher ausschließlich den Karnofsky-Index und den Primärtumortyp beinhaltete. In diesem wurden zwar die von 3 bis 18 Monate reichenden Überlebensraten für Mammakarzinome, Prostatakarzinome, Lungenkarzinome und weitere Primärtumore in Beziehung zu drei Abstufungen des Karnofsky-Index (90-100, 70-80 und 20-60) gesetzt, jedoch keine prognostischen Gruppen gebildet, welche üblicherweise Teil eines Überlebens-Scores sind.

Der zweite Score beinhaltete retrospektive Daten von 1043 Patienten, welche mit spinalen Knochenmetastasen zwischen 2001 und 2010 behandelt wurden (Bollen, 2014). 99% der Patienten erhielten eine alleinige oder eine auf eine vorangegangene Operation folgende Strahlentherapie, welche hauptsächlich als einzelfraktionierte Bestrahlung mit 1x8 Gy (43%) oder als fraktionierte Kurzzeit-Bestrahlung mit 2x8 Gy (16%) oder 5-6x4 Gy (31%) durchgeführt wurde. Es wurden vier Kategorien basierend auf dem Karnofsky-Index (80-100 gegenüber 10-70) und auf dem Vorkommen von viszerale oder zerebralen Metastasen erstellt, mit den entsprechenden Überlebenszeiten von 31,2, 15,4, 4,8 und 1,6 Monaten. Dieser Score ist wahrscheinlich auch nicht auf Patienten mit Knochenmetastasen an anderen Lokalisationen als der Wirbelsäule anwendbar. Im Gegensatz zu den anderen Überlebens-Scores für Patienten mit einer Strahlentherapie von Knochenmetastasen, hatten 49% der für diesen Score eingeschlossenen Patienten symptomatische MSCC mit motorischen und/oder sensiblen Defiziten. Es besteht eine generelle Übereinstimmung, dass für die Mehrheit der Patienten mit komplizierten, das heißt mit drohenden oder existierenden pathologischen Frakturen sowie mit MSCC oder ausgeprägter Weichteilkomponente assoziierten Knochenmetastasen, eine fraktionierte Bestrahlung die angemessene Therapie ist (Rades, 2010). Aufgrund der Tatsache, dass Patienten mit MSCC jedoch generell eine schlechtere Überlebensprognose haben als Patienten mit Knochenmetastasen ohne MSCC, sollten diese Kohorten für die Entwicklung eines Überlebens-Scores nicht vermischt werden, sondern es empfehlen sich hier separate Scores.

Der erst kürzlich publizierte Überlebensscore für Patienten mit Knochenmetastasen von Willeumier et al. basiert auf Daten von 1520 Patienten, welche bei symptomatischen Metastasen der langen Röhrenknochen zwischen 2000 und 2013 behandelt wurden (Willeumier, 2018). Basierend auf den drei unabhängigen prognostischen Faktoren klinisches Profil, Karnofsky-Index, und Vorkommen von viszerale/zerebralen Metastasen wurden vier Kategorien mit den entsprechenden medianen Überlebenszeiten von 21,9, 10,5, 4,6 und 2,2 Monaten erstellt. Da dieser Score ausschließlich aus Daten von Patienten mit Metastasen der langen Röhrenknochen entwickelt wurde, ist die Anwendbarkeit nicht auf Patienten mit Knochenmetastasen an anderen Lokalisationen übertragbar. Darüber hinaus ist es möglich, dass der Einschluss von 130 Patienten (8,6%), welche eine alleinige Operation ohne anschließende Strahlentherapie erhielten, zu einer Stichprobenverzerrung geführt haben könnte.

Vor dem Hintergrund der Limitationen der oben genannten Scores sind tumorspezifische Scores, die alle Metastasen-Lokalisationen berücksichtigen, aber Patienten mit MSCC und jene, die nach einer Operation der Metastasen keine Strahlentherapie erhalten haben, ausschließen, wünschenswert. Die vorliegende Dissertation soll diese Lücke schließen. Die neuen Überlebens-Scores wurden spezifisch dafür entwickelt, die 12-Monats-Überlebenszeit von Patienten, welche mit Knochenmetastasen bestrahlt werden, vorherzusagen, können aber auch dafür genutzt werden, das 6-Monats-Überleben abzuschätzen.

Patienten der Gruppe A (allgemeiner Score aus Publikation 1) beziehungsweise Patienten mit einem Ergebnis von 0 Punkten (tumorspezifische Scores aus den Publikationen 2,3 und 5) wiesen die schlechteste Überlebensprognose auf. Von den Patienten mit einem kolorektalen Karzinom als Primärtumor überlebten zum Beispiel nur 14% 3 Monate nach Bestrahlung und kein Patient überlebte 6 Monate oder länger. Bei den Patienten der Gruppe mit 0 Punkten beim Mammakarzinom überlebten nur 38% ein Jahr oder länger; bei den Patienten mit einem Lungenkarzinom als Primärtumor überlebten nur 37% bzw. 21% 3 bzw. die folgenden 6 Monate. In zwei großen randomisierten Studien mit 1171 und 765 Patienten, die mit schmerzhaften Knochenmetastasen bestrahlt wurden, traten wiederkehrende Knochenschmerzen erst nach einer medianen Zeit von 11 Monaten bzw. >12 Monaten auf (Steenland, 1999). Die Mehrheit der Patienten mit einer

ungünstigen Überlebensprognose wird daher voraussichtlich nicht lange genug leben, um eine Re-Bestrahlung für wiederkehrende Knochenschmerzen zu benötigen, sodass hier eine einzelfraktionierte Bestrahlung die angemessenste Therapie zu sein scheint. Vor 15 Jahren präsentierten Sze et al. ein systematisches Review aus 11 Studien und 3435 Patienten mit unkomplizierten schmerzhaften Knochenmetastasen. Die übergreifende Schmerz-Anspruchsrate betrug entsprechend 60% nach einzelfraktionierter und 59% nach multifraktionierter Bestrahlungstherapie (RR: 1,03, 95%-KI: 0,89-1,19). Eine komplette Schmerzfreiheit wurde bei 34% bzw. 32% der Patienten erreicht (RR: 1,11, 95%-KI: 0,94-1,30). Kürzlicher präsentierten Chow et al. ein aktualisiertes systematisches Review, welches 25 randomisierte Studien mit einer Gesamtzahl von 5617 Patienten mit unkomplizierten schmerzhaften Knochenmetastasen enthielt. Eine übergreifende Schmerzlinderung wurde bei 60% der Patienten nach einzelfraktionierter Bestrahlung im Gegensatz zu 61% der Patienten nach multifraktionierter Behandlung erreicht ($p=0,36$). Die Raten an kompletter Schmerzfreiheit betrugen 23% bzw. 24%. In Anlehnung daran kann eine einzelfraktionierte Bestrahlung mit 8 Gy als genau so effektiv in Bezug auf eine Schmerzlinderung wie ein stärker fraktioniertes Bestrahlungsregime (z.B. mit 10×3 Gy) angesehen werden und sollte somit die zu bevorzugende Therapie für eine Behandlung von unkomplizierten schmerzhaften Knochenmetastasen bei Patienten mit einer limitierten Überlebensprognose sein. Bei limitierter Überlebenszeit sollte die Anzahl der Therapiesitzungen so gering wie möglich gehalten werden, um die Lebensqualität der verbleibenden Lebenszeit nicht zu kompromittieren.

Patienten der Gruppe B (allgemeiner Score aus Publikation 1) beziehungsweise Patienten mit einem Ergebnis von 1 Punkt (tumorspezifische Scores aus den Publikationen 2,3 und 5) haben eine intermediäre 12-Monats-Überlebenswahrscheinlichkeit. Bei unkomplizierten Knochenmetastasen kann sowohl eine einzelfraktionierte Strahlentherapie mit 1×8 Gy als auch eine fraktionierte Kurzzeit-Strahlentherapie mit $5-6 \times 4$ Gy in Erwägung gezogen werden, abhängig von der Präferenz des Patienten. Da das Risiko eines lokalen Rezidivs der bestrahlten Knochenmetastasen besteht, kann im Falle von wiederkehrenden Schmerzen nach einer einzelfraktionierten Strahlentherapie ein zweiter Kurs einer einzelfraktionierten Bestrahlung verabreicht werden. Allerdings profitieren etwa 40% der Patienten nicht von einer Re-Bestrahlung (Huisman, 2012). Im Fall einer

(drohenden) pathologischen Fraktur oder einer großen Weichteilkomponente, ist eine Langzeitbestrahlungstherapie z.B. mit 10x3 Gy über 2 Wochen vorteilhaft, da hier eine ausgeprägtere Re-Kalzifizierung der osteolytischen Knochen im Gegensatz zu einer Therapie mit 1x8 Gy nachgewiesen wurde (Koswig, 1999). Im Speziellen Patienten mit 1 Punkt und einem Mammakarzinom als Primärtumor überlebten mit einem Anteil von 57% ein Jahr oder länger, daher könnten diese Patienten ebenfalls von einer Langzeitbestrahlungstherapie mit 10x3 Gy profitieren.

Patienten der Gruppe C (allgemeiner Score aus Publikation 1) beziehungsweise Patienten mit einem Ergebnis von 2 Punkten (tumorspezifische Scores aus den Publikationen 2,3 und 5) wiesen eine sehr günstige 12-Monats-Überlebensprognose auf. Analog hatten auch Patienten mit einem Prostatakarzinom als Primärtumor und einem guten ECOG Performance Status (0-1) eine günstige Prognose mit entsprechenden Überlebensraten von 83% zum Zeitpunkt nach 6 Monaten und 67% zum Zeitpunkt nach 12 Monaten. Voraussichtlich wird daher ein Großteil dieser Patienten lange genug leben, um wiederkehrende Knochenschmerzen an den bestrahlten Lokalisationen nach einzelfraktionierter Bestrahlung oder Kurzzeit-Strahlentherapie zu erfahren. Die zwei zuvor genannten systematischen Reviews machen deutlich, dass ein Rezidiv der bestrahlten schmerzhaften Knochenmetastasen nach einzelfraktionierter Bestrahlung signifikant häufiger auftritt und eine erneute Behandlung der gleichen Lokalisation signifikant häufiger notwendig ist, als nach stärker fraktionierter Bestrahlung. Im Review von Sze et al. waren die Raten an erneuten Behandlungen entsprechend 21,5% im Gegensatz zu 7,4% (RR: 3,44, 95%-KI: 2,67-4,43). In dem aktualisierten Review von Chow et al. betrugen die Raten an erneuten Behandlungen 20% und 8% ($p < 0,00001$) (Sze, 2011; Chow, 2012). Dementsprechend erscheinen Patienten mit einer günstigen Überlebensprognose als gute Kandidaten für Langzeitbestrahlungsregime. Zusätzlich benötigt die der Bestrahlungstherapie folgende Re-Mineralisation und Stabilisation der osteolytischen Metastasen normalerweise mehrere Monate. Laut einer prospektiven Studie mit 107 Patienten, die mit Knochenmetastasen mit entweder 1x8 Gy oder 10x3 Gy bestrahlt wurden, war die Re-Mineralisation (die relative Zunahme der Knochendichte) nach dem einzelfraktionierten Programm signifikant geringer ausgeprägt, das heißt 120% im Vergleich zu 173% ($p < 0,001$) (Koswig, 1999). Unter Berücksichtigung der Tatsache, dass somit eine

Langzeitbestrahlungstherapie einer einzelfraktionierten Behandlung in Bezug auf die lokale Kontrolle und die erfolgreiche Re-Mineralisation überlegen ist, wird deutlich, dass Patienten mit einer günstigeren Überlebensprognose besser für eine Langzeit-Strahlentherapie mit Gesamtdosen von 30-40 Gy und Einzeldosen von ≤ 3 Gy geeignet sind. Analog dazu wurde bereits gezeigt, dass bei Patienten mit günstiger Überlebensprognose und MSCC eine Bestrahlungstherapie mit einer Gesamtdosis von mehr als 30 Gy (z.B. 15x2,5 Gy oder 20x2 Gy) in einer verbesserten lokalen Kontrolle resultiert (Rades, 2010). Dies kann mit Einschränkungen eventuell auch auf Patienten mit guter Prognose bei Knochenmetastasen ohne MSCC extrapoliert werden.

Folgende Limitationen müssen bei der möglichen Anwendung der Scores berücksichtigt werden: Die Scores basieren auf retrospektiven Patientendaten mit den bekannten Risiken einer Stichprobenverzerrung. Darüber hinaus war die Patientenzahl bei einigen der tumorspezifischen Scores eher gering. Um das Risiko einer versteckten Stichprobenverzerrung abhängig von der Dosis-Fraktionierung zu minimieren, wurden ausschließlich Patienten mit Langzeitbestrahlungsregimen eingeschlossen. In Folge dessen sollten die Ergebnisse nicht für Patienten generalisiert werden, die mit einzelfraktionierter oder stereotaktischer Strahlentherapie behandelt werden, da diese in den Studien nicht berücksichtigt wurden. Weiterhin sollte beachtet werden, dass komplizierte Knochenmetastasen, das heißt Knochenmetastasen mit (drohender) pathologischer Fraktur, Spinalkanalkompression oder extensiver Weichteilkomponente, grundsätzlich eine multifraktionierte Bestrahlung erfordern.

Obwohl die Patientendaten, auf denen diese kumulative Dissertation beruht, mit dem Behandlungszeitraum zwischen 2009-2019 aktuell sind, haben sich die onkologischen Therapien auch in diesem Zeitraum stetig weiterentwickelt. Im Speziellen nimmt die Immuntherapie einen immer größeren Stellenwert ein. Zahlreiche Studien belegen bei unterschiedlichen Tumorentitäten hierunter einen Überlebensvorteil im Vergleich zu den bisherigen Standard-Therapien (Kruger, 2019). Die optimale Kombination einer Immuntherapie mit einer lokalen Strahlentherapie ist aber weder bei einer kurativen noch bei einer palliativ intendierten Therapie geklärt. Bislang existieren keine Studien, die den Einsatz einer Immuntherapie sowie der Bestrahlung von Knochenmetastasen untersucht

haben. Prinzipiell ist aber von einem synergistischen Effekt auszugehen; die Immuntherapie scheint den lokalen Effekt der Strahlentherapie zu erhöhen. Darüber hinaus gibt es zahlreiche klinische Fallbeschreibungen des sogenannten abskopalen Effektes, das heißt einem systemischen Tumoransprechen bei lokaler Bestrahlung nur einer Manifestation (Liu, 2019). Eine kleine retrospektive Studie konnte bei der Behandlung von Knochenmetastasen unter dem Einsatz einer weiteren Therapie (z.B. einer Strahlentherapie) zusätzlich zu einer Immuntherapie ein verbessertes Überleben zeigen (Grover, 2019). Bislang ist aber unklar, zu welchem Zeitpunkt und in welcher Dosierung die Strahlentherapie in die Immuntherapie einzubinden ist. Zu dieser Fragestellung laufen zurzeit verschiedene Studien.

