Independent Validation of a Risk Stratification Model Predicting Survival in Elderly Patients Irradiated for Bone Metastases

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Abstract. Background/Aim: The aim of this study was to analyze the validity of a prognostic model, originally developed by Rades *et al.*, because international variations in clinical practice and survival outcomes may impact on the performance of predictive tools. Materials and Methods: Retrospectively, data from a single institution were analyzed. The study included 305 patients managed with palliative radiotherapy for bone metastases. The Rades *et al.* score was assigned and the resulting 3 prognostic strata compared. Results: The median overall survival for the 3 strata was 48, 248 and 1065 days, respectively (p<0.001). However, the original break-down (17 points *versus* 18-25 points *versus* >25 points) was not in accordance with the overlapping survival curves in some of the subgroups, leading us to propose slight adjustments. The modified model also performed satisfactorily in the oldest patients (age ≥80 years; median survival 26, 192 and 489 days, respectively, p<0.001). Conclusion: The original Rades *et al.* score is a valid prognostic model in our Norwegian validation database. However, modification is suggested, in particular inclusion of patients with 18 points into the poor prognosis group.

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Population ageing has contributed to increasing numbers of cancer patients and consequently also rising demand for radiotherapy (1, 2). Depending on tumor stage, curative or palliative radiotherapy may be indicated in different settings and phases of the continuum of care (3, 4). Among palliative treatment indications, irradiation for painful uncomplicated bone metastases or complicated bone metastases (sometimes in the post-operative setting) represents a common scenario (5). Given that very convenient and well tolerable regimens such as single-fraction radiotherapy (8 Gy total dose for painful uncomplicated metastases) have been established, even frail or geriatric patients may be offered treatment (6-9). Nevertheless, selection of the appropriate fractionation regimen is not always trivial, especially in large or complicated bone metastases. When trying to avoid a mismatch between intense, locally highly effective but more time- and resource-consuming radiotherapy and remaining life span, many institutions have started utilizing prognostic models (10-12). Survival predictions obtained by such models may assist providers who are trying to avoid futile treatment in the final phase of cancer progression.

In order to support decision-making for elderly patients with bone metastases managed with palliative radiotherapy, Rades *et al.* have recently developed and validated a dedicated survival prediction model (13). They excluded the special setting of metastatic spinal cord compression resulting from bone metastases, because previous research already has resulted in diagnosis-specific models (14, 15). Their study included 348 patients who were ≥65 years of age and had received palliative radiotherapy in the time period 2009-2021, often 10 fractions of 3 Gy (47%). The cohort was divided into equally sized test and validation groups (174 patients each). Based on 4 parameters (gender, cancer type, Eastern Cooperative Oncology Group

performance status (ECOG PS) and presence of visceral metastases), 3 prognostic strata were derived (calibrated for 6-months survival rate). Their median survival was 1.5, 7 and 39 months in the test cohort, respectively. The validation confirmed the excellent performance of the model.

To support implementation in other institutions, additional external validation of the model should be performed. Open questions regarding its role relate to the subgroup of very elderly patients (is it equally useful in the oldest old?) and the fact that the 3 strata had very different group sizes (n=10 (6%), 141 (81%), 23 (13%)), resulting in a large group with intermediate prognosis. The present study was performed to answer these questions and validate the Rades *et al.* score.

Patients and Methods

Our group has previously validated prognostic models developed by other researchers and applied an identical approach in the present study (16, 17). A continuously maintained and updated database was employed, which collects data from unselected Norwegian patients with bone metastases irradiated in routine clinical practice (Nordland Hospital Trust Bodø, Norway) since 2007. The database was created for the purpose of regional quality-of-care analyses, has already been utilized and does not require additional approval by the local Ethics Committee (REK Nord). Fractionation regimens are selected by the clinical oncologist in charge at the time of first consultation and treatment planning. Stereotactic ablative radiotherapy was not utilized. To facilitate comparison with the Rades *et al.* study (13), only patients treated from 2009 onwards were included. Systemic therapy was tailored to disease burden and biology, organ function and patient preferences, and followed the National

guidelines. Staging of extra-osseous metastases consisted of computed tomography (CT). If clinically relevant, other modalities such as ultrasound og magnetic resonance imaging were added to clarify the overall distribution of metastases.

