ANTICANCER RESEARCH *41*: 1471-1474 (2021)
doi:10.21873/anticanres.14905

Independent Validation of a Comprehensive Machine Learning Approach Predicting Survival After Radiotherapy for Bone Metastases

CARSTEN NIEDER[1,2], BÅRD MANNSÅKER[1] and ROSALBA YOBUTA[1]

[1]*Department of Oncology and Palliative Medicine, Nordland Hospital, Bodø, Norway;*
[2]*Department of Clinical Medicine, Faculty of Health Sciences, University of Tromsø, Tromsø, Norway*

Abstract. *Background/Aim: The aim of this study was to analyze the survival predictions obtained from a web platform allowing for computation of the so-called Bone Metastases Ensemble Trees for Survival (BMETS). This prediction model is based on a machine learning approach and considers 27 prognostic covariates. Patients and Methods: This was a retrospective single-institution analysis of 326 patients, managed with palliative radiotherapy for bone metastases. Deviations between model-predicted survival and observed survival were assessed. Results: The median actuarial survival was 7.5 months. In total, 59% of patients survived for a period shorter than predicted. Twenty percent of the predictions of the median survival deviated from the observed survival by at least 6 months. Regarding actual survival <3 months (99 of 326 patients), the BMETS-predicted median survival was <3 months, i.e. correct in 67 of 99 cases (68%), whereas the model predicted a median of 4-6 months in 16 (16%) and of >6 months in another 16 cases. Conclusion: The model predicted survival with high accuracy in a large number of patients. Nevertheless, if the model predicts a low likelihood of 3-month survival, actual survival may be very poor (often 1 month or less). Also, in patients who died within 3 months from the start of radiotherapy, the model often predicted longer survival (16% had >6 months predicted median survival). It would, therefore, be interesting to feed the U.S. database utilized to develop the BMETS with additional poor-prognosis patients to optimize the predictions.*

Correspondence to: Carsten Nieder, Department of Oncology and Palliative Medicine, Nordland Hospital, 8092 Bodø, Norway. Tel: +47 75578449, Fax: +47 75534975, e-mail: carsten.nieder@nlsh.no

Key Words: Palliative radiation therapy, radiotherapy, bone metastases, prognostic model, biomarkers.

A large number of cancer patients worldwide receive palliative radiotherapy for bone metastases (1). However, the treatment scenarios are highly variable and include pain-alleviating irradiation of uncomplicated bone metastases, post-operative radiotherapy after surgical stabilization, irradiation of impending or established spinal cord and/or nerve root compression and others (2, 3). The survival prognosis of these patients is heterogeneous, too. Pain might be present already as the first sign of cancer in patients expected to survive for several years, or in the pre-terminal and terminal phase when all systemic therapies have been stopped due to futility and/or the patients' reduced general condition (4-8). This heterogeneity causes uncertainty regarding treatment decisions, such as the decision to irradiate at all and the choice of fractionation regimen (9-11). Several groups have proposed prognostic models, which may support decision making (12-14). Recently, new technology has resulted in improved opportunities to add complexity to such models, *e.g.* by integrating a much larger number of prognostic factors than older methods were able to handle. Alcorn *et al.* have utilized a machine learning approach to analyze whether they could optimize survival estimation for patients with symptomatic bone metastases (15). Their so-called Bone Metastases Ensemble Trees for Survival (BMETS) predict survival using 27 prognostic covariates. As briefly discussed in a recent correspondence to this study (16), some of the 27 covariates are prone to practice variation, in particular on an international level, *i.e.* between different healthcare systems. Examples include access to in-patient care and the type of systemic therapy. Thus, our group performed an independent validation study in a different geographical region (Norway as compared to USA), which has a different healthcare system (publicly-funded). Due to space limitations for correspondence, only a shortened report of the resulting concerns has been published. The present paper provides a broader set of results.