Auch in der Bestrahlungstechnik hat es in den letzten Jahren viele Innovationen gegeben. Neue Techniken wie die intensitätsmodulierte Strahlentherapie (IMRT) werden mittlerweile bei vielen Tumorentitäten standardmäßig eingesetzt. Bei spinalen Knochenmetastasen konnte durch den Einsatz einer IMRT (im Vergleich zur 3-D-konformalen Therapie) eine geringere akute Toxizität beobachtet werden (Sprave, 2018). Darüber hinaus war außerdem eine Fatigue-Symptomatik bei den Patienten nach IMRT weniger stark ausgeprägt (Sprave, 2018). Der Einsatz einer VMAT, einer dynamischen IMRT-Technik, wird bei Knochenmetastasen aktuell in einer Phase III Studie getestet (Olson et al., 2019, SUPR-3D Studie). Eine lokale Dosiserhöhung durch einen simultan integrierten Boost hat sich in ersten kleineren Fallserien als gut durchführbar erwiesen (Faroogi, 2019) und wird zurzeit ebenfalls in einer Phase III Studie untersucht (Cellini, 2019, PREST Studie). Darüber hinaus ist eine stereotaktische Bestrahlung (SBRT) eine weitere Möglichkeit lokal mit hohen Einzeldosen unter maximaler Aussparung des umliegenden Gewebes sehr präzise einzelne Herde zu bestrahlen. Bei fehlenden großen prospektiven Studien zeigen retrospektive Arbeiten bei der SBRT spinaler Metastasen neben einer hohen lokalen Kontrolle von ca. 90% und einem vollständigen Schmerzansprechen von ca. 50% auch eine sehr geringe Rate an schweren Nebenwirkungen (Husain, 2017). Die modernen Techniken und Möglichkeiten einer Dosisescalation werden bei der Behandlung von Knochenmetastasen zukünftig zu weiteren Optionen in der Therapiepersonalisierung führen.

Im Rahmen dieser kumulativen Dissertation wurden unterschiedliche prognostische Faktoren bei Patienten mit Bestrahlung von Knochenmetastasen identifiziert. Daraus sind mehrere neue Prognose-Scores entstanden, die bei der Wahl des optimalen (strahlentherapeutischen) Therapiekonzeptes hilfreich sein können und somit zur Personalisierung beitragen. In Zukunft wird sich die Therapie von Patienten mit Knochenmetastasen weiter personalisieren. Außerdem wird der Einsatz moderner Systemtherapien wie der Immuntherapie weiter zunehmen; zusätzlich wird sich die Frage nach dem optimalen Zeitpunkt und der optimalen Dosis sowie Technik der Strahlentherapie stellen.

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7. Anhang

Tabelle 4.1.1 12-Monats-Überlebensraten signifikanter und grenzwertig signifikanter prognostischer Faktoren und die korrespondierenden Faktoren-Scores für den allgemeinen Score aus Publikation 1

(Rades et al.: Prognostic factors and a new scoring system for survival of patients irradiated for bone metastases. BMC Cancer 19, 1156 (2019))

Prognostische Faktoren	12-Monats-Überlebensraten (%)	Faktoren-Score
Alter		
≤60 Jahre	48	5
61-70 Jahre	44	4
>70 Jahre	38	4
Karnofsky-Index		
≤70	23	2
80-100	55	6
Primärtumortyp		
Mammakarzinom	64	6
Prostatakarzinom	52	5
Lungenkarzinom	30	3
Nierenzellkarzinom	63	6
Kolorektales Karzinom	25	3
Andere Tumore	22	2

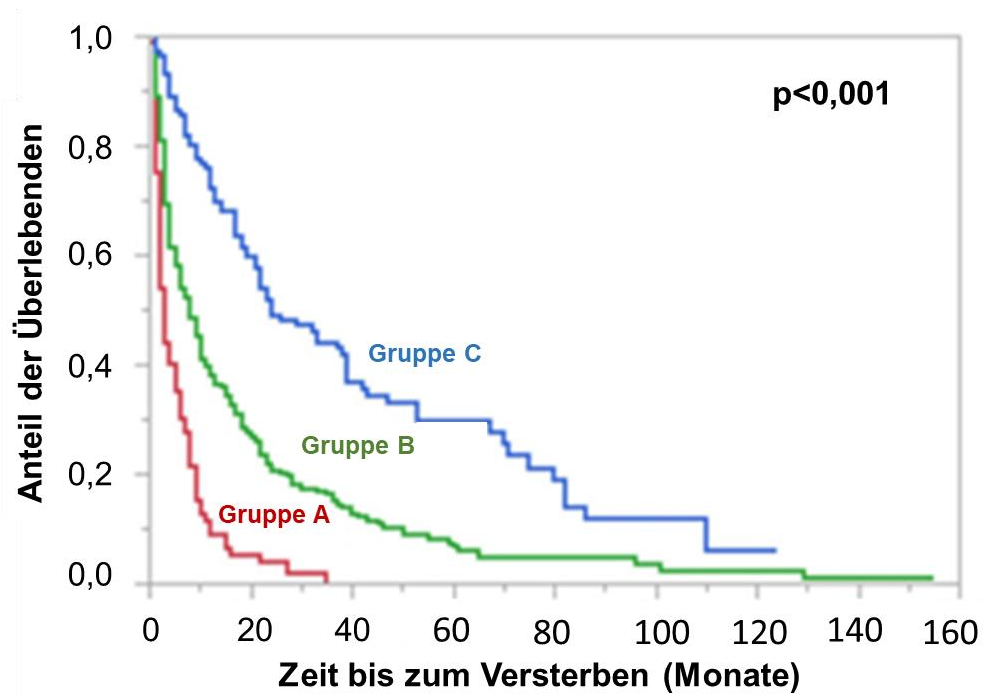


Abbildung 4.1.1 Überlebenskurven der drei prognostischen Gruppen des allgemeinen Scores aus Publikation 1

(Rades et al.: Prognostic factors and a new scoring system for survival of patients irradiated for bone metastases. BMC Cancer 19, 1156 (2019))

Tabelle 4.2.1 Überlebensraten der drei prognostischen Gruppen bei Patientinnen mit Mammakarzinom und Bestrahlung von Knochenmetastasen

(Janssen et al.: A Simple Clinical Instrument to Predict the Survival Probability of Breast Cancer Patients Receiving Radiotherapy for Bone Metastases. Anticancer Research 40, 367-371 (2020))

Prognostische Gruppe	Überlebensraten (%) zum Zeitpunkt				p-Wert
	6 Monate	12 Monate	18 Monate	24 Monate	
0 Punkte (n=22)	59	38	32	32	
1 Punkt (n=58)	72	57	45	36	
2 Punkte (n=46)	100	91	83	80	<0,001

Fettgedruckte Werte = signifikante p-Werte

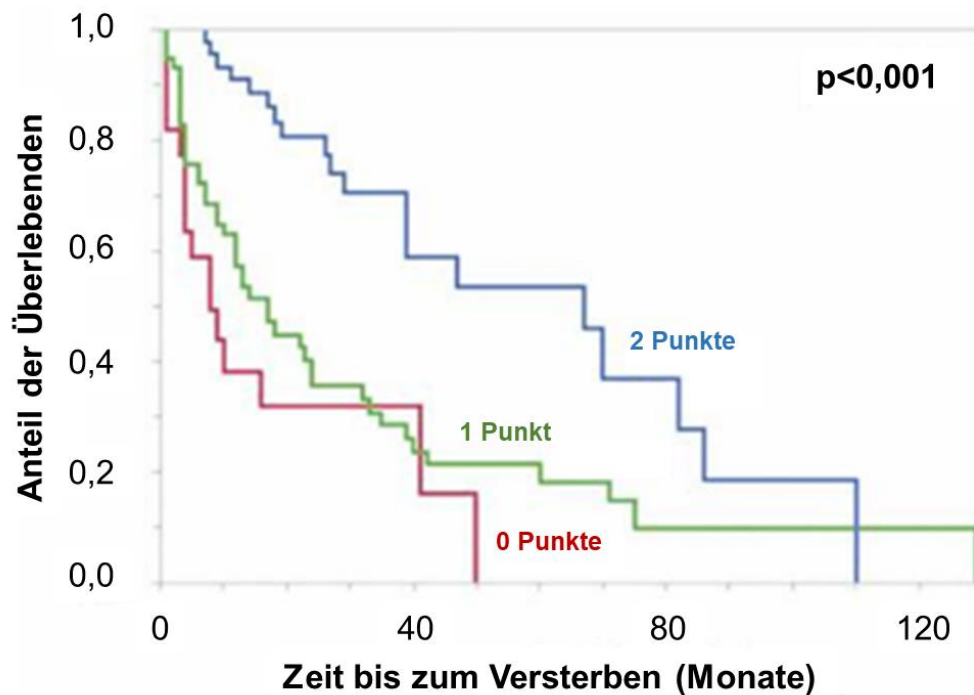


Abbildung 4.2.1 Überlebenskurven der drei prognostischen Gruppen bei Patientinnen mit Mammakarzinom und Bestrahlung von Knochenmetastasen

(Janssen et al.: A Simple Clinical Instrument to Predict the Survival Probability of Breast Cancer Patients Receiving Radiotherapy for Bone Metastases. Anticancer Research 40, 367-371 (2020))

Tabelle 4.3.1 Überlebensraten der drei prognostischen Gruppen bei Patienten mit kolorektalem Karzinom und Bestrahlung von Knochenmetastasen

(Haus et al.: A Disease-specific Score for Estimating Survival After Irradiation of Bone Metastases from Colorectal Cancer. Anticancer Research 40, 287-291 (2020))

Überlebensraten (%) zum Zeitpunkt					
Prognostische Gruppe	3 Monate	6 Monate	9 Monate	12 Monate	p-Wert
0 Punkte (n=7)	14	0	0	0	
1 Punkt (n=11)	73	64	45	27	
2 Punkte (n=2)	100	100	100	100	<0,001

Fettgedruckte Werte = signifikante p-Werte

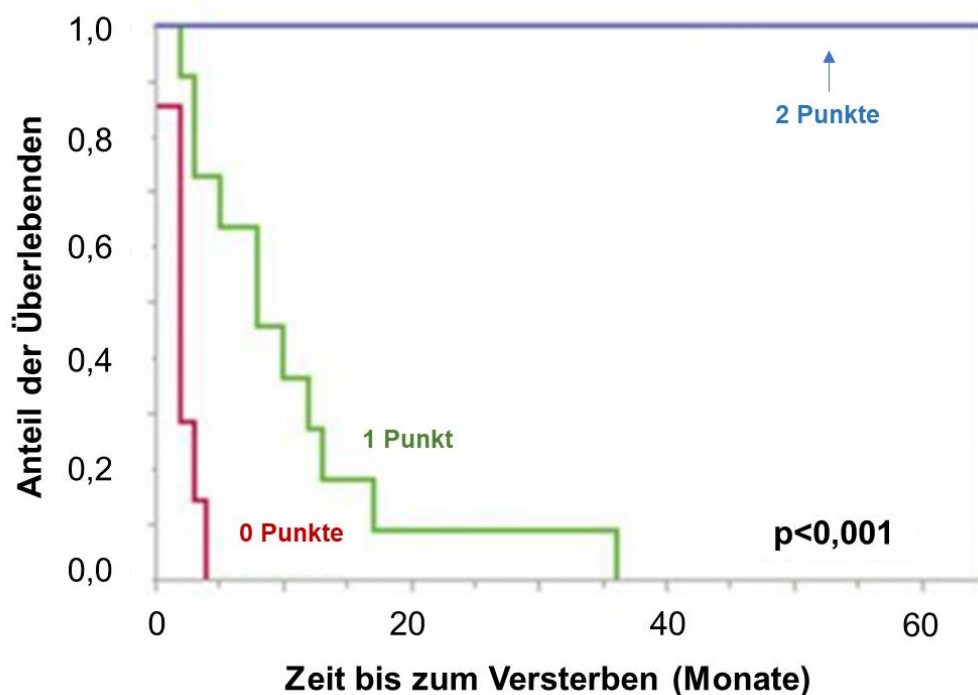


Abbildung 4.3.1 Überlebenskurven der drei prognostischen Gruppen bei Patienten mit kolorektalem Karzinom und Bestrahlung von Knochenmetastasen

(Haus et al.: A Disease-specific Score for Estimating Survival After Irradiation of Bone Metastases from Colorectal Cancer. Anticancer Research 40, 287-291 (2020))

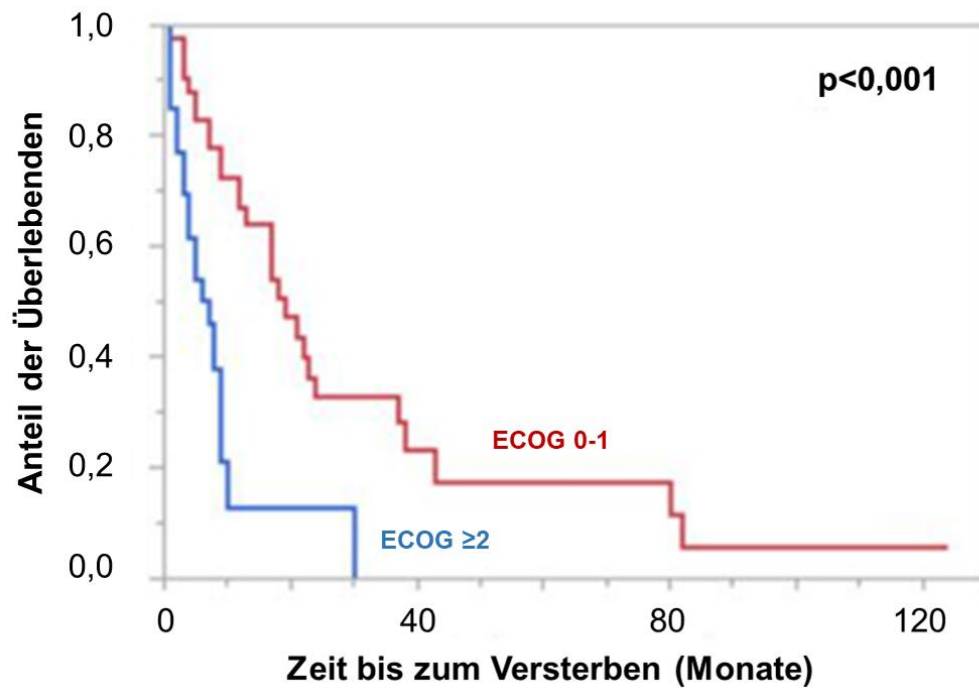


Abbildung 4.4.1 Überlebenskurven für unterschiedliche ECOG Gruppen bei Patienten mit einem Prostatakarzinom und Bestrahlung von Knochenmetastasen

(Haus et al.: Eastern Cooperative Oncology Group Performance Score is Associated with Survival after Radiotherapy of Bone Metastases from Prostate Cancer. In vivo 34, 679-682 (2020))

Tabelle 4.5.1 Überlebensraten der drei prognostischen Gruppen bei Patienten mit Lungenkarzinom und Bestrahlung von Knochenmetastasen

(Rades et al.: An easy-to-use scoring system to estimate the survival of patients irradiated for bone metastases from lung cancer. Translational Lung Cancer Research (accepted March 2020))

Überlebensraten (%) zum Zeitpunkt					
Prognostische Gruppe	3 Monate	6 Monate	9 Monate	12 Monate	p-Wert
0 Punkte (n=38)	37	21	11	7	
1 Punkt (n=71)	56	41	32	27	
2 Punkte (n=44)	84	75	66	56	<0.001

