ANTICANCER RESEARCH *40*: 367-371 (2020)
doi:10.21873/anticanres.13961

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

STEFAN JANSSEN[1,2], RAPHA HAUS[1], STEVEN E. SCHILD[3] and DIRK RADES[1]

[1]*Departments of Radiation Oncology, University of Lübeck, Lübeck, Germany;*
[2]*Medical Practice for Radiotherapy and Radiation Oncology, Hannover, Germany;*
[3]*Department 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 bisphosphates/denosumab	No	57 (45)
	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 *bis*phosphates 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%, respectively. An ECOG performance score of 0-1 ($p=0.003$), and absence of visceral metastases ($p=0.005$) were significantly positively associatend 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.

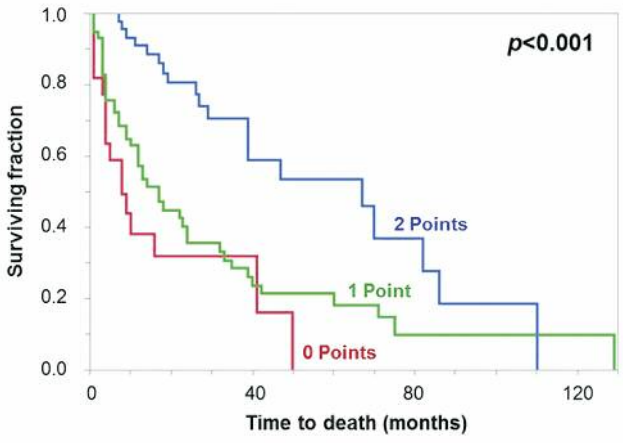

Figure 2. *Survival curves obtained with the Kaplan-Meier method for groups of patients with 0 points, 1 point and 2 points.*

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 6 Months	12 Months	18 Months	24 Months	*p*-Value
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 important for longer-term survivors, since according to randomized trials, median duration of control of pain may be longer than 1 year (29, 30).

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

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

Bold indicates significant *p*-values.

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.

References

1 Rades D, Schild SE and Abrahm JL: Treatment of painful bone metastases. Nat Rev Clin Oncol *7*: 220-229, 2010. PMID: 20234353. DOI: 10.1038/nrclinonc.2010.17

2 Siegel RL, Miller KD and Jemal A: Cancer statistics, 2019. CA Cancer J Clin *69*: 7-34, 2019. PMID: 30620402. DOI: 10.3322/caac.21551

3 Bolm L, Janssen S, Käsmann L, Wellner U, Bartscht T, Schild SE and Rades D: Predicting survival after irradiation of metastases from pancreatic cancer. Anticancer Res *35*: 4105-4108, 2015. PMID: 26124362.

4 Käsmann L, Janssen S, Schild SE and Rades D: Karnosky performance score and radiation dose predict survival of patients re-irradiated for a locoregional recurrence of small cell lung cancer. Anticancer Res *36*: 803-805, 2016. PMID: 26851043.

5 Kaesmann L, Janssen S, Schild SE and Rades D: Value of comorbidity scales for predicting survival after radiochemotherapy of small cell lung cancer. Lung *194*: 295-298, 2016. PMID: 26883133. DOI: 10.1007/s00408-016-9857-4

6 Rades D, Käsmann L, Schild SE and Janssen S: A survival score for patients receiving palliative irradiation for locally advanced lung cancer. Clin Lung Cancer *17*: 558-562, 2016. PMID: 27341791. DOI: 10.1016/j.cllc.2016.05.010

7 Rades D, Manig L, Janssen S and Schild SE: A survival score for patients assigned to palliative radiotherapy for metastatic bladder cancer. Anticancer Res *37*: 1481-1484, 2017. PMID: 28314321. DOI: 10.21873/anticanres.11473

8 Seidl D, Janssen S, Strojan P, Bajrovic A, Schild SE and Rades D: Prognostic factors after definitive radio(chemo)therapy of locally advanced head and neck cancer. Anticancer Res *36*: 2523-2526, 2016. PMID: 27127167.