Patients and Methods

Analogous to a previous validation approach (14), our single-institution database that includes unselected patients irradiated for complicated or uncomplicated bone metastases from histologically verified primary tumors (both completed and interrupted treatment courses according to the intention-to-treat principle, 2009-2018) was analyzed. Radiotherapy prescription was individualized (often 3 Gy ×10, 4 Gy ×5 or 8 Gy ×1), as was systemic therapy. Staging consisted of computed tomography. If clinically relevant, other modalities were added to clarify computed tomographic findings, *e.g.* isotope bone scan, ultrasound, and positron-emission tomography. Routine blood tests were assessed during treatment planning approximately 1 week before radiotherapy.

Alcorn *et al.* (15) developed a web platform for data entry and display of BMETS-predicted survival probabilities (https://oncospace.radonc.jhmi.edu/Tools/PalliationPrediction.aspx), which was utilized in the present study. The model-based Kaplan-Meier curves are truncated at 12-month follow-up and therefore, median survival cannot be assessed if the predicted survival is longer than 12 months. Both 3- and 12-month survival probabilities were tabulated [Results reported in (16)]. Furthermore, the predicted median survival was recorded.

Overall survival (time to death) from the first day of radiotherapy was calculated employing the Kaplan–Meier method (SPSS 25; IBM Corp., Armonk, NY, USA). The minimum follow-up was 6 months. The median follow-up of 26 censored patients was 48 months. As mentioned above, this database created for the purpose of quality-of-care analyses has already been utilized and does not require additional approval by the local Ethics Committee (REK Nord).

Table I. *Baseline data.*

Baseline parameter	Number	Percent
Female gender	119	37
Male gender	207	64
Prostate cancer	109	33
Breast cancer	58	18
Lung cancer	57	16
Other solid cancer	102	31
Hospitalized patients	114	35
Outpatients	212	65
Current opiate analgesic use	213	65
No opiate analgesic use	113	35
Current steroid use	172	53
No steroid use	154	47
Additional systemic therapy	256	79
No additional systemic therapy	70	21
Weight loss during preceding 6 months	95	29
No weight loss during preceding 6 months	199	61
Weight loss not recorded	32	10
Brain metastases present	22	7
Liver metastases present	89	27
Lung metastases present	91	28
Adrenal gland metastases present	25	8
Median KPS, range	70, 30-100	
Median age, range (years)	67, 32-90	
Median time interval, range (months)*	31, 1-324	
Median white blood cell count, range	7500, 1900-62000	
Median lymphocyte count, range	1300, 200-31000	

KPS: Karnofsky performance status. *Period from cancer diagnosis to actual radiotherapy.

Results

The aforementioned web platform was utilized to analyze the BMETS performance in 326 patients (Table I). Their median age was 67 years (minimum 32 years, maximum 90 years). The three most common cancer types were located in the prostate, breast or lung. Most patients who received systemic therapy had endocrine treatment (40%) or chemotherapy (30%). Treatment to more than one target volume, *e.g.* spine and femur, was common (59%). Eight patients (2%) failed to complete their prescribed course of radiotherapy. The median actuarial survival was 7.5 months.

The median survival according to the Kaplan-Meier curve derived from the web platform was ≤3 months in 58 patients (18%). Their median survival was 35 days (range=5-245) and 7 survived for >3 months. In 94 patients (29%), a median survival of more than 12 months was predicted. Of these, 20 died after less than 12 months (minimum 81 days). In total, 59% of all 326 patients survived shorter than predicted. Forty-five predictions of the median survival time in the 232 eligible patients (those whose Kaplan-Meier curves were not truncated at 12 months, see Methods) were within 1 month of the actual survival time (19%). Another 53 (23%) were within 2 months and 37 (16%) within 3 months. However, 47 (20%) deviated by at least 6 months. Figure 1 shows the observed deviations from predicted survival in these 232 patients (mean=60.5 days).

Regarding actual survival <3 months (99 of 326 patients), the BMETS-predicted median survival was correct in 67 of 99 cases (68%), whereas the model predicted a median of 4-6 months in 16 (16%) and of >6 months in another 16 cases.