Fettgedruckte Werte = signifikante p-Werte

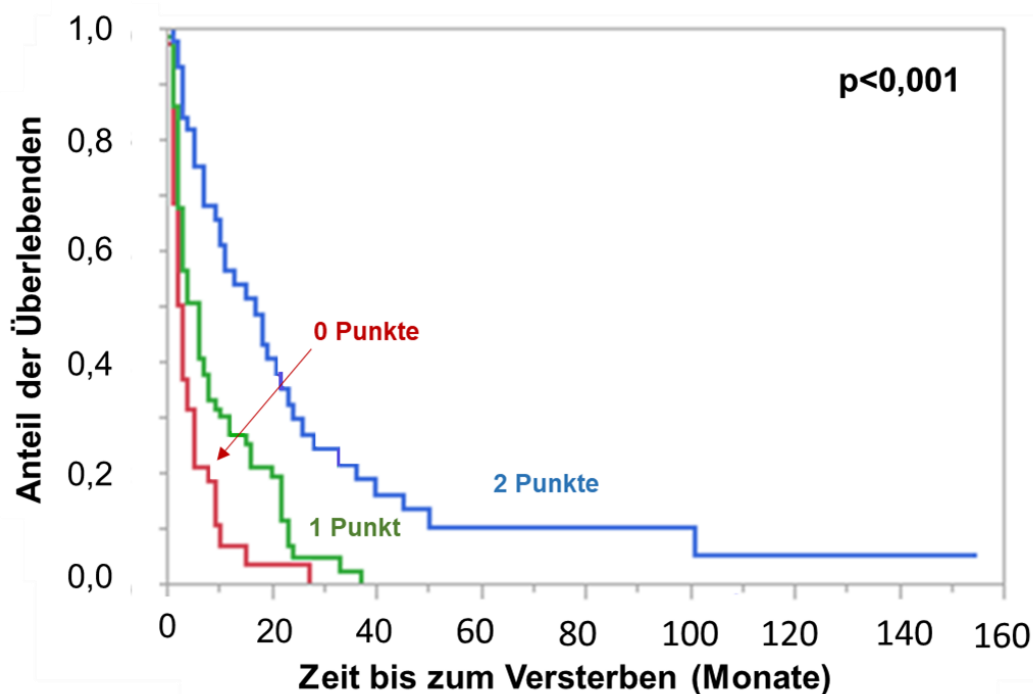


Abbildung 4.5.1 Überlebenskurven der drei prognostischen Gruppen bei Patienten mit Lungenkarzinom und Bestrahlung von Knochenmetastasen

(Rades et al.: An easy-to-use scoring system to estimate the survival of patients irradiated for bone metastases from lung cancer. Translational Lung Cancer Research (accepted March 2020))

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Lebenslauf Rapha Haus

Geboren am 01.10.1990 in Datteln



Ausbildung

04/2017 – 06/2020	Studium Humanmedizin, Universität zu Lübeck 2. Staatsexamen, 04/2019, Abschlussnote: befriedigend 3. Staatsexamen, 05/2020, Abschlussnote: gut
03/2014 – 03/2017	Studium Humanmedizin, Johannes Gutenberg-Universität Mainz 1. Staatsexamen, 04/2016, Abschlussnote: gut
11/2011 – 07/2013	Ausbildung zur Rettungsassistentin ASB Dortmund und ResQuality Essen
2001 – 2010	Abitur Reinoldus-Schiller-Gymnasium Dortmund Abschlussnote: 1,7

Praktische Erfahrung im Studium

05/2019 - 04/2020	Praktisches Jahr Innere Medizin: UKSH Lübeck Anästhesie: Sana Kliniken Lübeck Chirurgie: Sana Kliniken Lübeck
09/2017 - 10/2017 und 07/2018 - 08/2018	Hausarztfamulatur Dr. med. Hanna Schulz Fachärztin für Innere Medizin, Lübeck

02/2018 - 03/2018	Ambulante Famulatur Interdisziplinäre Notaufnahme (Bereich Innere Medizin), UKSH Lübeck
02/2017 - 03/2017	Krankenhausfamulatur Klinik für Anästhesiologie (Bereich Neurochirurgie) Universitätsklinikum Mainz
09/2016 - 10/2016	Krankenhausfamulatur Zentrum für Kardiologie, Universitätsklinikum Mainz

Berufserfahrung

06/2017 – 05/2019	Studentische Hilfskraft Schlaflabor der Klinik für HNO, UKSH Lübeck
05/2016 – 03/2017	Studentische Hilfskraft Studienzentrum Angiologie, Universitätsklinikum Mainz
10/2013 – 03/2014	Rettungsassistentin im Hauptamt ASB Dortmund

Promotion und Publikationen

10/2017 – 11/2020	Promotion , Klinik für Strahlentherapie, UKSH Lübeck " Prognostische Faktoren und neue tumorspezifische Scores für das Überleben von Patienten mit Bestrahlung von Knochenmetastasen" Betreuer und Doktorvater: Prof. Dr. Dirk Rades
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11/2019	Publikation BMC Cancer Dirk Rades, Rapha Haus, Steven E. Schild, Stefan Janssen: Prognostic factors and a new scoring system for survival of patients irradiated for bone metastases. BMC Cancer 19, 1156
01/2020	Publikation Anticancer Research Stefan Janssen, Rapha Haus, Steven E. Schild, Dirk Rades: A Simple Clinical Instrument to Predict the Survival Probability of Breast Cancer Patients Receiving Radiotherapy for Bone Metastases. Anticancer Research 40, 367-371
01/2020	Publikation Anticancer Research Rapha Haus, Stefan Janssen, Steven E. Schild, Dirk Rades: A Disease-specific Score for Estimating Survival after Irradiation of Bone Metastases from Colorectal Cancer. Anticancer Research 40, 287-291
03/2020	Publikation In vivo Rapha Haus, Stefan Janssen, Steven E. Schild, Dirk Rades: Eastern Cooperative Oncology Group Performance Score is Associated with Survival after Radiotherapy of Bone Metastases from Prostate Cancer. In vivo 34, 679-682
08/2020	Publikation Translational Lung Cancer Research Dirk Rades, Rapha Haus, Stefan Janssen, Steven E. Schild: An easy-to-use scoring system to estimate the survival of patients irradiated for bone metastases from lung cancer. Translational Lung Cancer Research 9(4), 1067-1073

RESEARCH ARTICLE

Open Access



Prognostic factors and a new scoring system for survival of patients irradiated for bone metastases

Dirk Rades^{1*}, Rapha Haus¹, Steven E. Schild² and Stefan Janssen^{1,3}

Abstract

Background: Personalized therapy for bone metastases should consider the patients' remaining lifespan. Estimation of survival can be facilitated with scoring tools. A new tool was developed, specifically designed to estimate 12-month survival.

Methods: In 445 patients irradiated for bone metastases, radiotherapy regimen plus 13 factors (age, gender, Karnofsky performance score (KPS), primary tumor type, interval between cancer diagnosis and RT of bone metastases, visceral metastases, other (non-irradiated) bone metastases, sites of bone metastases, number of irradiated sites, pathological fracture, fractionation of RT, pre-RT surgery, pre-RT administration of bisphosphonates/denosumab, pre-RT systemic anticancer treatment) were retrospectively analyzed for survival. Factors achieving significance ($p < 0.05$) or borderline significance ($p < 0.055$) on multivariate analysis were used for the scoring system. Twelve-month survival rates were divided by 10 (factor scores); factor scores were summed for each patient (patient scores).

Results: On multivariate analysis, survival was significantly associated with KPS (hazard ratio (HR) 1.91, $p < 0.001$) and primary tumor type (HR 1.12, $p < 0.001$); age achieved borderline significance (HR 1.14, $p = 0.054$). These factors were used for the scoring tool. Patient scores ranged from 8 to 17 points. Three groups were designated: 8–9 (A), 10–14 (B) and 15–17 (C) points. Twelve-month survival rates were 9, 38 and 72% ($p < 0.001$); median survival times were 3, 8 and 24 months.

Conclusions: This new tool developed for patients irradiated for bone metastases at any site without spinal cord compression allows one to predict the survival of these patients and can aid physicians when assigning the treatment to individual patients.

Keywords: Bone metastases, Radiotherapy, Survival, Prognostic factors, Scoring system

Background

The concept of personalized cancer care has become very popular during the last decade, particularly for patients with metastatic disease. The two most common metastatic sites treated by radiation oncologists are brain and bone. Bone metastases are quite common in adult cancer patients and occur in up to 70% of patients with breast or prostate cancer and up to 40% of patients with renal cell carcinoma during their malignant disease [1, 2]. Many of these patients

receive radiotherapy (RT), either alone or, for example, in the case of an impending pathological fracture preceded by surgery. For radiotherapy of bone metastases, different dose-fractionation regimens are applied worldwide including single-fraction RT (e.g. 1×8 Gy), short-course multi-fraction regimens lasting for about 1 week (e.g. 5×4 Gy and 6×4 Gy) and longer-course regimens mostly lasting for 2 to 4 weeks (e.g. 10×3 Gy, $14\text{--}15 \times 2.5$ Gy and $18\text{--}20 \times 2$ Gy) [2]. Major goals of radiotherapy for bone metastases include relief of symptoms (mainly pain) and prevention of complications such as pathological fractures and spinal cord compression. Based on the results of several meta-analyses comparing single-fraction to multi-fraction

* Correspondence: rades.dirk@gmx.net

¹Department of Radiation Oncology, University of Lübeck, Ratzeburger Allee 160, D-23538 Lübeck, Germany

Full list of author information is available at the end of the article



RT, single-fraction RT is recommended for uncomplicated painful bone metastases, since single-fraction RT was similarly effective in decreasing pain as multi-fraction regimens [3–5]. However, re-irradiation was given significantly more often after single-fraction than after multi-fraction RT. Moreover, in a randomized trial recalcification of osteolytic bone was more pronounced after longer-course RT than after single-fraction RT [6]. The need for re-treatment and recalcification of osteolytic bone appear less important for patients with a short expected survival and single-fraction RT is considered their best option, since these patients likely do not live long enough to experience long term problems [2]. Thus, it is important to account for a patient's remaining lifespan when personalizing treatment approach including the appropriate RT-regimen. Prognostic factors of survival and scoring instruments are very helpful for radiation oncologists in decision making. Estimation of a patient's survival prognosis is of great value also for the patients themselves and their relatives when taking part in selection of treatment and planning their remaining life.

Very few scoring tools are currently available. One of the three most recent tools was developed from patients treated before 1999 and likely does not reflect the impact of modern targeted therapies on survival of cancer patients [7–9]. This aspect likely applies also to another most recently presented scoring tool, which was created from patients irradiated between 2001 and 2010 [10], and to a certain extent also to the third study including patients treated between 2000 and 2013 [11]. In the latter study, patients receiving orthopedic surgery without radiotherapy were included, which may have led to a treatment-related selection bias [11]. In the present study, all patients had received radiotherapy. Moreover, the patients were treated more recently than in these three prior studies, i.e. between 2009 and 2017. Additionally, different potential prognostic factors and dose-fractionation regimens were included in the present study compared to the previous studies. In contrast to one of the most recent previous scores [10], patients with metastatic spinal cord compression (MSCC) were excluded from the present study, since validated specific survival scores for MSCC already exist [12–14]. Moreover, patients with MSCC generally have worse survival prognoses than those patients with non-MSCC bone metastases and should be considered separately [2, 15]. Thus, the scoring instrument developed in this study can be considered supplementary to existing tools designed for estimating survival of patients irradiated for bone metastases.

Methods

The data of 445 patients treated with fractionated RT for symptomatic (painful) bone metastases without spinal cord compression from a solid tumor at two

German institutions between 2009 and 2017 were retrospectively analyzed. The study was approved by the ethics committee of the University of Lübeck and performed in accordance with the Helsinki Declaration. Since this is a retrospective study in a palliative situation, the majority of patients died prior to the collection of the data for this study. Moreover, the data used for the study were anonymized after completion of the data entry. Therefore, the ethics committee approved the study without requesting written informed consent to participate from the patients. Criteria for inclusion in this study included evidence of bone metastases requiring palliative RT and confirmation of bone metastases by magnetic resonance imaging or computed tomography (CT). Patients with hematologic malignancies were excluded. Radiotherapy was performed with 6–18 MV photon beams from a linear accelerator after CT-based treatment planning. In Germany, the vast majority of patients with bone metastases are treated with fractionated RT, and single-fraction RT is generally limited to few patients with an extraordinarily poor estimated survival. Since fractionated RT is the standard treatment for bone metastases in the centers participating in this study and single-fraction RT represents a major exception, patients receiving single-fraction RT were not included in the present study to reduce the risk of a potential selection bias. The fractionation-regimen of RT (short-course with 5–6 × 4 Gy vs. longer-course RT with 30–40 Gy in 10–20 fractions, mainly (86%) 10 × 3 Gy and 14–15 × 2.5 Gy) plus 13 pre-RT factors were investigated for potential associations with survival. These factors included age at the time of RT (≤ 60 vs. 61–70 vs. > 70 years), gender, Karnofsky performance score (KPS) (≤ 70 vs. 80–100), primary tumor type ($N \geq 20$) (breast cancer vs. prostate cancer vs. lung cancer vs. renal cell carcinoma vs. colorectal cancer vs. other tumors), interval between cancer diagnosis and RT of bone metastases (≤ 8 vs. ≥ 9 months, median interval = 9 months), visceral metastases (no vs. yes), other (non-irradiated) bone metastases (no vs. yes), location of irradiated bone metastases (spinal site(s) only vs. extraspinal site(s) with or without spinal site(s)), number of irradiated sites (single vs. multiple), pathological fracture (no vs. yes), pre-RT surgery (no vs. yes), pre-RT administration of bisphosphonates/denosumab (no vs. yes), and pre-RT systemic anticancer treatment (no vs. yes). The distributions of these factors are shown in Table 1. The type of pre-RT systemic treatment (immunotherapy, chemotherapy, targeted therapy) was not considered as a separate factor, since this would apply to only 71% of the patients (Table 1). Moreover, since the type of systemic treatment is closely related to the type of primary tumor, tumor type and type of systemic treatment will likely be confounding variables. Comorbidity scores such as the

Table 1 Distributions of the factors investigated for potential associations with survival

	N patients (%)
Age	
≤ 60 years	132 (30)
61–70 years	131 (29)
> 70 years	182 (41)
Gender	
Female	226 (51)
Male	219 (49)
Karnofsky performance score	
≤ 70	165 (37)
80–100	237 (53)
Unknown	43 (10)
Type of primary tumor	
Breast cancer	125 (28)
Prostate cancer	59 (13)
Lung cancer	138 (31)
Renal cell carcinoma	24 (5)
Colorectal cancer	20 (4)
Other tumors	79 (18)
Interval between cancer diagnosis and RT of bone metastases	
≤ 8 months	226 (51)
≥ 9 months	219 (49)
Visceral metastases at the time of RT	
No	187 (42)
Yes	258 (58)
Other (non-irradiated) bone metastases at the time of RT	
No	109 (24)
Yes	334 (75)
Unknown	2 (< 1)
Location of irradiated bone metastases	
Spinal site(s) only	170 (38)
Extraspinal site(s) with or without spinal site(s)	275 (62)
Number of irradiated sites	
Single	186 (42)
Multiple	259 (58)
Pathological fracture	
No	309 (69)
Yes	136 (31)
Pre-RT surgery (no vs. yes)	
No	347 (78)
Yes	96 (22)
Unknown	2 (< 1)
Pre-RT administration of bisphosphonates/denosumab	
No	268 (60)

Table 1 Distributions of the factors investigated for potential associations with survival (*Continued*)

	N patients (%)
Yes	167 (38)
Unknown	10 (2)
Pre-RT systemic anticancer treatment	
No	127 (29)
Yes	317 (71)
Unknown	1 (< 1)
Fractionation of RT	
Short-course RT	43 (10)
Longer-course RT	402 (90)

Charlson comorbidity index or the age-adjusted Charlson comorbidity index were not considered, since these scores are generally dominated by the presence of a metastatic solid tumor, which applies to all patients of the present study [16, 17]. Moreover, since a high comorbidity index is usually associated with a poor performance score, comorbidity score and performance score will likely be confounding variables.