9 Rades D, Dziggel L, Nagy V, Segedin B, Lohynska R, Veninga T, Khoa MT, Trang NT and Schild SE: A new survival score for patients with brain metastases who received whole-brain radiotherapy (WBRT) alone. Radiother Oncol *108*: 123-127, 2013. PMID: 23830191. DOI: 10.1016/j.radonc.2013.06.009

10 Rades D, Douglas S, Veninga T, Stalpers LJ, Hoskin PJ, Bajrovic A, Adamietz IA, Basic H, Dunst J and Schild SE: Validation and simplification of a score predicting survival in patients irradiated for metastatic spinal cord compression. Cancer *116*: 3670-3673, 2010. PMID: 20564129. DOI: 10.1002/cncr.25223

11 Janssen S, Kaesmann L, Rudat V and Rades D: A scoring system for predicting the survival prognosis of patients receiving stereotactic body radiation therapy (SBRT) for 1-3 lung metastases. Lung *194*: 631-635, 2016. PMID: 27263126. DOI: 10.1007/s00408-016-9906-z

12 Manig L, Janssen S, Schild SE and Rades D: A new prognostic tool for patients undergoing radiotherapy plus upfront transurethral resection for bladder cancer. *In Vivo 31*: 745-748, 2017. PMID: 28652451. DOI: 10.21873/invivo.11125

13 Rades D, Veninga T, Stalpers LJ, Schulte R, Hoskin PJ, Poortmans P, Schild SE and Rudat V: Prognostic factors predicting functional outcome, recurrence-free survival, and overall survival after radiotherapy of metastatic spinal cord compression in breast cancer patients. Int J Radiat Oncol Biol Phys *64*: 182-188, 2006. PMID: 16198069. DOI: 10.1016/j.ijrobp.2005.06.036

14 Rades D, Lohynska R, Veninga T, Stalpers LJ and Schild SE: Evaluation of 2 whole-brain radiotherapy schedules and prognostic

factors for brain metastases in breast cancer patients. Cancer *110*: 2587-2592, 2007. PMID: 17893909. DOI: 10.1002/cncr.23082

15 Rades D, Douglas S, Veninga T, Stalpers LJ, Bajrovic A, Rudat V and Schild SE: Prognostic factors in a series of 504 breast cancer patients with metastatic spinal cord compression. Strahlenther Onkol *188*: 340-345, 2012. PMID: 22354333. DOI: 10.1007/s00066-011-0061-4

16 Rades D, Douglas S and Schild SE: A validated survival score for breast cancer patients with metastatic spinal cord compression. Strahlenther Onkol *189*: 41-46, 2013. PMID: 23138773. DOI: 10.1007/s00066-012-0230-0

17 Rades D, Dziggel L, Segedin B, Oblak I, Nagy V, Marita A, Schild SE, Trang NT and Khoa MT: A simple survival score for patients with brain metastases from breast cancer. Strahlenther Onkol *189*: 664-667, 2013. PMID: 23740157. DOI: 10.1007/s00066-013-0367-5

18 Rades D, Conde AJ, Garcia R, Cacicedo J, Segedin B, Perpar A and Schild SE: A new instrument for estimation of survival in elderly patients irradiated for metastatic spinal cord compression from breast cancer. Radiat Oncol *10*: 173, 2015. PMID: 26282125. DOI: 10.1186/s13014-015-0483-8

19 Rades D, Dziggel L, Janssen S, Blanck O, Hornung D and Schild SE: A survival score for patients receiving stereotactic radiosurgery alone for brain metastases from breast cancer. Anticancer Res *36*: 1073-1076, 2016. PMID: 26977000.