Discussion

The original BMETS study (15) included 397 patients (treatment period January 2007 to January 2013). Two previously validated, simpler models were also studied: Chow's 3-item and Westhoff's 2-item tools (12, 17). The model performance was assessed using cross-validation procedures and measured by time-dependent area under the curve (tAUC) for all 3 models. For temporal validation, a separate data set comprised of 85 patients treated in 2018 at the same U.S. institution was used. Median survival was 6.4 months (comparable to the present data, 7.5 months). BMETS (27 prognostic covariates, such as age, gender, primary cancer site, performance status, steroid and opioid medication, weight loss, pattern of other metastases) outperformed the simpler models at each time. For the

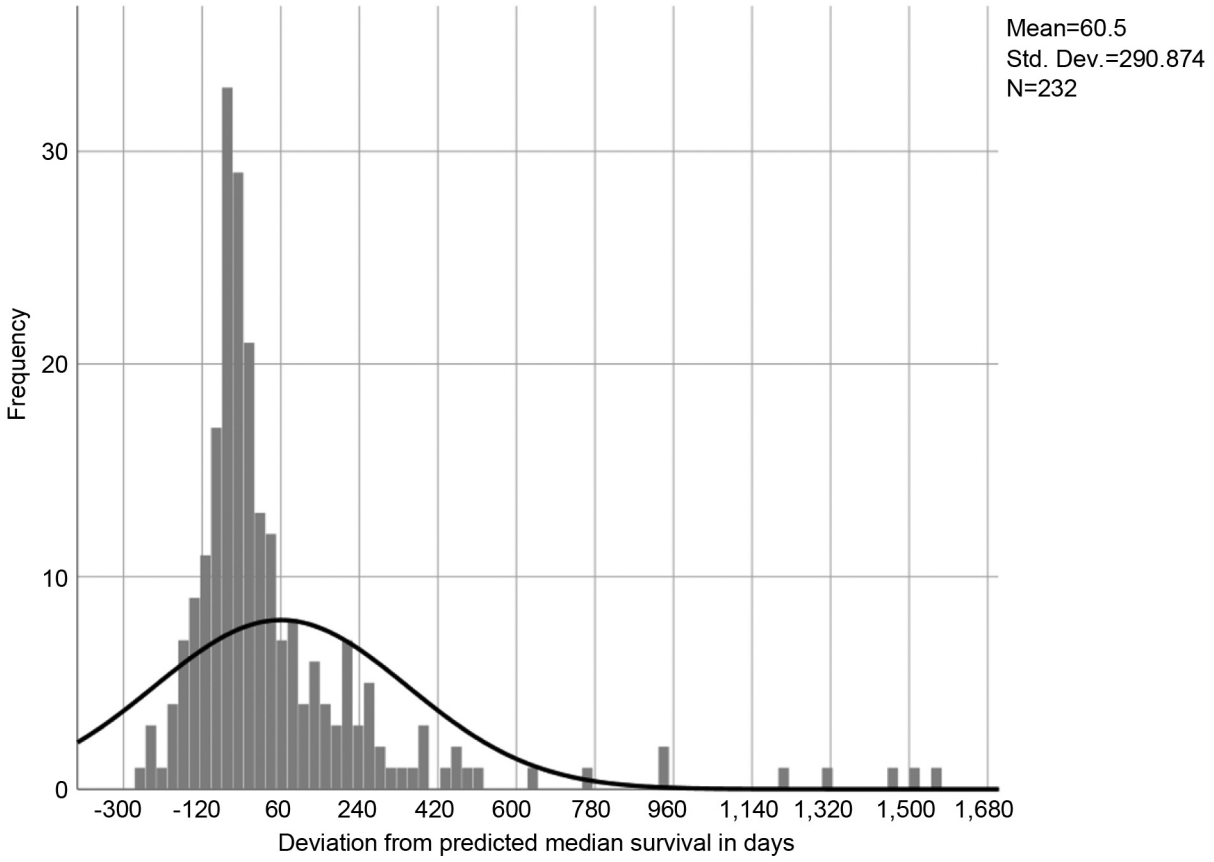

Figure 1. *Deviation from predicted median survival in days*.

temporal validation set, respective tAUC was 0.86, 0.82, and 0.78. These statistically sound validation methods lack an intuitively understandable dimension, telling clinicians how much agreement or disagreement they can expect if they decide to use the web platform in clinical routine. In a previous nomogram study, our group developed a visual validation plot comparable to the one shown in Figure 1 (18). This method illustrates how much deviation from the predicted median survival can be observed in individual patients. Even a good and complex prognostic model such as the BMETS is associated with large deviations in a minority of patients.