Survival time was referenced from the first day of RT. Survival rates were calculated with the Kaplan-Meier method, and differences between the Kaplan-Meier curves were calculated with the log-rank test (univariate analyses). Those factors that achieved significance ($p < 0.05$) or borderline significance ($p < 0.055$) on univariate analysis were included in a multivariate analysis performed with the Cox proportional hazards model. Factors achieving significance ($p < 0.05$) or borderline significance ($p < 0.055$) on multivariate analysis were used to generate the scoring system.

Results

On univariate analyses, improved survival was significantly associated with female gender ($p < 0.001$), KPS 80–100 ($p < 0.001$), more favorable primary tumor type (breast cancer, prostate cancer, renal cell carcinoma) ($p < 0.001$), longer interval (≥ 9 months) between cancer diagnosis and RT of bone metastases ($p = 0.044$), absence of visceral metastases ($p = 0.002$), absence of a pathological fracture ($p = 0.049$) and longer-course RT ($p = 0.022$). The complete results (6-month and 12-month survival rates) of the univariate analyses are shown in Table 2.

On multivariate analysis (Cox proportional hazards model, Table 3), survival was significantly associated with KPS (hazard ratio (HR) 1.91, 95%-confidence interval (CI) 1.51–2.41, $p < 0.001$) and primary tumor type (HR 1.12, 95%-CI 1.07–1.17, $p < 0.001$). Age achieved borderline significance (HR 1.14, 95%-CI 1.00–1.30, $p = 0.054$). Therefore, these three factors were used for creating the scoring

Table 2 Univariate analyses of survival

	Survival rate at 6 months (%)	Survival rate at 12 months (%)	<i>p</i> -value
Age			
≤ 60 years	61	48	
61–70 years	60	44	
> 70 years	60	38	0.052
Gender			
Female	64	50	
Male	56	35	< 0.001
Karnofsky performance score			
≤ 70	42	23	
80–100	70	55	< 0.001
Type of primary tumor			
Breast cancer	78	64	
Prostate cancer	78	52	
Lung cancer	46	30	
Renal cell carcinoma	79	63	
Colorectal cancer	45	25	< 0.001
Other tumors	42	22	
Interval between cancer diagnosis and RT of bone metastases			
≤ 8 months	54	40	
≥ 9 months	66	45	0.044
Visceral metastases at the time of RT			
No	67	49	
Yes	55	38	0.002
Other (non-irradiated) bone metastases at the time of RT			
No	53	36	
Yes	63	45	0.23
Location of irradiated bone metastases			
Spinal site(s) only	59	40	
Extraspinal site(s) with or without spinal site(s)	61	44	0.95
Number of irradiated sites			
Single	59	43	
Multiple	61	42	0.41
Pathological fracture			
No	61	46	
Yes	57	35	0.049
Pre-RT surgery (no vs. yes)			
No	57	42	
Yes	72	48	0.17
Pre-RT administration of bisphosphonates/denosumab			
No	56	41	
Yes	65	45	0.55
Pre-RT systemic anticancer treatment			
No	55	40	

Table 2 Univariate analyses of survival (Continued)

	Survival rate at 6 months (%)	Survival rate at 12 months (%)	<i>p</i> -value
Yes	62	44	0.33
Fractionation of RT			
Short-course RT	40	26	
Longer-course RT	62	45	0.022

Bold values = significant *p*-values

tool. Since the KPS was not known in 43 patients (9.7%), the scoring system was built using the data of 402 patients. The 12-month survival rates of each significant factor (in percent) were divided by 10 to obtain the factor scores (Table 4). The factor scores were added for each patient, and the patient scores were received that ranged from 8 to 17 points (Fig. 1). Based on the patient scores, three prognostic groups were designated: 8–9 points (group A), 10–14 points (group B) and 15–17 points (group C). The 12-month survival rates of these groups were 9, 38 and 72%, respectively (Fig. 2, $p < 0.001$). The 6-month survival rates were 30, 54 and 85%, respectively, and the median survival times were 3 months, 8 months and 24 months, respectively ($p < 0.001$).

Discussion

Bone metastases are common in cancer patients with advanced disease. Radiotherapy, either alone or following orthopedic surgery, is the most frequently used treatment to control symptoms and prevent complications. In order to provide a treatment that is optimally tailored to a patient's individual situation, it is important to estimate his remaining lifespan as precisely as possible. This can be facilitated with prognostic tools. Some survival scores specifically designed for patients irradiated for bone metastases are available. Most scores are relatively old and likely do not consider the potential impact of modern targeted therapies on survival of these patients [11, 12].

In 2005, scoring tool was developed from 342 patients of the Dutch Bone Metastasis Study who were irradiated with 1×8 Gy or 6×4 Gy for spinal metastases without major neurologic impairment and vertebral collapse between 1996 and 1998 [18]. Based on three independent significant predictors, i.e. KPS ($p < 0.001$), primary tumor type ($p < 0.001$) and visceral metastases ($p = 0.02$), three prognostic groups were formed with median survival times of 3.0, 9.0 and 18.7 months, respectively. For several years, this was the only well-recognized survival score developed in patients irradiated for bone metastases. However, in contrast to our present study, it was limited to metastases of the spine and did not consider other sites such as pelvis, ribs, shoulders, extremities and skull. Therefore, the prognostic groups identified in that study may not be applicable to patients with metastatic sites

Table 3 Multivariate analyses of survival (Cox proportional hazards model)

	Hazard ratio	95% confidence interval	p-value
Age	1.14	1.00–1.3	0.054
Gender	1.20	0.95–1.51	0.13
Karnofsky performance score	1.91	1.51–2.41	< 0.001
Type of primary tumor	1.12	1.07–1.17	< 0.001
Interval between cancer diagnosis and RT of bone metastases	1.14	0.92–1.42	0.23
Visceral metastases at the time of RT	1.19	0.96–1.49	0.12
Pathological fracture	1.19	0.93–1.51	0.16
Fractionation of RT	1.02	0.86–1.22	0.84

Bold values = significant p-values

other than the spinal column [18]. In 2014, two additional survival scores for patients receiving radiotherapy for bone metastases were presented [7, 10]. One score was also developed from patients treated within the Dutch Bone Metastasis Study with 1×8 Gy or 6×4 Gy, this time from the entire cohort of 1157 patients [7]. Several independent predictors of survival were identified including gender, primary tumor type, KPS, visceral metastases and two self-rating scores for patients regarding general health and overall valuation of life. Since this model appeared very complex, the authors added a simpler tool including only KPS and primary tumor type. They stated the 3 to 18 months survival rates for breast cancer, prostate cancer, lung cancer and other cancer patients related to three KPS levels (90–100, 70–80 and 20–60) but did not create prognostic groups that are usually part of a scoring instrument. The second tool published in 2014 included the retrospective data of 1043 patients treated for spinal metastases between 2001

and 2010 [10]. Ninety-nine percent of the patients received RT with or without surgery that was mainly delivered as single-fraction RT with 1×8 Gy (43%) or short-course RT with 2×8 Gy (16%) or $5-6 \times 4$ Gy (31%). Four categories were designated based on KPS (80–100 vs. 10–70) and visceral/brain metastases (no vs. yes) with median survival times of 31.2, 15.4, 4.8 and 1.6 months, respectively. Also this score may not be applicable to patients with bone metastases at sites other than spinal column. In contrast to the other survival scores for patients irradiated for bone metastases, 49% of the patient used for this tool had symptomatic MSCC with motor and/or sensory deficits [10]. Due to the fact that in general patients with MSCC have worse survival prognoses than patients with painful bone metastases and no MSCC [2, 15], we believed that these cohorts should not be mixed for the development of a survival score and that separate tools for patients with bone metastases with and without MSCC should be provided to facilitate optimal personalization of the treatment. The most recent survival score for patients irradiated for bone metastases was presented in 2018 and was created from the data of 1520 patients treated for symptomatic metastases of the long bones between 2000 and 2013 [11]. Based on three independent prognostic factors, clinical profile, KPS and visceral/brain metastases, four categories were designed with median survival times of 21.9, 10.5, 4.6 and 2.2 months, respectively. Since this tool was developed from patients with long bone metastases only, its applicability may not be generalized to patients with bone metastases at other sites. Moreover, the fact that 130 patients (8.6%) received surgery alone without radiotherapy may have led to a selection bias during the development of the scoring tool.

Considering the existing scoring instruments, we feel that an additional tool for patients irradiated for bone metastases that considers all sites but excludes patients with MSCC and those not receiving radiotherapy would be particularly useful. The present study was performed to close this gap. The new tool was specifically designed to predict the 12-month survival probability of patients receiving

Table 4 Survival rates at 12 months of the prognostic factors found significant or almost significant on multivariate analysis and the corresponding factor scores

Prognostic factor	Survival rate at 12 months (%)	Factor score
Age		
≤ 60 years	48	5
61–70 years	44	4
> 70 years	38	4
Karnofsky performance score		
≤ 70	23	2
80–100	55	6
Type of primary tumor		
Breast cancer	64	6
Prostate cancer	52	5
Lung cancer	30	3
Renal cell carcinoma	63	6
Colorectal cancer	25	3
Other tumors	22	2

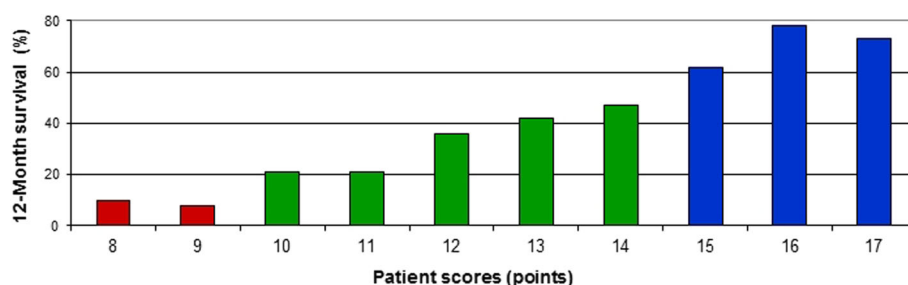


Fig. 1 Patient scores related to the corresponding 12-month survival rates

radiotherapy for bone metastases but can also be used to estimate the 6-month survival. When using this tool, the retrospective nature of the data needs to be considered. Retrospective studies bear the risk of hidden selection biases. To reduce the risk of a fractionation-related bias, only patients treated with fractionated RT were included. Fractionated RT is the standard treatment for bone metastases in the centers contributing to this study, whereas single-fraction RT is used only for a small minority of patients with very limited survival times. In the present study, longer-course RT was associated with a better survival than short-course multi-fraction RT on univariate analysis (Table 2). Although no significant association between the fractionation regimen and survival was found on multivariate analysis (Table 3), a selection bias caused by the fact that longer-course RT was applied more frequently to patients with longer expected survival cannot be completely excluded. Another potential limitation of the study is the fact that the performance score was unknown in 43 patients (9.7%).

For selection of the appropriate dose-fractionation regimen for an individual, one should keep in mind that in a randomized trial, recalcification of the osteolytic bone was more pronounced after longer-course

RT with 10×3 Gy than after single-fraction RT with 1×8 Gy, which is particularly important for patients with favorable survival prognoses [9]. In the present study, patients of group A had the worst prognoses with a median survival time of only 3 months and 6- and 12-month survival rates of only 30 and 9%, respectively. Therefore, the majority of these patients will likely not live long enough to require re-irradiation for bone pain and, therefore, appear good candidates for single-fraction RT. Also patients with very limited survival prognoses were reported to benefit from RT in terms of symptom relief [19, 20]. According to several studies, single-fraction RT with 8 Gy was superior to 4 Gy with respect to pain relief and should be the preferred dose for single-fraction RT of painful bone metastases [21–24]. For patients of group B who had a median survival time of 8 months and an intermediate 12-month survival probability of 38%, single-fraction RT with 1×8 Gy and short-course multi-fraction RT with $5-6 \times 4$ Gy may be considered, depending on patient preference. If recurrent pain occurs after single-fraction RT, a second course of single-fraction RT can be safely administered [25]. However, about 40% of the patients do not benefit from re-irradiation [26]. Patients of group C had very favorable survival prognoses with a median survival time of 24 months and a 12-month survival probability of 72%. Thus, many of these patients will likely live long enough to experience recurrent bone pain in irradiated sites after single-fraction RT or short-course RT. Therefore, these patients appear more suitable for longer-course RT with total doses of 30–40 Gy and doses per fraction of ≤ 3 Gy. Particularly patients of group C with spinal metastases may be candidates for stereotactic body RT (SBRT) rather than conventional RT, since SBRT can result in considerable long-term control of pain [27]. When following these suggestions, the retrospective nature of the present study should be considered. Moreover, the results may not be generalized to patients treated with single-fraction RT or SBRT. Since the predictive factors used for the scoring tool include the primary

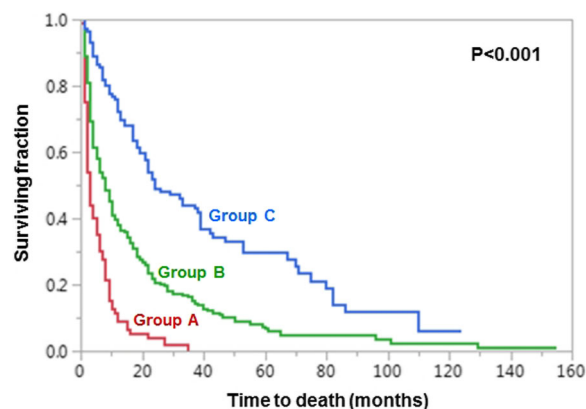


Fig. 2 Kaplan-Meier curves of the three prognostic groups A (8–9 points), B (10–14 points) and C (15–17 points). The *p*-value was calculated with the log-rank test

tumor type, estimation of a patient's prognosis may be made by experienced (radiation) oncologists, who are specialized in the treatment of a specific tumor entity, without using this new tool.

Conclusion

This new tool allows predict the survival prognoses of patients to be irradiated for bone metastases without MSEC and allow physicians to choose the best treatment for an individual patient. It was designed to be used for bone metastases at any site. Since visceral metastases were not included in this score, a complete staging of the malignant disease is not required, which facilitates the use of this tool. External validation is planned to be performed in Europe and North America within the next years.

Abbreviations

CI: Confidence interval; CT: Computed tomography; HR: Hazard ratio; KPS: Karnofsky performance score; MSEC: Metastatic spinal cord compression; RT: Radiotherapy; SBRT: Stereotactic body radiation therapy

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Not applicable.

Authors' contributions

D.R., R.H., S.E.S. and S.J. participated in the design of the study. D.R., R.H. and S.J. provided data for the study. D.R., R.H., S.E.S. and S.J. performed the analyses and the interpretation of the data. D.R. and S.E.S. drafted the manuscript, which has been reviewed and approved in its final form by all other authors.