Overall survival (time to death) from the start of radiotherapy was calculated employing the Kaplan–Meier method (SPSS 28; IBM Corp., Armonk, NY, USA). The minimum follow-up was 12 months (median 36 months in patients alive in October 2022 when analyzing the database, n=30). Log-rank tests were employed to compare actuarial survival curves. Cox regression was employed to assess the correlation between survival and the point sum calculated by administering the Rades *et al.* scoring system (continuous variable). Rades *et al.* assigned 7 points for ECOG PS 0-1, 4 points for ECOG PS ≥2, 7 points for female gender, 5 points for male gender, 6 points for bone-only metastases, 5 points for visceral metastases, and 8 points for breast cancer (prostate: 7, colorectal/kidney: 5, lung/unknown primary: 3, other primary: 4). Patients with highest point sum, *i.e.* 26-28, were allocated to the best prognostic group (sum 18-25: intermediate, sum 17: short survival).

Results

The study included 305 patients whose baseline characteristics are shown in Table 1. The largest subgroup consisted of patients with prostate cancer (41%). In 36 patients (12%) radiotherapy was administered in the last month of life. Median overall survival was 8.2 months. The median point sum was 22, range 17-28. Point sum was significantly associated with overall survival in univariate Cox regression analysis, $p<0.001$. Table 2 shows survival outcomes stratified by point sum. Figure 1 displays the Kaplan-Meier survival curves. Based on these curves, modification of the final 3-

tiered score developed by Rades *et al.* appears warranted, because the original break-down (17 points *versus* 18-25 points *versus* >25 points) is not in accordance with the overlapping survival curves in patients with 17 and 18 points (median survival 48 and 47 days, 6-months rate 7 and 8%, respectively). In addition, survival of patients with 25 points was very close to that of patients with >25 points. The proposed score modification (17-18 points *versus* 19-24 points *versus* >24 points, as shown in Figure 2, $p<0.001$) would result in slightly more balanced group size (unfavorable: 9%, intermediate: 66%, favorable: 25%) and higher chi-square statistics (120 *versus* 47).

A subgroup analysis was performed, which included all 74 patients who were at least 80 years old (median 83). Stratification according to the original Rades *et al.* score was not useful, because 72 patients (97%) were assigned to the intermediate group. The modified score performed satisfactorily (median survival 26, 192 and 489 days, respectively, $p<0.001$). The Kaplan-Meier curves are displayed in Figure 3.

Discussion

This study was performed primarily to provide additional validation of the recent prognostic model developed by Rades *et al.*, which predicts survival of patients with bone metastases who receive palliative radiotherapy (13). On one hand, palliative radiotherapy is a well-established and highly efficacious treatment for painful bone metastases (6). On the other hand, not all patients were shown to benefit and several studies have also suggested that measures reducing utilization of futile treatment close to the end-of-life (final month) are needed (18-20). Even if the perfect model predicting short survival has yet to be developed, existing models may be implemented to support decision making. The Rades *et al.* score focused on a particularly important subgroup

of patients, namely elderly patients irradiated for bone metastases (age ≥65 years). Oncology care in the elderly or geriatric population is challenging because of higher risk for toxicity (frailty, reduced organ function, lower PS) and shorter remaining life-span, also due to comorbidity (21, 22). On the other hand, good symptom palliation after radiotherapy has been reported also in the oldest old (8). It is therefore tempting to offer these patients well-tolerable, convenient fractionation regimens such as a single fraction of 8 Gy for uncomplicated painful bone metastases.

Rades *et al.* successfully validated their score (13), however both test and validation group included only 174 patients each. The present external validation was based on 305 patients. The main differences between the two studies relate to primary tumor site (Rades *et al.*: lung 30%, breast 26%, prostate 20%; present: lung 20%, breast 12%, prostate 41%) and preferred fractionation regimen (Rades *et al.*: 10 fractions of 3 Gy in 47%; present: 32%). Despite these differences, similar 6-months survival rates were obtained (unfavorable Rades *et al.*: test group 0%, validation group 9%; present: 7%). The corresponding figures for the favorable groups were 100, 86 and 92%, respectively. Thus, external validation was successful. However, a closer look at the present survival curves (Figure 1), revealed that unfavorable patients defined by a point sum of 17 had survival undistinguishable from those with a point sum of 18. Also, those with a point sum of 25 had relatively similar survival to their counterparts with higher point sum. If one modifies the break-down to adjust for these findings, as reflected in the survival curves shown in Figure 2, excellent discrimination can be maintained. The main advantage of this modification lies in the increased group sizes for both unfavorable and favorable patients, while the intermediate group can be reduced to 66% of patients (still representing a large proportion).