Prediction of very short survival was not the main goal of the BMETS study. Nevertheless, the present results and those published in (16) suggest that, if the model predicts a low likelihood of 3-month survival, actual survival may be very poor. This means that some patients are unlikely to experience the potential benefit palliative radiotherapy may cause if survival is long enough. Also, in patients who died within 3 months from the start of radiotherapy, the model often predicted longer survival (16% had >6 months predicted median survival). It would, therefore, be interesting to feed the U.S. database with additional poor-prognosis patients to optimize the predictions. A possible explanation for deviating results are international practice variations such as the threshold for hospitalization and the choice of systemic therapy, variables that are part of the prediction model. For example, a 70-year old male with prostate cancer, bone-only metastases, Karnofsky performance status of 70, not admitted to hospital and on endocrine systemic therapy has a predicted 12-month survival probability of 56%. This probability drops to 48% if the same patient is admitted to hospital, and to 31% if the systemic therapy changes to intravenous chemotherapy and the patient is still hospitalized (calculated at https://oncospace.radonc.jhmi.edu/Tools/PalliationPrediction.aspx on December 31, 2020).

The BMETS approach has several strengths such as the large number of prognostic covariates, careful validation, comparison to simpler models and easy-to-use web platform. However, weaknesses of this model need to be acknowledged, *e.g.* the impact of practice variations on survival predictions and the time needed to collect and enter all covariates. A larger

multi-institutional or even international database might be a good starting point for refinement of the model, aiming at further improvement of the prediction accuracy.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

CN participated in the design of the study and performed the statistical analysis. CN, BM and RY conceived the study and drafted the article. All Authors read and approved the final article.

References

1 Coleman RE, Croucher PI, Padhani AR, Clézardin P, Chow E, Fallon M, Guise T, Colangeli S, Capanna R and Costa L: Bone metastases. Nat Rev Dis Primers *6(1)*: 83, 2020. PMID: 33060614. DOI: 10.1038/s41572-020-00216-3

2 Nieder C, Pawinski A and Dalhaug A: Continuous controversy about radiation oncologists' choice of treatment regimens for bone metastases: should we blame doctors, cancer-related features, or design of previous clinical studies? Radiat Oncol *8*: 85, 2013. PMID: 23574944. DOI: 10.1186/1748-717X-8-85

3 Hata M, Koike I, Miyagi E, Asai-Sato M, Kaizu H, Mukai Y, Takano S, Ito E, Sugiura M and Inoue T: Radiation therapy for patients with bone metastasis from uterine cervical cancer: Its role and optimal radiation regimen for palliative care. Anticancer Res *38(2)*: 1033-1040, 2018. PMID: 29374737. DOI: 10.21873/anticanres.12319

4 Nieder C, Dalhaug A and Pawinski AR: Management of patients with metastatic renal cell cancer and bone metastases. In Vivo *34(2)*: 675-678, 2020. PMID: 32111768. DOI: 10.21873/invivo.11822

5 Nieder C, Dalhaug A, Pawinski A, Mannsåker B and Haukland E: Survival after palliative radiotherapy in patients with breast cancer and bone-only metastases. In Vivo *30(6)*: 879-883, 2016. PMID: 27815475. DOI: 10.21873/invivo.11008

6 Nieder C, Haukland E, Mannsåker B and Norum J: Impact of intense systemic therapy and improved survival on the use of palliative radiotherapy in patients with bone metastases from prostate cancer. Oncol Lett *12(4)*: 2930-2935, 2016. PMID: 27698881. DOI: 10.3892/ol.2016.5003

7 Nieder C, Haukland E, Mannsåker B, Pawinski A and Dalhaug A: Early palliative radiation therapy in patients with newly diagnosed cancer: Reasons, clinical practice, and survival. Pract Radiat Oncol *5(5)*: e537-e542, 2015. PMID: 25823382. DOI: 10.1016/j.prro.2015.02.008