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Availability of data and materials

The data analyzed for this paper cannot be shared on a publicly available repository due to data protection regulations. According to the local ethics committee, only the evaluation of anonymized data is allowed for this study.

Ethics approval and consent to participate

The study was approved by the ethics committee of the University of Lübeck (reference number: 18-254A). The study was conducted in accordance with the principles laid out in the Declaration of Helsinki and in accordance with the principles of Good Clinical Practice.

Consent for publication

Not applicable.

Competing interests

D.R. and S.J. are associate editors of BMC Cancer. Otherwise, the authors declare that they have no competing interest related to the study presented here.

Author details

¹Department of Radiation Oncology, University of Lübeck, Ratzeburger Allee 160, D-23538 Lübeck, Germany. ²Department of Radiation Oncology, Mayo Clinic Scottsdale, Scottsdale, AZ, USA. ³Medical Practice for Radiotherapy and Radiation Oncology, Hannover, Germany.

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A Simple Clinical Instrument to Predict the Survival Probability of Breast Cancer Patients Receiving Radiotherapy for Bone Metastases

STEFAN JANSSEN^{1,2}, RAPHA HAUS¹, STEVEN E. SCHILD³ and DIRK RADES¹

¹Departments of Radiation Oncology, University of Lübeck, Lübeck, Germany;

²Medical Practice for Radiotherapy and Radiation Oncology, Hannover, Germany;

³Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, U.S.A.

Abstract. *Background/Aim:* Individualization of treatment may improve the outcome of patients with bone metastases from breast cancer. To support physicians when selecting individualized programs for these patients, a simple instrument for predicting survival was created. *Patients and Methods:* In 126 female patients with breast cancer irradiated for bone metastases, 11 characteristics were evaluated with respect to survival. *Results:* On Cox regression analysis, Eastern Cooperative Oncology Group performance score (0-1 vs. ≥ 2 ; $p=0.032$) and visceral metastases (absence vs. presence; $p=0.017$) were independently associated with survival and incorporated into the scoring instrument. Three prognostic groups (0, 1 or 2 points) were designated with 12-month survival rates of 38%, 57% and 91%, and 24-month survival rates of 32%, 36% and 80%, respectively ($p<0.001$). *Conclusion:* This easy-to-use scoring instrument allows physicians to estimate the lifespan of patients irradiated for bone metastases from breast cancer and can facilitate individualization of their treatment.

Bone metastases are very common in patients with breast cancer and can be found in up to 70% of these patients during their lifetimes (1, 2). Although patients with bone metastases from breast cancer have more favorable prognoses than those with bone metastases from other types of solid cancer, their outcomes should be improved further (1). In addition to the administration of novel anticancer agents, this goal may be achieved with the comparatively

new approach of personalized care including treatment regimens tailored to the specific needs of each patient. To choose the best possible treatment for an individual, one should be aware of the life expectancy. For patients with a short-expected lifespan, the treatment program should be as least onerous and as short as is practical. For patients with a longer expected lifetime, long-term local control and late treatment-related sequelae need to be considered to a greater extent.

To estimate a patient's life expectancy, survival scores have been established for different oncological situations, including metastatic disease (3-12). Considering the variations in biological behavior of the different cancer types, it is generally agreed that diagnosis-specific scoring instruments for each major entity would be desirable, ideally for each type of metastasis. For patients with metastatic breast cancer, specific prognostic instruments have already been developed for radiotherapy of brain metastases and vertebral metastasis associated with epidural spinal cord compression (13-19). This study was performed to contribute to optimal individualization of the treatment for patients with breast cancer. The goal was to add a specific survival score for those with breast cancer requiring radiation treatment for bone metastases not associated with spinal cord compression.

Patients and Methods

Eleven characteristics were retrospectively analyzed for potential associations with survival in a series of 126 females who received conventional multi-fraction longer-course radiotherapy for bone metastases from breast cancer. Dose-fractionation programs included 10×3 Gy over 2 weeks ($n=77$), 12-13×3.0 Gy over 2.5 weeks ($n=4$), 14-15×2.5 Gy ($n=26$) or 15×2.0 Gy ($n=5$) over 3 weeks and 18-20×2.0 Gy over 3.5-4 weeks ($n=14$). Patients with spinal metastases associated with cord compression were not included in this study, which was approved by the Ethics Committee of the University of Lübeck (18-254A, extension in 2019). The 11 potential prognostic characteristics, which are summarized in Table

Correspondence to: Professor Dirk Rades, MD, Department of Radiation Oncology, University of Lübeck, Ratzeburger Allee 160, 23562 Lübeck, Germany. Tel: +49 45150045401, Fax: +49 45150045404, e-mail: rades.dirk@gmx.net

Key Words: Breast cancer, survival probability, radiotherapy, bone metastases, scoring instrument.

Table I. The potential prognostic factors and their distribution.

		Patients, n (%)
Age at radiotherapy	≤65 Years	65 (52)
	≥66 Years	61 (48)
ECOG performance score	0-1	86 (68)
	≥2	40 (32)
Period from breast cancer diagnosis until irradiation of bone metastases	≤39 Months	63 (50)
	≥40 Months	63 (50)
Visceral metastases	No	62 (49)
	Yes	64 (51)
Non-irradiated bone metastases	No	27 (21)
	Yes	99 (79)
Location of bone metastases	Spine	39 (31)
	Extra-spinal	31 (25)
	Both	56 (44)
Number of irradiated metastatic sites	1	37 (29)
	≥2	89 (71)
Pathological fracture	No	83 (66)
	Yes	43 (34)
Preceding surgery of bone metastases	No	90 (71)
	Yes	36 (29)
Pre-radiotherapy	No	57 (45)
bisphosphates/denosumab	Yes	69 (55)
Pre-radiotherapy systemic treatment	No	21 (17)
	Yes	105 (83)

ECOG: Eastern Cooperative Oncology Group.

I, included: i) age on the first day of radiotherapy (≤65 years vs. ≥66 years, median=65 years), ii) performance score according to the Eastern Cooperative Oncology Group (ECOG 0-1 vs. ≥2), iii) period from breast cancer diagnosis until irradiation of bone metastases (≤39 vs. ≥40 months, median=39.5 months), iv) visceral metastases (no vs. yes) or v) additional non-irradiated bone (no vs. yes) metastases, vi) location of bone metastases (spine vs. other and both), vii) number of irradiated metastatic sites (1 site vs. ≥2 sites), viii) pathological fracture(s) (no vs. yes), ix) preceding surgery of bone metastases (no vs. yes), x) pre-radiotherapy treatment with bisphosphates or denosumab (no vs. yes), and xi) pre-radiotherapy systemic treatment (no vs. yes).

The time to death was referenced from the first day of radiotherapy. Statistical analyses were performed with the Kaplan-Meier method and the log-rank test (univariate analyses). Factors that proved to be significant ($p<0.05$) or showed a strong trend ($p<0.06$) for an association with survival were also evaluated in a multivariate manner (Cox regression model). Those characteristics that proved to be independently associated with survival were incorporated in the scoring instrument.

Results

Median follow up times were 16.5 (1-129) months in the entire series and 22 (3-102) months in those patients who were alive at their last follow-up visit. For the entire cohort, the median survival was 27 months. At 6, 12, 18 and 24 months, the survival rates were 80%, 66%, 57% and 51%,

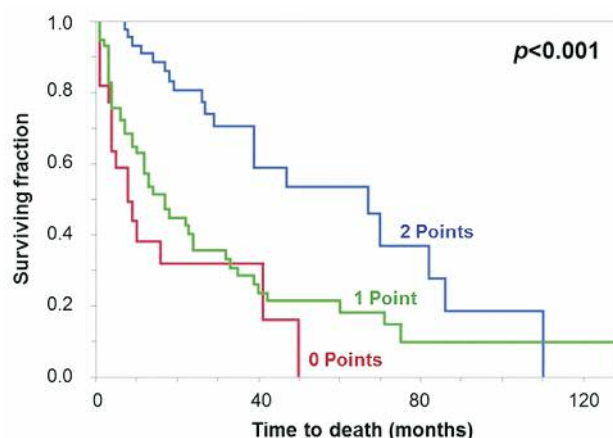


Figure 2. Survival curves obtained with the Kaplan-Meier method for groups of patients with 0 points, 1 point and 2 points.

respectively. An ECOG performance score of 0-1 ($p=0.003$), and absence of visceral metastases ($p=0.005$) were significantly positively associated with survival in the univariate analyses. Additionally, the absence of pathological fracture(s) showed a strong trend for being associated with better survival ($p=0.058$). The univariate analyses of all 11 investigated characteristics are summarized in Table II.

On Cox regression analysis, the ECOG performance score [risk ratio (RR)=1.70, 95% confidence interval (CI)=1.05-2.72), $p=0.032$] and visceral metastases (RR=1.75, 95% CI=1.11-2.79, $p=0.017$) maintained significance. Pathological fracture(s) did not achieve significance (RR=1.40, 95% CI=0.86-2.23, $p=0.17$) in the Cox regression analysis.

The two independent prognostic factors, *i.e.* ECOG performance score and visceral metastases, were incorporated into the scoring instrument. Taking into account the corresponding survival rates, 0 points were given for an ECOG performance score of ≥2 and for the presence of visceral metastases, and 1 point was given for an ECOG performance score of 0-1 and for absence of visceral metastases. Based on these points, three groups were created, namely: 0 points, 1 point and 2 points. The survival rates of these groups at 6, 12, 18 and 24 months are summarized in Table II. The corresponding Kaplan-Meier curves are shown in Figure 1.

Discussion

During recent years, several studies have been carried out to improve the outcomes of patients with metastatic breast cancer (20-24). For patients with breast cancer who require irradiation for bone metastases, a variety of dose-fractionation regimens are available (1). A radiotherapy regimen can be extremely short, such as a single fraction of 8 Gy or 10 Gy, or longer,

Table II. Univariate analyses: Survival rates at 6, 12, 18 and 24 months.

Characteristic	Subgroup	Survival (%) at				p-Value
		6 Months	12 Months	18 Months	24 Months	
Age at radiotherapy	≤65 Years	78	66	62	56	0.88
	≥66 Years	82	67	51	47	
ECOG performance score	0-1	89	76	68	59	0.003
	≥2	60	47	34	34	
Interval from breast cancer diagnosis until irradiation of bone metastases	≤39 Months	79	69	56	50	0.62
	≥40 Months	81	63	57	53	
Visceral metastases	No	87	79	67	65	0.005
	Yes	73	54	46	37	
Other bone metastases	No	78	74	69	64	0.13
	Yes	81	64	54	48	
Type of metastatic sites	Spine	79	68	62	52	0.78
	Extra-spinal	74	68	52	47	
	Both	84	64	56	53	
Number of irradiated sites	1	78	64	49	40	0.22
	≥2	81	67	60	55	
Pathological fracture	No	85	73	63	58	0.058
	Yes	70	53	45	38	
Upfront surgery of bone metastases	No	80	67	58	51	0.89
	Yes	81	65	55	51	
Pre-radiotherapy bisphosphates/denosumab	No	79	70	62	57	0.47
	Yes	81	64	53	46	
Pre-radiotherapy systemic treatment	No	90	80	68	63	0.20
	Yes	78	64	55	49	

ECOG: Eastern Cooperative Oncology Group. Bold indicates significant *p*-values.

lasting for several weeks. These fractionated programs include lower dose per fraction (mainly 2-4 Gy) and higher total doses (mainly 20-40 Gy). When treating a patient with a fractionated regimen, physicians can choose between short-course (*e.g.* 5×4 Gy in 1 week) and longer-course (*e.g.* 10×3 Gy in 2 weeks or 20×2 Gy in 4 weeks) programs. It is generally agreed that for the majority of patients with bone metastases associated with impending or existing pathological fractures, metastatic spinal cord compression or an extensive soft-tissue component (so-called complicated bone metastases), fractionated radiotherapy is appropriate (1). The situation is different when a patient presents with uncomplicated painful bone metastases, *i.e.* without the above stated complications. For alleviating osseous pain in these patients, 1×8 Gy is as effective as fractionated radiotherapy programs. This has been demonstrated in several meta-analyses of randomized trials (25-28). Single-fraction irradiation appears particularly appropriate for patients with a limited survival time to avoid spending much of their short lifespan with radiation treatment. However, following irradiation with 1×8 Gy, a recurrence of the irradiated painful bone metastases was observed about 2.5 to 3 times more often than after fractionated, particularly after longer-course radiotherapy (25, 28). This aspect is particularly

Table III. Survival rates of the different prognostic groups.

Prognostic group	Survival rates (in %) at				p-Value
	6 Months	12 Months	18 Months	24 Months	
0 Points (n=22)	59	38	32	32	<0.001
1 Point (n=58)	72	57	45	36	
2 Points (n=46)	100	91	83	80	

Bold indicates significant *p*-values.

important for longer-term survivors, since according to randomized trials, median duration of control of pain may be longer than 1 year (29, 30).

In addition, remineralization and stabilization of osteolytic metastases following radiotherapy generally takes several months. According to a prospective randomized trial of 107 patients irradiated for bone metastases with either 1×8 Gy or 10×3 Gy, remineralization (relative increase in bone density) was significantly less pronounced after the single-fraction program, *i.e.* 120% compared to 173%

($p < 0.001$) (31). Taking into account that longer-course radiotherapy is superior to single-fraction treatment with respect to local control and successful remineralization, it becomes clear that patients with more favorable survival prognoses appear to be good candidates for longer-course radiation programs with higher total doses such as 10×3 Gy and 20×2 Gy.

To make sure that each patient requiring irradiation for uncomplicated painful bone metastases from breast cancer receives the best personalized regimen, one should be able to estimate survival as precisely as possible. To facilitate this process, a new scoring system was developed particularly for these patients. Patients of the group with 2 points had excellent survival prognoses, with survival rates of 91% at 1 year and 80% at 2 years, respectively. Therefore, these patients can be considered suitable candidates for longer-course radiotherapy. For patients with vertebral metastases leading to spinal cord compression, longer-course programs with doses higher than 30 Gy were reported to result in better local control than 10×3 Gy (32). If this finding also applies to patients with uncomplicated bone metastases, patients achieving 2 points in the current study might be optimally irradiated with 15×2.5 Gy or 20×2 Gy. Of the patients of the 1-point group, 57% survived for 1 year or longer, but only 36% for 2 years or more. These patients may also benefit from radiotherapy with a longer-course; however, 10×3 Gy may be more appropriate. Patients of the group with 0 points had the least favorable survival prognoses, only 38% survived for 1 year or more. Therefore, these patients may be considered for single-fraction or short-course multifraction radiotherapy. When physicians consider these recommendations, it must be noted that the scoring system was created from retrospective data. This may have led to hidden selection biases, although we aimed to reduce such a risk by including only patients who received longer-course radiotherapy.

In summary, this new scoring instrument allows physicians to estimate the lifespan of breast cancer patients to be irradiated for bone metastases and may facilitate individualization of their treatment. This instrument may also contribute to proper stratification of patients to be included in future clinical trials.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there is no conflict of interest related to this study.

Authors' Contributions

S.J., R.H., S.E.S. and D.R. participated in the design of the study. R.H., S.J. and D.R. provided data. D.R. and S.E.S. performed the analyses of the data. S.J., S.E.S. and D.R. drafted the manuscript, which has been reviewed and approved by all Authors.