20 Ozawa H, Sata A, Fukui R, Bun A, Higuchi T, Fujimoto Y, Miyagawa Y, Imamura M and Miyoshi Y: A single-centre, retrospective, observational analysis of fulvestrant for recurrent/metastatic breast cancer according to metastatic site. Anticancer Res *39*: 5653-5662, 2019. PMID: 31570463. DOI: 10.21873/anticanres.13762

21 Juzeniene A, Bernoulli J, Suominen M, Halleen J and Larsen RH: Antitumor activity of novel bone-seeking, α-emitting 224Ra-solution in a breast cancer skeletal metastases model. Anticancer Res *38*: 1947-1955, 2018. PMID: 29599310. DOI: 10.21873/anticanres.12432

22 Ampil F, Sangster G, Caldito G, Richards T, Ngo Y, Kim D and Chu Q: Palliative radiotherapy as a treatment for carcinoma invasion of the sacrum: An observational case series study. Anticancer Res *38*: 6797-6800, 2018. PMID: 30504392. DOI: 10.21873/anticanres.13051

23 Kordoni M, Rigakos G, Kim YHM, Kaklamanis L, Nikolatou-Galitis O, Hadjiyassemi L, Labropoulos S and Razis E: Atypical femoral fractures (AFF) from bone remodeling agents in patients with cancer. Anticancer Res *38*: 6439-6444, 2018. PMID: 30396969. DOI: 10.21873/anticanres.13005

24 Yapijakis C, Papakosta V and Vassiliou S: ACE gene variant causing high blood pressure may be associated with medication-related jaw osteonecrosis. *In Vivo 33*: 559-562, 2019. PMID: 30804141. DOI: 10.21873/invivo.11510

25 Chow E, Zeng L, Salvo N, Dennis K, Tsao M and Lutz S: Update on the systematic review of palliative radiotherapy trials for bone metastases. Clin Oncol (R Coll Radiol) *24*: 112-124, 2012. PMID: 22130630. DOI: 10.1016/j.clon.2011.11.004

26 Wu JS, Wong RK, Lloyd NS, Johnston M, Bezjak A and Whelan T; Supportive Care Guidelines Group of Cancer Care Ontario: Radiotherapy fractionation for the palliation of uncomplicated painful bone metastases - an evidence-based practice guideline. BMC Cancer *4*: 71, 2004. PMID: 15461823. DOI: 10.1186/1471-2407-4-71

27 Dennis K, Makhani L, Zeng L, Lam H and Chow E: Single fraction conventional external beam radiation therapy for bone metastases: A systematic review of randomised controlled trials. Radiother Oncol *106*: 5-14, 2013. PMID: 23321492. DOI: 10.1016/j.radonc.2012.12.009

28 Sze WM, Shelley M, Held I and Mason M: Palliation of metastatic bone pain: single fraction *versus* multifraction radiotherapy - a systematic review of the randomised trials. Cochrane Database Syst Rev *2*: CD004721, 2004. PMID: 15106258. DOI: 10.1002/14651858.CD004721

29 Bone Pain Trial Working Party (no authors listed): 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up. Bone Pain Trial Working Party. Radiother Oncol *52*: 111-121, 1999. PMID: 10577696.

30 Rasmusson B, Vejborg I, Jensen AB, Andersson M, Banning AM, Hoffmann T, Pfeiffer P, Nielsen HK and Sjøgren P: Irradiation of bone metastases in breast cancer patients: a randomized study with 1 year follow-up. Radiother Oncol *34*: 179-184, 1995. PMID: 7631024. DOI: 10.1016/0167-8140(95)01520-q

31 Koswig S and Budach V: Remineralization and pain relief in bone metastases after after different radiotherapy fractions (10 times 3 Gy *vs*. 1 time 8 Gy). A prospective study. Strahlenther Onkol *175*: 500-508, 1999. PMID: 10554645. DOI: 10.1007/s000660050061

32 Rades D, Panzner A, Rudat V, Karstens JH and Schild SE: Dose escalation of radiotherapy for metastatic spinal cord compression (MSCC) in patients with relatively favorable survival prognosis. Strahlenther Onkol *187*: 729-735, 2011. PMID: 22037654. DOI: 10.1007/s00066-011-2266-y

Received November 29, 2019
Revised December 5, 2019
Accepted December 12, 2019