A secondary purpose of our study was to analyze the subgroup of the oldest old, defined as age ≥80 years, a particularly vulnerable and potentially frail population. We found that the original Rades *et al.* model assigned almost all patients to the intermediate group, while the modified model sorted out patients with favorable and unfavorable prognosis. Survival of the latter group (17-18 points) was very short (median 26 days, maximum 47), which is shorter than that of all patients with 17-18 points in the study (median 48 days), and raises concern about the appropriateness of radiotherapy in this age group when adverse prognostic features are present.

Alternative prognostic models have already been published. The most complex one is the so-called Bone Metastases Ensemble Trees for Survival (BMETS) with 27 co-variates (11, 16). Simpler models include Chow's 3-item (non-breast primary cancer, metastases other than bone only, and Karnofsky PS ≤ 60) (12) and Westhoff's 2-item tools (PS, primary tumor) (10). The Rades *et al.* model is only slightly more complex than the 3- or 2-item models. No head-to-head comparison in a sufficiently large database, ideally with >500 patients to ensure excellent statistical power, and stratified by age, is yet available. In principle, estimation of the remaining life span with a simple, validated model is better than no prognostic assessment at all. The limitations of our study include its single-institution methodology and predominance of male gender/prostate cancer. Before wide-spread application of our modified score, additional validation in at least one large, external database is needed.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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Figure 1. Actuarial overall survival for all different point sums according to the Rades *et al.* score, $p<0.001$ (pooled over all strata).

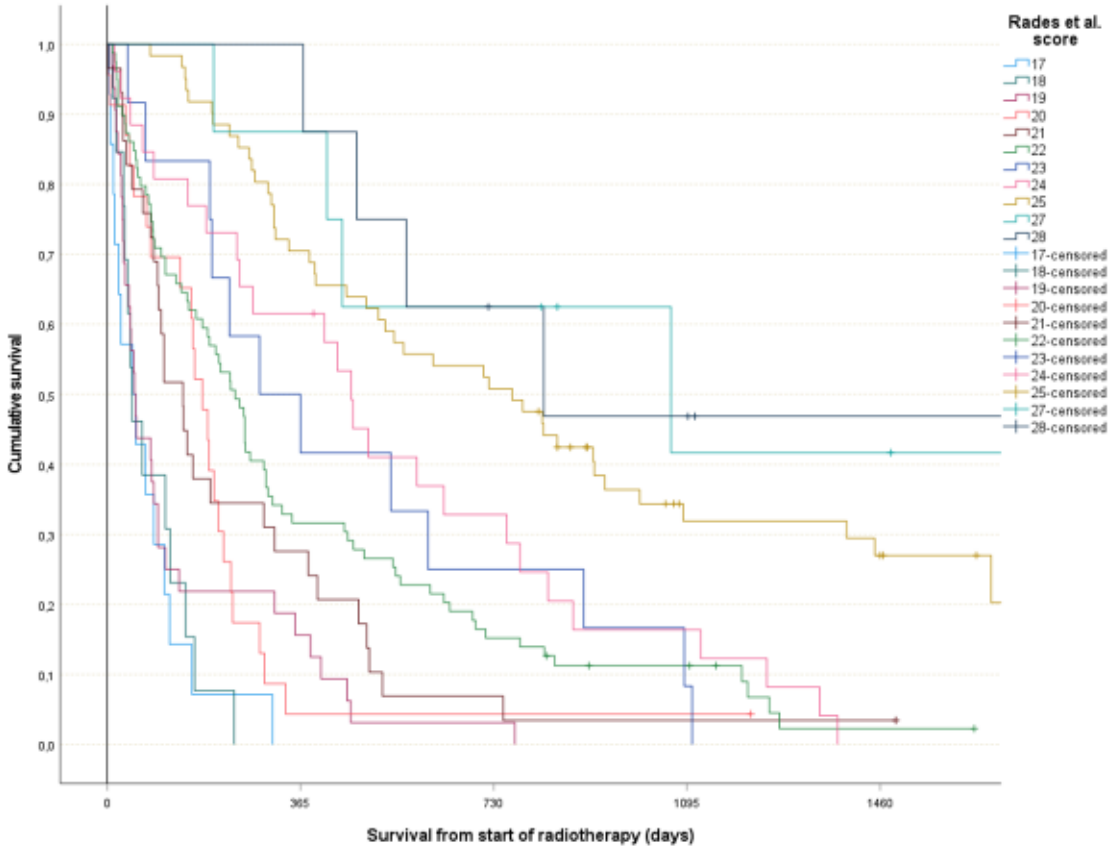

Figure 2. Actuarial overall survival for three different strata, $p<0.001$ (pooled over all strata, chi-square 120). Group size: n=27, 201 and 77, respectively. Poor prognosis: median 48 days. Intermediate prognosis: median 194 days. Good prognosis: median 822 days. For comparison, the original grouping resulted in median 48, 248 and 1065 days, respectively ($p<0.001$, chi-square 47).