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A Disease-specific Score for Estimating Survival After Irradiation of Bone Metastases from Colorectal Cancer

RAPHA HAUS¹, STEFAN JANSSEN^{1,2}, STEVEN E. SCHILD³ and DIRK RADES¹

¹Department of Radiation Oncology, University of Lübeck, Lübeck, Germany;

²Medical Practice for Radiotherapy and Radiation Oncology, Hannover, Germany;

³Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, U.S.A.

Abstract. *Background/Aim:* Estimating survival is important for treatment personalization in patients with metastatic cancer. In this study, we aimed to develop a survival score for patients irradiated for bone metastases from colorectal cancer. *Patients and Methods:* Eleven factors were retrospectively analyzed in 25 patients, including age, gender, Eastern Cooperative Oncology Group performance score, tumor site, time between diagnosis of colorectal cancer and irradiation, visceral or other bone metastases, type and number of irradiated sites, upfront surgery and previous systemic treatment. *Results:* On multivariate analysis, performance score ($p=0.005$) and previous systemic treatment ($p=0.007$) were significantly associated with survival and used for the score. One point (performance score 0-1 or no previous systemic treatment) or 0 points (performance score ≥ 2 or previous systemic treatment) were assigned resulting in 0, 1 or 2 points. Six-month survival rates of these groups were 0%, 64% and 100%, respectively. *Conclusion:* This new survival score can support physicians during personalization of treatment for patients with bone metastases from colorectal cancer.

Due to improved treatment of primary tumors and loco-regional recurrences, many cancer patients have better survival prognoses and may live long enough to experience metastatic spread (1). For these patients, personalized treatment approaches have become more popular during the last decade aiming to meet the personal needs of an individual patient. The remaining lifetime is an important aspect that needs to be

considered when designing a personalized treatment concept. For patients with a short survival time, the treatment regimen should be little burdensome and as short as reasonably possible. For patients with more favorable prognoses, longer-term local control and prevention of late treatment-related toxicities become more important. Estimation of the survival prognosis of an individual patient may be considerably facilitated with survival scores. In order to allow for an optimal personalization of a treatment program for cancer patients with metastatic disease, specific scores should ideally be available for the different metastatic sites and the different primary tumor types. Colorectal cancer is one of the most common primary tumor types in industrial nations (1). Bone metastases from colorectal cancer are comparatively rare and require more attention (1, 2). The present study was performed to develop a specific survival score for colorectal cancer patients with bone metastases.

Patients and Methods

Twenty-five patients who were treated with radiotherapy for bone metastases from colorectal cancer without spinal cord compression were included in the present study. Their data were retrospectively analyzed to identify significant prognostic factors of survival following radiotherapy and develop a prognostic score. The study has been approved by the local ethics committee. Radiotherapy was administered as a multi-fraction treatment with either 6×4 Gy ($n=1$), 10×3 Gy ($n=5$), 12×3 Gy ($n=1$), 14-15×2.5 Gy ($n=16$), 15×2 Gy ($n=1$) or 20×2.0 Gy ($n=1$). In this cohort, eleven factors (Table I) were evaluated for a potential impact on survival, including i) age (≤ 65 vs. ≥ 66 years), ii) gender, iii) Eastern Cooperative Oncology Group (ECOG) performance score (0-1 vs. ≥ 2) (3), iv) primary tumor site (colon vs. rectum), v) time between diagnosis of colorectal cancer and radiotherapy for bone metastases (≤ 12 vs. ≥ 13 months, median=12 months), vi) visceral metastases (no vs. yes), vii) other bone metastases (no vs. yes), viii) type of metastatic sites (spinal vs. extraspinal vs. both), ix) number of irradiated sites of bone metastases (1 vs. ≥ 2), x) upfront surgery of irradiated bone metastases (no vs. yes) and xi) systemic treatment prior to irradiation (no vs. yes).

Correspondence to: Professor Dirk Rades, MD, Department of Radiation Oncology, University of Lübeck, Ratzeburger Allee 160, 23562 Lübeck, Germany. Tel: +49 45150045401, Fax: +49 45150045404, e-mail: rades.dirk@gmx.net

Key Words: Colorectal cancer, bone metastases, radiotherapy, survival, prognostic score.

Survival was calculated since the first day of radiotherapy. Univariate analyses of survival were performed using the Kaplan–Meier method and the log-rank test. Factors that proved to be significant ($p<0.05$) or showed at least a trend ($p<0.10$) on univariate analyses were included in the multivariate analysis (Cox proportional hazards model). Those factors achieving significance in the multivariate analysis were used for the development of the prognostic score.

Results

In the entire cohort, the median follow-up time was 4 months (range=0-65 months). The survival rates at 3, 6, 9 and 12 months were 56%, 44%, 32% and 23%, respectively. On univariate analyses, a better (0-1) ECOG performance score ($p=0.005$), absence of other bone metastases ($p=0.001$) and a lower number ($n=1$) of irradiated sites of bone metastases ($p=0.049$) were significantly associated with favorable survival prognoses. In addition, no systemic treatment prior to radiotherapy showed a trend for a favorable survival ($p=0.067$). The results of the univariate analyses are shown in Table II.

On multivariate analysis, the ECOG performance score [hazard ratio (HR)=6.97, 95%confidence interval (CI)=1.75-36.34, $p=0.005$] and the systemic treatment prior to radiotherapy (HR=7.50, 95%CI=1.64-60.17, $p=0.007$) were significant. Other bone metastases (HR=2.05, 95%CI=0.51-9.74, $p=0.32$) and the number of irradiated sites of bone metastases (HR=1.25, 95%CI=0.35-4.54, $p=0.73$) did not achieve significance in the multivariate analysis.

Thus, the ECOG performance score and the systemic treatment prior to radiotherapy were used for the development of the scoring tool. Based on the outcomes with respect to survival, 1 point (favorable outcome: ECOG performance score of 0-1 or no previous systemic treatment) or 0 points (unfavorable outcome: ECOG performance score of ≥ 2 or previous systemic treatment) were assigned resulting in three prognostic groups of 0 points ($n=7$), 1 point ($n=11$) or 2 points ($n=2$). The survival data of the three groups are shown in Table III and Figure 1.

Discussion

Many patients with metastatic colorectal cancer have a comparatively poor survival (1). A considerable number of studies regarding this situation, including application of novel anti-cancer agents, have been performed during recent years to improve the prognoses of these patients (4-9). In addition, the use of personalized treatment programs taking into account individual patients' lifespans may contribute to the improvement of their prognoses. The design of such programs can be considerably facilitates with the application of specific survival scores. A considerable number of patients with metastatic colorectal cancer receive radiotherapy,

Table I. Factors evaluated for a potential impact on survival.

	Number of patients (%)
Age at RT	
≤ 65 Years	11 (44)
≥ 66 Years	14 (56)
Gender	
Female	10 (40)
Male	15 (60)
ECOG performance score	
0-1	11 (44)
≥ 2	9 (36)
Unknown	5 (20)
Tumor site	
Colon	16 (64)
Rectum	9 (36)
Interval between diagnosis of colorectal cancer and RT of bone metastases	
≤ 12 Months	13 (52)
≥ 13 Months	12 (48)
Visceral metastases	
No	2 (8)
Yes	23 (92)
Other bone metastases	
No	12 (48)
Yes	13 (52)
Type of metastatic sites	
Spinal	9 (36)
Extraspinal	12 (48)
Both	4 (16)
Number of irradiated sites	
1	14 (56)
≥ 2	11 (44)
Upfront surgery of bone metastases	
No	21 (84)
Yes	4 (16)
Systemic treatment prior to RT	
No	5 (20)
Yes	20 (80)

RT: Radiotherapy; ECOG: Eastern Cooperative Oncology Group.

particularly for brain and bone metastases. Prognostic factors have already been identified and specific survival scores already exist for colorectal cancer patients with brain metastases or metastatic spinal cord compression (10-16). However, no specific survival score has been available so far for patients with colorectal cancer irradiated for bone metastases without compression of the spinal cord, hence the purpose of the present study. All patients included in this study received multi-fraction radiotherapy with an overall treatment time longer than one week. Longer-course multi-fraction radiotherapy is the standard regimen for bone metastases in the contributing centers. Short-course radiotherapy with an overall treatment time of one week or less is generally limited to patients with an extremely poor survival prognosis. Therefore, patients treated with short-

Table II. *Survival rates of the 11 potential prognostic factors (univariate analysis).*

Factor	Survival rates (in %) at				<i>p</i> -Value
	3 months	6 months	9 months	12 months	
Age at RT					
≤65 Years	64	55	45	45	0.15
≥66 Years	50	36	21	7	
Gender					
Female	60	60	50	38	0.61
Male	53	33	20	13	
ECOG performance score					
0-1	73	64	55	44	0.005
≥2	33	22	11	0	
Tumor site					
Colon	50	38	23	16	0.11
Rectum	67	56	44	33	
Time between diagnosis of colorectal cancer and RT of bone metastases					
≤12 Months	69	54	37	37	0.17
≥13 Months	42	33	25	8	
Visceral metastases					
No	100	100	100	100	0.18
Yes	52	39	26	17	
Other bone metastases					
No	67	67	67	48	0.001
Yes	46	23	0	0	
Type of metastatic sites					
Spinal	56	44	33	22	0.69
Extraspinal	58	50	31	21	
Both	50	25	25	25	
Number of irradiated sites					
1	57	57	49	33	0.049
≥2	55	27	9	9	
Upfront surgery of bone metastases					
No	57	43	28	22	0.91
Yes	50	50	50	25	
Systemic treatment prior to RT					
No	100	100	53	27	0.067
Yes	45	30	25	20	

RT: Radiotherapy; ECOG: Eastern Cooperative Oncology Group; bold *p*-value: significant.

Table III. *Survival rates of the three prognostic groups.*

Prognostic group	Survival rates (in %) at				<i>p</i> -Value
	3 months	6 months	9 months	12 months	
0 Points	14	0	0	0	<0.001
1 Point	73	64	45	27	
2 Points	100	100	100	100	

Bold *p*-value: significant.

course radiotherapy were not included to avoid a selection bias due to the dose-fractionation program.

Based on two independent prognostic factors of survival, *i.e.* ECOG performance score and systemic treatment prior to

radiotherapy, a scoring tool has been designed that includes three prognostic groups. Of those patients with 0 points, only 14% survived for 3 months and no patient for 6 months or more. These patients should be strongly considered for single-

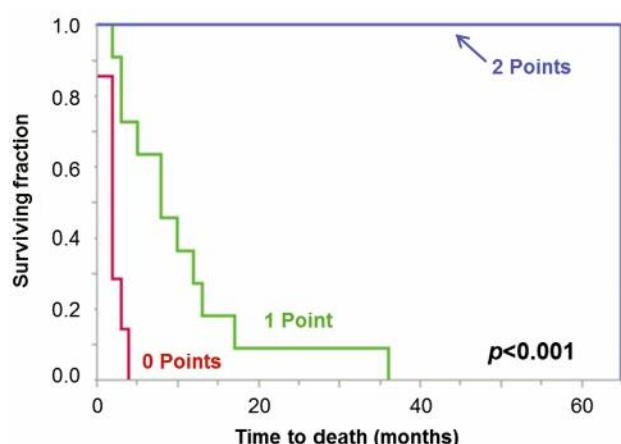


Figure 1. Kaplan-Meier curves for the survival of the three prognostic groups (0 points, 1 point and 2 points). The *p*-value was obtained using the log-rank test.

fraction radiotherapy if they have symptoms, such as bone pain, that need to be relieved. According to a meta-analysis of randomized trials, single-fraction radiotherapy with 1×8 Gy is as effective as multi-fraction regimens, mainly 10×3 Gy for two weeks, with respect to pain relief (17). Patients treated with 1×8 Gy require re-irradiation in the same region significantly more often compared to patients receiving multi-fraction radiotherapy. However, patients of the present study with 0 points have such a short remaining life time that they are unlikely to live long enough to experience recurrent bone pain in the irradiated regions. Patients achieving 1 point had a better survival prognosis; 64% survived for 6 months and 27% for 12 months. Thus, a considerable proportion of this group will live long enough to be at risk of developing a local recurrence of the irradiated bone metastases. If these patients have uncomplicated painful bone metastases without a (pending) pathological fracture or a large soft tissue component, they may also be treated with 1×8 Gy, since a local recurrence can be successfully treated with another single fraction of radiotherapy (18, 19). In case of a (pending) pathological fracture or a large soft tissue component, the patients appear better treated with longer-course radiotherapy, e.g. 10×3 Gy in two weeks, which was shown to result in a better re-calcification of the osteolytic bone compared to 1×8 Gy (20). Patients with 2 points had very favorable prognoses; all patients survived for at least 12 months. Since the risk of a local recurrence increases with lifetime, these patients should be considered for longer-course radiotherapy with higher doses, such as 14-15×2.5 Gy for three weeks and 20×2 Gy for four weeks. These dose-fractionation regimens have already been recommended for patients with favorable survival prognoses and vertebral metastases associated with symptomatic compression of the spinal cord (12, 14, 20, 21). When following these recommendations, the limitations of this

study, including the retrospective design and the small number of patients, must be regarded. Moreover, since patients receiving single-fraction or short-course multi-fraction radiotherapy were not included, the recommendations may not be generalized to these patients.

In conclusion, this new scoring tool includes three prognostic scores with significantly different survival prognoses. It can support physicians during the process of personalization of the radiation treatment for patients with bone metastases from colorectal cancer.

Conflicts of Interest

On behalf of all Authors, the corresponding author states that there are no conflicts of interest related to this study.

Authors' Contributions

R.H., S.J., S.E.S and D.R. participated in the design of the study. R.H., S.J. and D.R. provided data. D.R. and S.E.S. performed the analyses of the data. R.H. and D.R. drafted the manuscript, which has been reviewed and approved by all authors.

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Eastern Cooperative Oncology Group Performance Score Is Associated With Survival After Radiotherapy of Bone Metastases from Prostate Cancer

RAPHA HAUS¹, STEFAN JANSSEN^{1,2}, STEVEN E. SCHILD³ and DIRK RADES¹

¹Department of Radiation Oncology, University of Lübeck, Lübeck, Germany;

²Medical Practice for Radiotherapy and Radiation Oncology, Hannover, Germany;

³Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, U.S.A.

Abstract. *Background/Aim:* Understanding prognostic factors of survival are important for treatment personalization in cancer patients. This study aimed to identify such factors for patients irradiated for bone metastases from prostate cancer. *Patients and Methods:* Data from 74 patients irradiated between 01/2009 and 04/2019 were retrospectively evaluated. Ten characteristics were investigated for survival. *Results:* Median survival in the entire cohort was 12 months. Survival rates at 3, 6, 9 and 12 months were 84%, 73%, 56% and 47%, respectively. On univariate analyses, the Eastern Cooperative Oncology Group (ECOG) performance score of 0-1 was associated with improved survival ($p<0.001$), absence of visceral metastases ($p=0.099$) and only one irradiated metastatic site ($p=0.099$) showed a trend. On Cox regression analysis, only ECOG performance score (risk ratio=3.58, $p<0.001$) was significant. *Conclusion:* ECOG performance score is an independent prognostic factor of survival after irradiation of bone metastases from prostate cancer and may allow better personalization of care.