8 Nieder C, Haukland E, Mannsåker B, Pawinski A, Yobuta R and Norum J: Initiation of systemic therapy during the last 30 days of life in patients with metastatic castration-resistant prostate cancer. Anticancer Res *39(1)*: 335-340, 2019. PMID: 30591477. DOI: 10.21873/anticanres.13116

9 Saito T, Yamaguchi K, Toya R and Oya N: Single – *versus* multiple-fraction radiation therapy for painful bone metastases: A Systematic review and meta-analysis of nonrandomized studies. Adv Radiat Oncol *4(4)*: 706-715, 2019. PMID: 31673664. DOI: 10.1016/j.adro.2019.06.003

10 Ganesh V, Chan S, Raman S, Chow R, Hoskin P, Lam H, Wan BA, Drost L, DeAngelis C and Chow E: A review of patterns of practice and clinical guidelines in the palliative radiation treatment of uncomplicated bone metastases. Radiother Oncol *124(1)*: 38-44, 2017. PMID: 28629871. DOI: 10.1016/j.radonc.2017.06.002

11 Sprave T, Verma V, Förster R, Schlampp I, Hees K, Bruckner T, Bostel T, El Shafie R, Nicolay NH, Debus J and Rief H: Quality of life and radiation-induced late toxicity following intensity-modulated *versus* three-dimensional conformal radiotherapy for patients with spinal bone metastases: Results of a randomized trial. Anticancer Res *38(8)*: 4953-4960, 2018. PMID: 30061275. DOI: 10.21873/anticanres.12813

12 Westhoff PG, de Graeff A, Monninkhof EM, Bollen L, Dijkstra SP, van der Steen-Banasik EM, van Vulpen M, Leer JW, Marijnen CA, van der Linden YM and Dutch Bone Metastasis Study Group: An easy tool to predict survival in patients receiving radiation therapy for painful bone metastases. Int J Radiat Oncol Biol Phys *90(4)*: 739-747, 2014. PMID: 25260489. DOI: 10.1016/j.ijrobp.2014.07.051

13 Janssen S, Haus R, Schild SE and Rades D: A Simple Clinical Instrument to Predict the Survival Probability of Breast Cancer Patients Receiving Radiotherapy for Bone Metastases. Anticancer Res *40(1)*: 367-371, 2020. PMID: 31892588. DOI: 10.21873/anticanres.13961

14 Nieder C, Mannsaker B and Dalhaug A: Independent external validation of a score predicting survival after radiotherapy for bone metastases and expansion to patients treated with single fraction radiotherapy. J Clin Med Res *12(2)*: 90-99, 2020. PMID: 32095178. DOI: 10.14740/jocmr4060

15 Alcorn SR, Fiksel J, Wright JL, Elledge CR, Smith TJ, Perng P, Saleemi S, McNutt TR, DeWeese TL and Zeger S: Developing an improved statistical approach for survival estimation in bone metastases management: The Bone Metastases Ensemble Trees for Survival (BMETS) Model. Int J Radiat Oncol Biol Phys *108(3)*: 554-563, 2020. PMID: 32446952. DOI: 10.1016/j.ijrobp.2020.05.023

16 Nieder C:In regard to Alcorn *et al*.Int JRadiat Oncol Biol Phys, 2021. DOI: 10.1016/j.ijrobp.2020.12.055 (in press)

17 Chow E, Abdolell M, Panzarella T, Harris K, Bezjak A, Warde P and Tannock I: Predictive model for survival in patients with advanced cancer. J Clin Oncol *26(36)*: 5863-5869, 2008. PMID: 19018082. DOI: 10.1200/JCO.2008.17.1363

18 Nieder C, Hintz M and Grosu AL: Predicted survival in patients with brain metastases from colorectal cancer: Is a current nomogram helpful? Clin Neurol Neurosurg *143*: 107-110, 2016. PMID: 26914143. DOI: 10.1016/j.clineuro.2016.02.022

Received January 11, 2021
Revised January 29, 2021
Accepted February 11, 2021