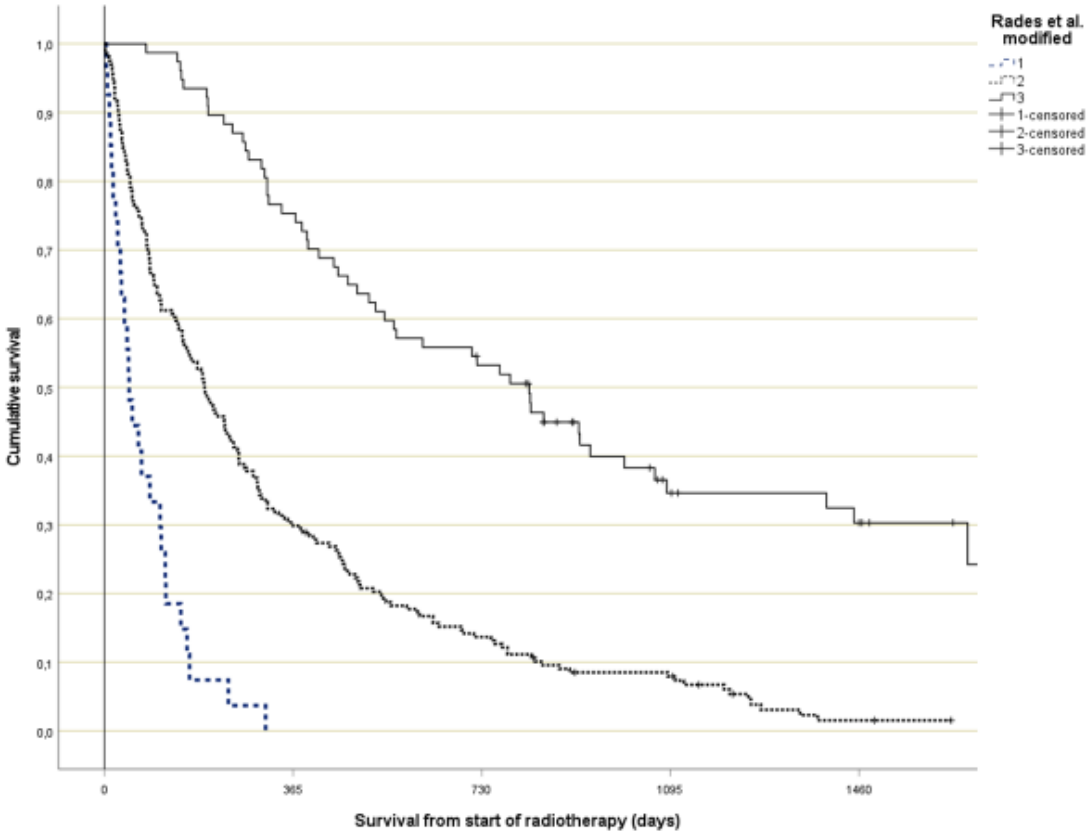

Figure 3. Actuarial overall survival (age ≥80 years) for three different strata, $p<0.001$ (pooled over all strata). Group size: n=5, 51 and 18, respectively. Poor prognosis: median 26 days. Intermediate prognosis: median 192 days. Good prognosis: median 489 days.