Up to 70% of prostate cancer patients experience bone metastases during the course of their disease (1). Many of these patients receive radiotherapy mainly to relieve pain and to stabilize bones affected by osteolytic lesions (2). For the irradiation of osseous metastases, several dose-fractionation regimens are administered worldwide, including single-

fraction radiotherapy, multifraction short-course programs (overall treatment time up to one week) and longer-course programs (usually lasting 2-4 weeks) (2). In cases of uncomplicated bone metastases, *i.e.* bone metastases without malignant spinal cord compression or an extensive soft-tissue component and/or an (impending) pathological fracture, single-fraction radiotherapy can be recommended for patients with a short survival time (2-4). Unfortunately, recurrent bone pain occurs significantly more often after single-fraction treatment compared to treatment with a multifraction regimen (2-4). Moreover, recalcification of osteolytic bone metastases is more prominent when multiple fractions are used (5). Since significant recalcification can only be expected after several months following radiotherapy, this endpoint is mainly important for patients with more favorable survival prognoses. Also, since the risk of a local recurrence of bone metastases associated with another episode of pain increases with time, this aspect should be considered when treating patients with longer-time expected survival (2-4). Thus, the optimal radiation program for a patient with bone metastases should take into account the predicted remaining lifespan. For predicting a patient's survival independent prognostic factors can be quite valuable. Since cancer types are different with respect to biology, prognosis and patterns of metastatic spread, it is generally agreed that independent prognostic factors should ideally be available for the different cancer types. This study was conducted to identify independent prognostic factors for survival after radiotherapy of bone metastases from prostate cancer.

This article is freely accessible online.

Correspondence to: Dirk Rades, Department of Radiation Oncology, University of Lübeck, Ratzeburger Allee 160, 23562 Lübeck, Germany. Tel: +49 45150045401, Fax: +49 45150045404, e-mail: rades.dirk@gmx.net

Key Words: Prostate cancer, bone metastases, multi-fraction irradiation, survival, prognostic factors.

Patients and Methods

The data of 74 patients irradiated for bone metastases from prostate cancer between 01/2009 and 04/2019 were retrospectively evaluated. This study was approved by the ethics committee of the University of Lübeck. All 74 patients received multi-fraction longer-course irradiation with i) 10×3 Gy in 2 weeks (n=31), ii) 12×3 Gy in 2.5 weeks (n=1), iii) 14-15×2.5 Gy in 3 weeks (n=32),

Table I. Distribution of the investigated factors.

	Number of patients (%)
Age at RT	
≤75 Years	34 (46)
≥76 Years	40 (54)
ECOG performance score	
0-1	40 (54)
≥2	26 (35)
Unknown	8 (11)
Interval from diagnosis of prostate cancer to RT of bone metastases	
≤24 Months	37 (50)
≥25 Months	37 (50)
Visceral metastases	
No	53 (72)
Yes	21 (28)
Further bone metastases	
No	6 (8)
Yes	68 (92)
Location of metastatic sites	
Spine	24 (32)
Extraspinal	28 (38)
Both	22 (30)
Number of irradiated sites	
1	30 (41)
≥2	44 (59)
Pathological fracture	
No	61 (82)
Yes	13 (92)
Upfront surgery of bone metastases	
No	66 (89)
Yes	8 (11)
Systemic treatment prior to RT	
No	9 (12)
Yes	64 (86)
Unknown	1 (1)

RT: Radiotherapy; ECOG: Eastern Cooperative Oncology Group.

iv) 15×2 Gy in 3 weeks (n=3) or v) 18-20×2.0 Gy in 3.5-4 weeks (n=7). The following ten characteristics (Table I) were investigated with respect to survival: i) age (≤75 vs. ≥76 years), ii) Eastern Cooperative Oncology Group (ECOG) performance score (6) (ECOG 0-1 vs. ≥2), iii) interval from diagnosis of prostate cancer to irradiation of bone metastases (≤24 vs. ≥25 months, median interval=24.5 months), iv) visceral metastases (no vs. yes) or v) further bone metastases (no vs. yes) prior to irradiation of bone metastases, vi) location of metastatic sites (spinal vs. extraspinal vs. both), vii) number of irradiated metastatic sites (1 vs. ≥2), viii) pathological fracture (no vs. yes), ix) upfront surgery of the bone metastases (no vs. yes) and x) previous systemic treatment prior to irradiation (no vs. yes).

Survival time was referenced from the start of irradiation of the bone metastases. For univariate analyses, the Kaplan-Meier method and the log-rank test were applied. Characteristics that were significant ($p<0.05$) or showed at least a trend ($p<0.10$) on univariate analyses were additionally investigated for independence in a multivariate Cox regression analysis.

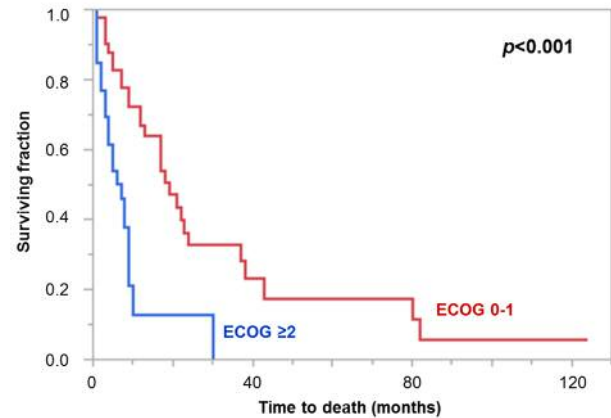


Figure 1. Kaplan-Meier curves for Eastern Cooperative Oncology Group (ECOG) performance scores of 0-1 vs. ≥2.

Results

Median survival in the entire cohort was 12 months. Survival rates at 3, 6, 9 and 12 months were 84%, 73%, 56% and 47%, respectively. On univariate analyses, an ECOG performance score of 0-1 was significantly associated with improved survival (Figure 1, $p<0.001$). In the absence of visceral metastases ($p=0.099$) and for only one irradiated metastatic site ($p=0.099$), a trend towards better survival was found ($p=0.099$). The data of the univariate analyses are summarized in Table II.

In the Cox regression analysis, the ECOG performance score (risk ratio=3.43, 95%-confidence interval=1.67-7.12, $p<0.001$) achieved significance, whereas absence of visceral metastases (risk ratio=1.07, 95% confidence interval=0.54-2.05, $p=0.83$) and one irradiated metastatic site (risk ratio=1.12, 95% confidence interval=0.59-2.11, $p=0.73$) did not.

Discussion

Prostate cancer is the most common type of cancer in men in industrial nations (1). A considerable number of patients with prostate cancer develop metastases. To improve the prognoses of these patients, novel anticancer drugs have been introduced (7-10). Another approach aiming to improve their outcomes is through personalized care. Personalization of treatment should be based on the patient's individual situation, including his expected survival time. For the estimation of survival prognoses independent prognostic factors are very useful. For patients with prostate cancer, such factors have been identified for other metastatic situations, including brain metastases and malignant spinal cord compression (11-15). The current study was conducted to identify independent prognostic factors for prostate cancer patients with bone metastases.

Table II. Survival rates of the 11 potential prognostic factors (univariate analysis).

Factor	Survival rates (in %) at				p-Value
	3 months	6 months	9 months	12 months	
Age at RT					
≤75 Years	88	76	58	46	0.61
≥76 Years	80	70	54	49	
ECOG performance score					
0-1	90	83	72	67	<0.001
≥2	69	50	21	13	
Interval from diagnosis of prostate cancer to RT of bone metastases					
≤24 Months	89	73	59	48	0.66
≥25 Months	78	73	53	47	
Visceral metastases					
No	89	77	60	53	0.099
Yes	71	62	48	33	
Further bone metastases					
No	83	67	67	50	0.93
Yes	84	74	55	47	
Location of metastatic sites					
Spine	88	79	57	53	0.13
Extraspinal	79	68	54	46	
Both	86	73	58	42	
Number of irradiated sites					
1	83	77	70	63	0.099
≥2	84	70	46	36	
Pathological fracture					
No	82	72	55	48	0.37
Yes	92	77	60	43	
Upfront surgery of bone metastases					
No	83	73	57	49	0.23
Yes	88	75	45	30	
Systemic treatment prior to RT					
No	100	89	63	63	0.58
Yes	81	70	56	46	

RT: Radiotherapy; ECOG: Eastern Cooperative Oncology Group; bold p-values=significant.

The ECOG performance score was found to be independently associated with survival. This factor can aid physicians when personalizing treatment for patients with osseous metastases from prostate cancer.

Patients with a good performance status (ECOG score of 0-1) had a favourable prognosis with survival rates of 83% at 6 months and 67% at 12 months, respectively. Since many of these patients will live long enough to be at risk of experiencing another episode of bone pain in the irradiated regions, they may be considered for multi-fraction longer-course radiotherapy (2). According to previous meta-analyses, re-treating painful bone metastases was significantly less often required after longer-course than after single-fraction radiotherapy (3, 4). Moreover, in a prospective randomized trial, recalcification after longer-course treatment with 10×3 Gy given over 2 weeks was significantly stronger compared to single-fraction radiotherapy with 1×8 Gy (5). In this trial, the relative increases in bone density were 173% compared to 120% ($p<0.001$).

On the other hand, patients with a poor performance status (ECOG score of ≥2) had much less favorable survival rates of 50% at 6 months and only 13% at 12 months, respectively. In two large randomized trials of 1,171 and 765 patients, who were irradiated for painful bone metastases, recurrent bone pain occurred only after a median time of 11 months or >12 months, respectively (16,17). Most of the patients with an ECOG performance score of ≥2 will not live long enough to experience a second episode of bone pain and, therefore, appear suitable candidates for single-fraction radiotherapy. When following these considerations and suggestions, one should be aware of the retrospective nature of the data analyzed in this study that may have introduced a hidden selection bias. Although only patients receiving longer-course radiotherapy were included in this study to reduce the risk of a selection bias, the risk of hidden biases remained. Moreover, our suggestions may not be applicable to patients receiving single-fraction radiotherapy, since these patients were not included in the present study. Furthermore, one has to bear in mind that complicated bone metastases, *i.e.* bone metastases with an (impending) fracture, spinal cord compression or extensive soft-tissue component do generally require radiotherapy with multiple fractions (2).

In conclusion, the ECOG performance score was independently associated with survival. This prognostic factor can guide physicians when personalizing a dose-fractionation program for a patient with bone metastases from prostate cancer.

Conflicts of Interest

On behalf of all authors, the corresponding author states that there are no conflicts of interest related to this study.

Authors' Contributions

R.H., S.J., S.E.S and D.R. participated in the design of the study. R.H., S.J. and D.R. provided data. D.R. and S.E.S. performed the analyses of the data and drafted the manuscript, which has been reviewed and approved by all authors.

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An easy-to-use scoring system to estimate the survival of patients irradiated for bone metastases from lung cancer

Dirk Rades¹, Rapha Haus¹, Stefan Janssen¹, Steven E. Schild²

¹Department of Radiation Oncology, University of Lübeck, Lübeck, Germany; ²Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: D Rades; (III) Provision of study materials or patients: D Rades, R Haus, S Janssen; (IV) Collection and assembly of data: D Rades, R Haus, S Janssen; (V) Data analysis and interpretation: D Rades, SE Schild; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Prof. Dr. med. Dirk Rades. Chair of the Department of Radiation Oncology, University of Lübeck, Ratzeburger Allee 160, 23562 Lübeck, Germany. Email: rades.dirk@gmx.net.

Background: The remaining lifespan of patients with metastatic lung cancer should be considered when designing a personalized treatment program. To facilitate the estimation survival in lung cancer patients with bone metastases, a specific scoring system was created.

Methods: One-hundred-and-fifty-three patients receiving fractionated radiotherapy for bone metastases without spinal cord compression from lung cancer were included in this retrospective study. Age, gender, Eastern Cooperative Oncology Group (ECOG) performance score, histology, interval from lung cancer diagnosis until irradiation of bone metastases, visceral metastases, additional bone metastases, type and number of irradiated sites, pathological fracture, upfront surgery and previous systemic treatment were evaluated for potential associations with survival. Those factors that were significant ($P < 0.05$) or showed a trend ($P \leq 0.10$) on multivariate analysis were used to create the scoring system.

Results: On multivariate analysis, ECOG performance score was significant (risk ratio: 2.77, $P < 0.001$), and age showed a trend (risk ratio: 1.34, $P = 0.10$). The following scoring points were assigned: age ≤ 65 years = 1 point, age ≥ 66 years = 0 points, ECOG performance score of 0–1 = 1 point, and ECOG performance score of ≥ 2 = 0 points. Three prognostic groups were obtained: 0 points ($n = 38$), 1 point ($n = 71$) and 2 points ($n = 44$). Six-month survival rates were 21%, 41% and 75%, 12-month survival rates 7%, 27% and 56% ($P < 0.001$).

Conclusions: This scoring system can help estimate the remaining lifespan of lung cancer patients to be irradiated for bone metastases and will contribute to the personalization of their treatment.

Keywords: Non-small cell lung cancer; bone metastases; irradiation; survival; scoring system

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Introduction

In patients with bone metastases, lung cancer is one of the most frequent primary tumors (1). To administer optimal care for individuals with bone metastases from lung cancer, personalized treatment programs are very important. Since many of these patients receive radiotherapy, these programs often include a choice of the most appropriate radiation regimen. Radiation regimens used for treating of bone

metastases range from single-fraction to longer-course multi-fraction programs lasting weeks (2). When choosing a personalized radiation regimen, several aspects should be considered including the indication for radiotherapy and the patient's remaining lifespan. In case of uncomplicated painful bone metastases, a single fraction of radiotherapy is as effective as multi-fraction radiotherapy in achieving pain relief (3–7). However, single-fraction radiotherapy is less effective than multi-fraction programs with respect to

Table 1 Distribution of the factors evaluated for a potential impact on survival

Factor	N patients [%]
Age	
≤65 years	77 [50]
≥66 years	76 [50]
Gender	
Female	66 [43]
Male	87 [57]
ECOG performance score	
0–1	83 [54]
≥2	70 [46]
Histology	
SCLC	21 [14]
NSCLC	132 [86]
Interval from diagnosis of lung cancer until irradiation of bone metastases	
≤2 months	92 [60]
≥3 months	61 [40]
Visceral metastases	
No	56 [37]
Yes	97 [73]
Additional bone metastases	
No	37 [24]
Yes	116 [76]
Site(s) of irradiated bone metastases	
Spine	55 [36]
Extra-spinal	56 [37]
Both	42 [27]
Number of irradiated metastatic sites	
1	70 [46]
≥2	83 [54]
Pathological fracture	
No	118 [77]
Yes	35 [23]
Upfront surgery	
No	124 [80]
Yes	29 [20]
Previous systemic treatment	
No	72 [47]
Yes	81 [53]

ECOG, Eastern Cooperative Oncology Group.

longer-term symptom control, particularly when compared longer-course programs. Longer-course multi-fraction radiotherapy resulted in significantly better recalcification of the osteolytic bone than single-fraction treatment in a randomized trial (8). Since the risk of local failure increases with lifetime, patients with bone metastases and favorable survival prognoses can benefit from longer-course radiotherapy programs. In contrast, patients with a poor survival prognosis, who likely will die before local recurrence, are good candidates for single-fraction radiotherapy (2). These considerations illustrate that it is very important to take into account a patient's remaining survival time when designing a personalized treatment approach.

Prediction of individual survival prognoses can be considerably facilitated with the use of scoring systems. To achieve the best possible personalization of the treatment for patients with bone metastases, specific scoring systems are desirable for each primary tumor with metastatic spread to the bone including lung cancer. The concept of developing specific survival scores for lung cancer patients irradiated for metastatic disease has already been realized for patients with brain metastases and patients with metastatic epidural spinal cord compression (9–11). The current study was performed to create a specific survival score for lung cancer patients irradiated for bone metastases.

Methods

A total of 153 patients who received fractionated radiotherapy for bone metastases without spinal cord compression from lung cancer between January 2009 and April 2019 were included in this retrospective study. Twelve factors (*Table 1*) were evaluated for a potential impact on survival including age (≤65 *vs.* ≥66 years, median age: 65 years), gender, Eastern Cooperative Oncology Group (ECOG) performance score (0–1 *vs.* ≥2), histology (SCLC *vs.* NSCLC), interval from first diagnosis of lung cancer until irradiation of bone metastases (≤2 *vs.* ≥3 months, median interval: 2 months), visceral metastases at the time of radiotherapy (no *vs.* yes), additional bone metastases (no *vs.* yes), site(s) of irradiated bone metastases (spine *vs.* extra-spinal *vs.* both), number of irradiated metastatic sites (1 *vs.* ≥2), pathological fracture (no *vs.* yes), upfront surgery of irradiated bone metastases (no *vs.* yes), and previous systemic treatment (no *vs.* yes).

Patients included in this study had complete data regarding the twelve investigated potential prognostic factors and survival. In order to reduce a selection bias due to the dose-fractionation regimen of radiotherapy, only patients treated with multi-fraction longer-course radiotherapy (the standard regimen in the centers participating in this study) were included. The dose-fractionation regimens were either 10×3 Gy over 2 weeks (n=76), 12×3–13×3 Gy over 2.5 weeks (n=4), 14×2–15×2 Gy over 3 weeks (n=12), 14×2.5–15×2.5 Gy over 3 weeks (n=49) or 18×2–20×2 Gy over 2.5–3 weeks (n=12).

Time to death has been calculated from the first day of radiotherapy. Univariate analyses of survival were performed with the Kaplan-Meier-method and the log-rank test. The potential prognostic factors that were significantly ($P<0.05$) associated with survival on univariate analyses were subsequently included in a Cox regression analysis. Those factors that were significant ($P<0.05$) or showed a trend ($P\leq 0.10$) in the Cox regression analysis were used to create the scoring system for estimation of survival.

All procedures performed were in accordance with ethical standards and the Helsinki declaration from 1964 as revised in 2013. The study was approved by an institutional review board (IRB), namely the Ethics Committee of the University of Lübeck, (reference number 18-254A). Due to its retrospective design, informed consent specifically for this study was not required by the IRB. For protection of the patient's personal data, only anonymized data have been used for the analyses of this study.

Results

Median follow up times were 5 months (range, 0–155 months) in the entire cohort and 13 months (range, 4–155 months) in those patients who were still alive at the last follow up. In the entire cohort, the survival rates were 59%, 46%, 36% and 30%, respectively, at 3, 6, 9 and 12 months. On univariate analysis, age ≤ 65 years ($P=0.017$) and an ECOG performance score of 0–1 ($P<0.001$) were significantly associated with survival. The results of the complete univariate analyses are summarized in *Table 2*. In the Cox regression analysis, ECOG performance score remained significant (risk ratio: 2.77, 95% confidence interval: 1.93–4.00, $P<0.001$), and age showed a trend (risk ratio: 1.34, 95% confidence interval: 0.94–1.89, $P=0.10$).

Both factors were used to create the scoring system for estimation of survival. The following scoring points were

assigned: age ≤ 65 years =1 point, age ≥ 66 years =0 points, ECOG performance score of 0–1 =1 point, and ECOG performance score of ≥ 2 =0 points. Thus, three prognostic groups were obtained, i.e. 0 points (n=38), 1 point (n=71) and 2 points (n=44). The survival rates of these groups at 3, 6, 9 and 12 months are summarized in *Table 3*, and the corresponding Kaplan-Meier curves are given in *Figure 1*.

Discussion

The survival prognoses of patients irradiated for bone metastases vary between a few weeks and several years. This should be taken into account when tailoring a treatment regimen to an individual patient. Patients with uncomplicated painful bone metastases, i.e., without a pending or existing pathological fracture, metastatic epidural spinal cord compression or an extensive soft-tissue component, and a short survival time appear optimally treated with single-fraction radiotherapy such as 1×8 Gy or 1×10 Gy (2–7). This regimen would allow the patients to spend more time without treatment for other important issues. Reviews and meta-analyses of randomized trials demonstrated single-fraction radiotherapy to be as effective in relieving pain as multi-fraction radiation regimens (3–7). Fifteen years ago, Sze *et al.* presented a systematic review of 11 trials and 3,435 patients with uncomplicated painful bone metastases (6). The overall pain response rates were 60% after single-fraction and 59% after multi-fraction radiotherapy, respectively (odds ratio: 1.03, 95% confidence interval: 0.89–1.19). Complete pain relief was achieved in 34% and 32% of the patients, respectively (odds ratio: 1.11, 95% confidence interval: 0.94–1.30). More recently, Chow *et al.* presented an updated systematic review that included 25 randomized trials with a total of 5,617 patients with bone pain from uncomplicated metastases (7). Overall pain relief was achieved in 60% of patients after single-fraction radiotherapy compared to 61% after multi-fraction treatment ($P=0.36$). Complete pain relief rates were 23% and 24%, respectively (7).

The systematic reviews revealed that re-treatment of the same bone metastases was required significantly more often after single-fraction than after multi-fraction radiotherapy. In the review of Sze *et al.*, the re-treatment rates were 21.5% and 7.4%, respectively (odds ratio: 3.44, 95% confidence interval: 2.67–4.43) (6). In the updated review of Chow *et al.*, the re-treatment rates were 20% and 8%, respectively ($P<0.00001$) (7). Moreover, a randomized trial

Table 2 Univariate analyses of survival rates of the 12 potential prognostic factors

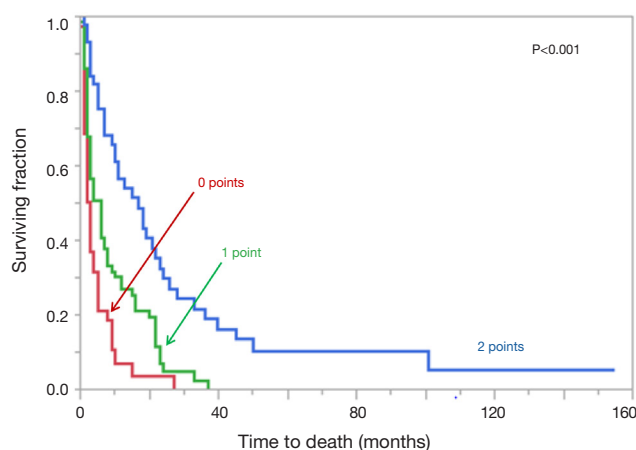
Factor	Survival (%) at				P value
	3 mos.	6 mos.	9 mos.	12 mos.	
Age					0.017*
≤65 years	66	52	44	36	
≥66 years	53	39	28	25	
Gender					0.85
Female	61	44	36	29	
Male	59	47	37	32	
ECOG performance score					<0.001*
0–1	75	65	55	48	
≥2	41	23	14	10	
Histology					0.40
SCLC	71	57	48	41	
NSCLC	58	44	34	29	
Interval from diagnosis of lung cancer until irradiation of bone metastases					0.91
≤2 months	62	45	38	33	
≥3 months	56	46	34	27	
Visceral metastases					0.12
No	70	53	40	32	
Yes	54	41	34	30	
Additional bone metastases					0.80
No	59	51	39	26	
Yes	59	44	35	32	
Site(s) of irradiated bone metastases					0.55
Spine	58	45	35	26	
Extra-spinal	63	48	38	31	
Both	57	43	36	36	
Number of irradiated metastatic sites					0.16
1	66	50	41	34	
≥2	54	42	33	28	
Pathological fracture					0.45
No	57	43	36	32	
Yes	69	54	37	25	
Upfront surgery					0.81
No	56	42	33	30	
Yes	76	62	50	29	
Previous systemic treatment					0.56
No	64	47	37	30	
Yes	59	46	36	30	

*, significant P values. ECOG, Eastern Cooperative Oncology Group.

Table 3 Survival rates of the prognostic groups 0 points, 1 point and 2 points

Prognostic group	Survival (%) at				P value
	3 mos.	6 mos.	9 mos.	12 mos.	
0 points (n=38)	37	21	11	7	<0.001*
1 point (n=71)	56	41	32	27	
2 points (n=44)	84	75	66	56	

*, significant P value.

**Figure 1** Kaplan-Meier curves for survival of the prognostic groups 0 points, 1 point and 2 points. The P value was calculated using the log-rank test.

demonstrated that re-calcification of the osteolytic bone was significantly more pronounced after 10×3 Gy over 2 weeks than after 1×8 Gy (173% *vs.* 120%, $P<0.0001$) (8). Since re-calcification takes time and can generally be expected only several months following radiotherapy, it becomes more of an issue in longer-term survivors (2). Also the risk of recurrent bone pain in the irradiated regions rises with lifetime. Therefore, patients with bone metastases and favorable survival prognoses appear better treated with multi-fraction radiotherapy. It has been shown for patients with vertebral bone metastases associated with spinal cord compression and favorable survival prognoses that radiotherapy with total doses beyond 30 Gy (e.g., 15×2–15×5 Gy or 20×2 Gy) resulted in improved local control (12). If these findings can be transferred to patients with bone metastases without spinal cord compression, one may consider using longer-course radiotherapy with doses

beyond 30 Gy also for long-term survivors of this group.

To be able to select the most appropriate dose-fractionation regimen and to avoid over- or under-treatment, it would be very helpful if one could predict an individual patient's survival time prior to the start of treatment. A few scoring system already exist for patients irradiated for bone metastases (13-16). However, these tools were developed in cohorts of patients with many different primary tumor types. In order to account for the individual biology and other individual characteristics of a particularly tumor type, specific scoring systems for single tumor entities would be important. In the current study, a scoring system has been developed specifically for bone metastases from lung cancer. Based on the prognostic factors age and performance status, which can be assessed easily and fast, three prognostic groups were designed. Patients with 0 points had poor survival prognoses; only 37% and 21% of the patients survived for 3 and 6 months, respectively. Thus, patients of this group with symptomatic bone metastases appear good candidates for single-fraction radiotherapy. Patients with 1 point had an intermediate survival prognosis with 41% of the patients surviving for 6 months and 27% for 12 months. They may be considered for multi-fraction radiotherapy of intermediate duration, for example with 10×3 Gy. Patients with 2 points had the most favorable survival prognoses with 75% surviving for 6 months and 56% for 12 months. These patients may be candidates for longer-course radiotherapy with total doses beyond 30 Gy. However, when considering these suggestions, one should bear in mind the retrospective design of this study. Although only patients treated with longer-course multi-fraction radiotherapy were included to reduce the risk of a selection bias due to the dose-fractionation regimen, the risk of hidden selection biases still exists. The findings of this study may not be applicable to patients treated with single-fraction or short-course multi-fraction irradiation, because these patients were not included. Moreover, it has to be noticed that patients with complicated bone metastases should always be considered for multi-fraction radiotherapy (2).

Conclusions

The new scoring system including three prognostic groups may help estimating the lifespan of lung cancer patients to be irradiated for bone metastases. It can be used easily and fast during clinical routine. It may be useful for physicians

when tailoring the treatment regimen to the individual. Moreover, it can be valuable in the stratification of patients with bone metastases from lung cancer in future trials.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tlcr-19-642>). DR reports personal fees from Elsevier, personal fees and non-financial support from Roche Pharma, Bristol Myers Squibb, Astra Zeneca, Bayer HealthCare, Novartis Oncology, Amgen, Janssen-Cilag, MerckSerono outside the submitted work. SES reports personal fees from Noxopharm, other from UpToDate outside the submitted work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed were in accordance with ethical standards and the Helsinki declaration from 1964 as revised in 2013. The study was approved by an institutional review board (IRB), namely the Ethics Committee of the University of Lübeck, (reference number 18-254A). Due to its retrospective design, informed consent specifically for this study was not required by the IRB. For protection of to the patient's personal data, only anonymized data have been used for the analyses of this study.

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UNIVERSITÄT ZU LÜBECK

Universität zu Lübeck · Ratzeburger Allee 160 · 23538 Lübeck

Prof. Dr. D. Rades

Klinik f. Strahlentherapie

Im Haus

Ethik-Kommission

Vorsitzender:

Herr Prof. Dr. med. Alexander Katalinic

Stellv. Vorsitzender:

Herr Prof. Dr. med. Frank Gieseler

Geschäftsstelle:

Frau Dr. A. Hüppe

Tel.: +49 451 500 51217

ethikkommission@uni-luebeck.de

Aktenzeichen: 18-254A

Datum: 06. September 2018

Anzeige einer retrospektiven Datenanalyse (03.09.2018), Beratung im verkürzten Verfahren

Vorhaben: *Entwicklung eines Prognose-Scores zur Abschätzung des Gesamtüberlebens nach Bestrahlung von Knochenmetastasen*

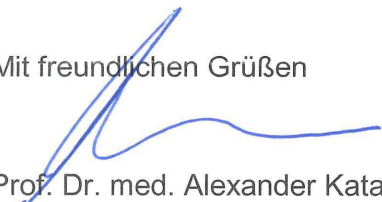
Sehr geehrter Herr Rades,

die Kommission äußert **keine Bedenken** gegen das von Ihnen beschriebene Vorhaben.

Sie setzt dabei voraus, dass die erhobenen Daten frühzeitig anonymisiert werden.

Die ärztliche und juristische Verantwortung des Studienleiters und der an der Studie teilnehmenden Ärzte bleibt entsprechend der Beratungsfunktion der Ethikkommission durch unsere Stellungnahme unberührt.

Mit freundlichen Grüßen


Prof. Dr. med. Alexander Katalinic
Vorsitzender



UNIVERSITÄT ZU LÜBECK

Universität zu Lübeck · Ratzeburger Allee 160 · 23538 Lübeck

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

im Hause

Ethik-Kommission

Vorsitzender:
Herr Prof. Dr. med. Alexander Katalinic
Stellv. Vorsitzender:
Herr Prof. Dr. med. Frank Gieseler

Ratzeburger Allee 160
23538 Lübeck

Sachbearbeitung: Frau Janine Erdmann
Tel.: +49 451 3101 1008
Fax: +49 451 3101 1024
ethikkommission@uni-luebeck.de

Aktenzeichen: 18-254A

Datum: 21. November 2019

**Entwicklung eines Prognosescores zur Abschätzung des Gesamtüberlebens
nach Bestrahlung von Knochenmetastasen
Ihre E-Mail vom 19. November 2019**

Sehr geehrter Herr Prof. Rades,

mit Ihrem o.g. Schreiben informieren Sie die Ethik-Kommission die Erweiterung des Vorhabens.
Der Erfassungszeitraum wird bis April 2019 ausgeweitet.

Es werden ausschließlich anonymisierte Daten verarbeitet.

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

Mit freundlichen Grüßen


Prof. Dr. med. Alexander Katalinic
Vorsitzender