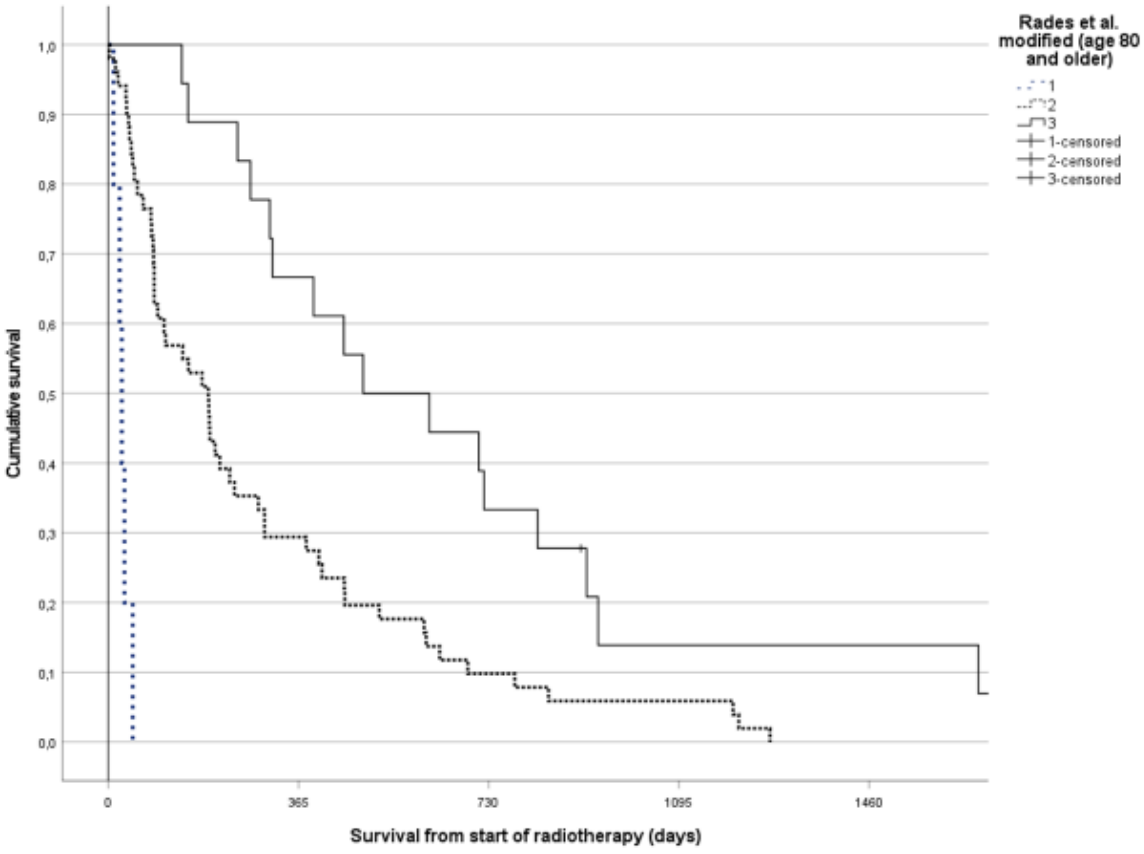

Table I. Baseline characteristics in 305 patients

Parameter	n	%
Female gender	98	32
Male gender	207	68
Outpatient	195	64
Inpatient	110	36
Prostate cancer	126	41
Lung cancer	60	20
Breast cancer	37	12
Kidney cancer	30	10
Colorectal cancer	15	5
Other cancer type	37	12
Visceral metastases	132	43
No visceral metastases	173	57
No previous or ongoing systemic cancer therapy	75	25
Endocrine treatment	147	48
Chemotherapy	57	19
Targeted agent (tyrosine kinase inhibitor)	18	6
Immune checkpoint inhibitor	8	3
Single fraction radiotherapy	70	23
Short-course radiotherapy, typically 5 fractions of 4 Gy	125	41
Longer course radiotherapy, typically 10 fractions of 3 Gy	96	32
Radiotherapy with >10 fractions, e.g. 3 Gy x13	14	5
Simultaneous irradiation of none-bone target, e.g. lung	32	10
Irradiation of a single target	123	40
Irradiation of 2 targets in the same course	110	36
Irradiation of >2 targets in the same course	72	24
Unable to complete radiotherapy as prescribed	7	2
Opioid analgesic prescribed	179	59
No opioid analgesic prescribed	126	41
Palliative care team involved	81	27
Performance status 0	21	7

Performance status 1	111	36
Performance status 2	85	28
Performance status >2	88	29
Median values		
Median age, range (years)	73	65-91
Median time interval (cancer diagnosis to radiotherapy, months)	35	1-312

Table II. Survival outcomes in 305 patients

Point sum	n	n, lmof	%, lmof	Median (days)	% 6-mo
17	14	6	43	48	7
18	13	2	15	47	8
19	32	10	31	52	22
20	23	2	9	180	47
21	29	5	17	143	38
22	79	9	11	242	58
23	12	0	0	288	83
24	26	2	8	461	77
25	61	0	0	765	92
26	0	-	-	-	-
27	8	0	0	1065	100
28	8	0	0	825	100

lmof: last month of life